Aging and Disease
www.aginganddisease.org
Early access date: March 31, 2026
http://dx.doi.org/10.14336/AD.2025.1456

Review

The Interplay Between Physical Exercise, Nutritional Strategies, and Brain-Derived Neurotrophic Factor in Promoting Cognitive Performance

Jacopo Givralli[1,2], Tatiana Moro[1], Tõnis Timmusk[3], Antonio Paoli[1*]

[1]Department of Biomedical Science, University of Padua, Padua, Italy.
[2]Department of Neurosciences, Biomedicine and Movement. University of Verona, Verona, Italy.
[3]Department of Chemistry and Biotechnology, Tallinn University of Technology, Tallinn, Estonia.

[Received November 27, 2025; Revised January 16, 2026; Accepted January 19, 2026]

ABSTRACT: Physical exercise and nutritional strategies have become powerful tools for improving brain health, boosting cognitive performance, slowing cognitive decline, and reducing the risk of neurodegenerative diseases, primarily by influencing neurotrophic factors such as brain-derived neurotrophic factor (BDNF). This review examines the impact of various exercise types (endurance, high-intensity interval training, and resistance) along with dietary approaches (ketogenic diet and intermittent fasting) on BDNF, with a focus on their potential to promote cognition and neuroprotective benefits, particularly in the middle-aged and older population. Several molecular and physiological pathways may be involved, including activation of the PGC-1α–FNDC5–BDNF pathway, lactate signaling, increased blood flow to the brain and body, splenic platelet release, and stimulation of TrkB, IGF-1, irisin, and cathepsin B. Nutritional interventions may also boost BDNF through mechanisms involving β-HB and Notch 1 signaling. Research from both animal and human studies highlights the potential benefits of exercise and dietary modifications in supporting brain health and cognitive function. However, differences in study design and methodological limitations make it difficult to draw firm conclusions. These effects appear to be influenced by factors such as exercise characteristics (intensity, modality, and duration), the timing of blood collection, and the type of cognitive assessments. Future studies should focus on identifying the most effective intervention protocols and mechanisms, as well as understanding the individual factors that influence responsiveness to neurotrophic changes. Overall, targeted exercise and dietary strategies offer a promising approach to maintain brain health and reduce cognitive decline associated with aging and disease.

Keywords: diet, endurance training, cognition, BDNF, HIIT, resistance training.

Introduction

Physical exercise and nutritional strategies have been widely recognized for their numerous benefits on brain health and functionality. They have been shown to improve cognitive performance and decrease the risk of neurodegenerative diseases [1]. The mechanisms behind this crosstalk are various and not completely understood. However, one of the main characters is undoubtedly the action of neurotrophic factors.

Neurotrophic factors consist of a large family of dimeric polypeptides, including neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5. Through their actions on neuronal survival, differentiation, and growth, these dimeric polypeptides are essential for neurodevelopment and adult brain plasticity [1–3]. BDNF has been implicated in many different functions in the central (CNS) and peripheral (PNS) nervous systems [4–7]. Particularly, mounting

***Correspondence should be addressed to:** Dr. Antonio Paoli, Department of Biomedical Science, University of Padua, Padua Italy. Email: antonio.paoli@unipd.it.

evidence has shown that BDNF promotes neuroplasticity, receptor trafficking [8], dendritic modification [9], facilitating synaptic transmission [10], and the process of long-term potentiation (LTP) [8]. Furthermore, BDNF supports neurogenesis [11], synaptic growth [12], and repair [13]. Thus, due to its significant impact on brain changes, BDNF is considered a potential mediator of cognitive functions [14].

Cognition can be defined in several ways (e.g., cognitive function, cognitive performance) as it covers a variety of cognitive domains, including complex attention, executive functions, memory and learning, social cognition, language, and perceptual-motor function [15]. Supporting the link between BDNF and cognition, studies in animals with enhanced BDNF levels, induced by enriched environments and exercise, have shown better performance on behavioural testing. For instance, increased BDNF expression in mice was associated with significantly enhanced spatial learning and memory, as assessed by the Morris water maze test [16]. Moreover, research extensively agrees on the presence of BDNF in most brain areas, including the olfactory bulb, cortex, hippocampus, basal forebrain, thalamus, hypothalamus, brainstem (consisting of midbrain, pons, and medulla), cerebellum, and spinal cord [17]. Most of these cerebral areas are known to be related to cognitive functions. These findings, along with imbalances in BDNF levels and downstream signaling association with neurodegenerative and psychiatric diseases, such as Alzheimer's, Huntington's disease, schizophrenia, and major depressive disorder [18], suggest the implication of BDNF in regulating learning and memory processes in young and adult mammals [19]. Furthermore, healthy lifestyle, exercise, and dietary programs have been shown to upregulate BDNF levels [20, 21] positively and improve cognitive functions as well [22]. Thus, a summary of recent findings is necessary, considering the critical role of BDNF in brain structural changes and cognition, as well as the positive effects of simple interventions, such as exercise and diet, in enhancing BDNF levels and, consequently, cognitive performance.

This narrative review will provide a brief description of the mechanisms of production and secretion, as well as the principal function of BDNF in the brain. Then, a detailed focus will be given to the influence of interventions based on different types of exercise (endurance exercise, high-intensity interval training, and resistance exercise) and diet (ketogenic diet and intermittent fasting), with an emphasis on their relationship with BDNF and cognitive functions, particularly in the middle-aged and older population. We will discuss several factors, such as intensity, duration of the intervention, modality, and the mechanism beyond the production and release of peripheral BDNF, mainly related to plasma and serum.

BDNF and Cognitive Performance

The BDNF protein is synthesized and folded in the endoplasmic reticulum as preproBDNF (32–35kDa). After being translocated to the Golgi apparatus, the signal sequence of the preregion is rapidly cleaved, and the isoform proBDNF (28–32kDa) is generated [23]. Then, proBDNF is cleaved again, intracellularly by furin and other protein convertases [24, 25], or extracellularly by plasmin and metalloproteinases [26, 27], to reach the mature isoform (mBDNF, 13kDa) [23, 28].

For many years, it has been assumed that only secreted mBDNF had biologically significant effects, while pro-BDNF was considered its inactive precursor, located in the intracellular compartment. Actually, the two forms of BDNF follow different pathways, exerting different effects on the brain and tissues. Pro-BDNF exhibits high-affinity binding to p75 neurotrophin receptor (p75NTR), thereby facilitating mechanisms such as long-term depression (LTD), dendritic spine retraction, and apoptosis [29–31]. On the other hand, mBDNF selectively binds tropomyosin receptor kinase B (TrkB) [32, 33], activating multiple intracellular signaling cascades, including PI3K/AKT, MAPK/ERK, and TrkB-mediated PLCγ pathways [34], leading to cell survival and proliferation [35–37], axonal and dendritic growth, and the facilitation of LTP with concomitant maturation of dendritic spines [38–40]. The opposing actions of pro-BDNF/p75 and mBDNF/TrkB signaling pathways underscore the complex regulatory role of BDNF in neuroplasticity, with the relative proportion of secreted pro-BDNF and mBDNF serving as a critical determinant of the direction of neuroplastic changes in target neurons.

Although BDNF is highly expressed in the CNS [41], hippocampus, cortex, amygdala, striatum, and hypothalamus [42], a significant amount is also present in the circulation [43, 44]. The cellular origin of BDNF in platelets is the megakaryocytes, the progenitors of platelets [45]. In fact, peripherally, mBDNF is stored mainly in platelets [46–50], with serum levels 100/200-fold higher than in plasma. Thus, given the impracticality of directly measuring cerebral BDNF in vivo, and because of some evidence that BDNF can cross the blood-brain barrier (BBB) [51], it is assumed that peripheral BDNF is a proxy of BDNF levels in the brain. Consistently, in some animal models like rats and pigs, measures of BDNF in the CNS correlate with measures of BDNF from the circulation and other tissues [44, 51], with as much as 75% of BDNF originating from the brain. Nevertheless, this relationship is not universal. BDNF was previously undetectable in mouse blood, despite comparable brain

levels, until the recent development of a sensitive assay [52], suggesting species-specific differences and potential limitations in using blood BDNF across different animals.

Recent evidence suggests that blood BDNF levels do not accurately reflect brain BDNF levels. First, there is no clear evidence that BDNF crosses the BBB [53]. Second, brain BDNF levels are relatively consistent across mammals, including humans and mice, whereas blood BDNF differs by orders of magnitude. This discrepancy arises because human blood [54], but not mouse blood [55], contains high platelet-derived BDNF, complicating cross-species comparisons of peripheral BDNF. Interestingly, when the expression of BDNF in mice was genetically increased in platelets to the levels present in humans, blood-derived BDNF was able to prevent dendritic atrophy of retinal ganglion cells after optic nerve crush. This suggests that even if BDNF does not cross the blood-brain barrier, BDNF can be released from blood platelets by extracellular vesicles and delivered to brain neurons after lesions of blood vessels in the human brain [52].

Although the mechanisms of production and secretion have been extensively studied in animal models, research in human models is limited, with a primary focus on peripheral BDNF. Thus, a clear specification of the biospecimen considered (e.g., serum or plasma BDNF) is necessary to better understand its specific effect and response to different types of interventions (e.g., exercise or diet) in human studies. As mentioned earlier, the importance of BDNF in brain function, through its role in neuroplasticity and synaptic plasticity mechanisms, is well-documented in the literature. Neuroplasticity, or brain plasticity, is the ability of the nervous system to change its structure, function, and connections in response to extrinsic or intrinsic stimuli [56]. The classic theory "neurons that fire together wire together [57] accurately illustrates how repetitive neuronal activity strengthens synaptic connections, thereby driving experience-dependent plasticity through distinct neurobiological mechanisms. Molecular mechanisms contributing to neuroplasticity include synaptogenesis (formation of new synaptic connections), neurogenesis (development of new neurons), angiogenesis (formation of new blood vessels), and gliogenesis (generation of non-neuronal glial cells in the brain) [58]. Collectively, these processes are essential for cognitive functions, directly influencing learning, memory, and perceptual abilities [59]. Furthermore, BDNF modulates synaptic plasticity, the capacity for strengthening and weakening neural connections over time, which underlies cognitive processes such as memory formation and recall [60]. Evidence has linked these structural adaptations in the brain with improvements in cognitive performance [61].

Conversely, cognitive abilities tend to decline with age, likely reflecting cellular and metabolic alterations that progressively diminish synaptic plasticity across brain regions critical for cognitive functions [62]. Mattson et al. [63] proposed that age-related cognitive impairments may be linked to reductions in BDNF expression within key brain regions affected by aging. Consistent with this hypothesis, plasma BDNF concentrations have been observed to decrease with age. One study [64] stratified median plasma BDNF levels across several age groups: young adults (20–33 years, ~100 pg/mL, n = 45), mid-life adults (34–47 years, ~80 pg/mL, n = 59), and older adults (48–60 years, ~50 pg/mL, n = 36). This declining trend persists into later life, as evidenced by a large cohort study of serum BDNF in adults aged 65–97 years (n = 5,104), which reported an average concentration of 21 ng/mL (SD = 5.4 ng/mL) [65]. In addition, emerging evidence has suggested that cognitive decline can begin earlier in life, particularly during middle age (the age range from 40 to 65) [66], affecting domains such as memory, processing speed, and executive functions [67].

Therefore, BDNF can significantly impact the improvement or maintenance of cognitive performance, particularly in middle-aged and older individuals. Measuring changes in cognitive functioning (e.g., neuropsychological tests) is necessary to assess neuroplasticity, as improvements in performance on a cognitive task may represent changes in the activity of neural networks that execute these mental processes [68]. Moreover, techniques such as functional Magnetic Resonance Imaging (fMRI) and cerebrospinal fluid (CSF) measures could be useful for evaluating structural and functional changes in the brain. Furthermore, when assessing cognitive functions, it is important to acknowledge the baseline cognitive status of the subjects. Baseline cognitive status, which reflects cognitive reserve, can modulate the responsiveness to interventions, thereby affecting observed changes in cognitive performance [69]. For example, a study of cognitively healthy older adults found that the strongest baseline predictor of subsequent episodic memory decline was the baseline episodic memory score, highlighting the value of baseline cognitive performance in predictive models [70]. Moreover, comorbid neurodegenerative conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD) are often associated with alterations in circulating BDNF and accelerated cognitive decline. Patients with AD exhibit reduced peripheral BDNF than cognitively healthy controls, and lower BDNF has been linked with greater neurodegeneration and smaller hippocampal volume [71]. In Parkinson's disease, serum BDNF levels are reduced compared to controls and positively correlate with cognitive function, suggesting an

association between lower BDNF levels and cognitive deficits [72].

Cognitive performance, neuroplasticity, and BDNF could be influenced by various factors, including age, physical exercise, nutrition, sleep, stress levels, sex differences, and potential impairments from medical or psychological conditions. Among these factors, exercise and nutrition have garnered interest due to their beneficial impact on overall health. Research over the last few years has focused on identifying the mechanisms and subsequent improvements related to enhanced cognitive functions through the release of BDNF following exercise or dietary interventions. Although exercise and diet are widely recognized as effective strategies for enhancing BDNF levels and cognitive performance independently, research often yields conflicting results when examining the correlation between BDNF and cognition as simultaneous outcomes. Several factors, such as population, intensity, type of intervention, duration, and biospecimen, must be considered when analyzing the results of a study. Moreover, the mechanisms behind the BDNF-related improvement after an exercise or diet intervention are not fully understood.

Physical exercise and cognitive performance

Physical exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposeful, with the aim of improving or maintaining one or more components of physical fitness [73].

In its various forms, exercise provides several benefits to almost all human organs and physiological systems, including the metabolic, musculoskeletal, cardiovascular, respiratory, immune, and digestive systems. Endurance exercise is defined as any activity that engages large muscle groups, can be maintained continuously, and is rhythmic in nature [73]. It requires the metabolic system to utilize oxygen to produce energy, thereby enhancing the cardiovascular system's capacity to uptake and transport oxygen. Examples of endurance exercise include cycling, dancing, hiking, jogging/long-distance running, swimming, and walking. High-intensity interval training (HIIT) is characterised by alternating short bursts of intense activity, typically performed at 80–90% of maximal heart rate (HRmax), with periods of low-intensity recovery, typically 60% of HRmax, or rest. This method targets improvements in cardiovascular fitness, endurance, and metabolic rate within a relatively brief time frame [74]. Conversely, resistance training is defined as any form of physical activity that requires the production of muscular force against external resistance, with the intention of increasing muscle size, strength, and/or endurance [75].

Among the general, well-recognised, healthy effects of exercise on the physiology of the body, in recent years, many studies have focused on its positive effects on cognition. Regarding endurance exercise, evidence in older adults suggests that it may improve cognitive performance [76–81], promote brain plasticity [76, 82], and attenuate hippocampal atrophy while improving visual attention and memory [76]. Similarly, in young, healthy individuals, 30 minutes of moderate-intensity cycling has been reported to enhance cognitive performance, including memory, reasoning, attention, and planning, compared to baseline measures [83]. In another study, 24 healthy young adults completed a pinch-grip motor task before and after 30 minutes of moderate-intensity running. The results indicated that an acute bout of aerobic exercise facilitated motor skill acquisition, primarily through improvements in task accuracy [84].

Thus, endurance training appears to be particularly effective in enhancing cognitive performance across different age groups. A recent meta-analysis [85] found that HIIT can elicit moderate acute improvements in executive function (standardized mean difference [SMD] = 0.50), with larger effects observed in studies employing moderately to highly demanding HIIT protocols. Nevertheless, the relatively small number of studies included warrants cautious interpretation of these findings. Regarding resistance exercise, two recent meta-analyses [86, 87] analyzing studies consisting of a supervised exercise program lasting at least four weeks, have demonstrated its benefits for executive function, memory, and working memory. Additionally, improvements in executive function have been observed in young to middle-aged adults, even after a single bout of resistance exercise[88]. Although several reviews and studies highlight the effectiveness of endurance, HIIT, and resistance exercises in enhancing cognitive performance, in most cases, BDNF was not assessed. Overall, both aerobic and anaerobic exercise, whether acute (one session) or chronic (two or more sessions), have been shown to improve cognitive performance across various populations.

Endurance exercise and its influence on cognition and BDNF

Endurance exercise has been extensively documented, both acutely and chronically, as a potent stimulus for elevating levels of BDNF [89]. Several mechanisms have been proposed to explain how endurance exercise may enhance peripheral BDNF concentrations, as illustrated in Figure 1. Generally, it can increase tissue metabolism, which in turn induces a range of physiological responses, such as increased cardiac output, augmented vascular shear stress, and energetic demands, as well as triggering

hypoxic responses. Specifically, the primary physiological mechanisms in BDNF release include enhanced cerebral and peripheral blood flow [90], splenic platelet release [91], hypoxia [93], and possibly an increase in body temperature [93] (Fig. 1). At the molecular level, endurance exercise may upregulate the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) gene expression in neurons, promoting the secretion of fibronectin type III domain-containing protein 5 (FNDC5) and irisin synthesis, which subsequently increases BDNF levels (Fig. 1). Moreover, activation of the PGC-1α or FNDC5 pathway, coupled with enhanced penetration of cathepsin B across the BBB during aerobic exercise [94, 95], further contributes to BDNF elevation (Fig. 1). However, the precise mechanism remains to be fully elucidated, and factors such as exercise dosage and intensity may modulate these responses.

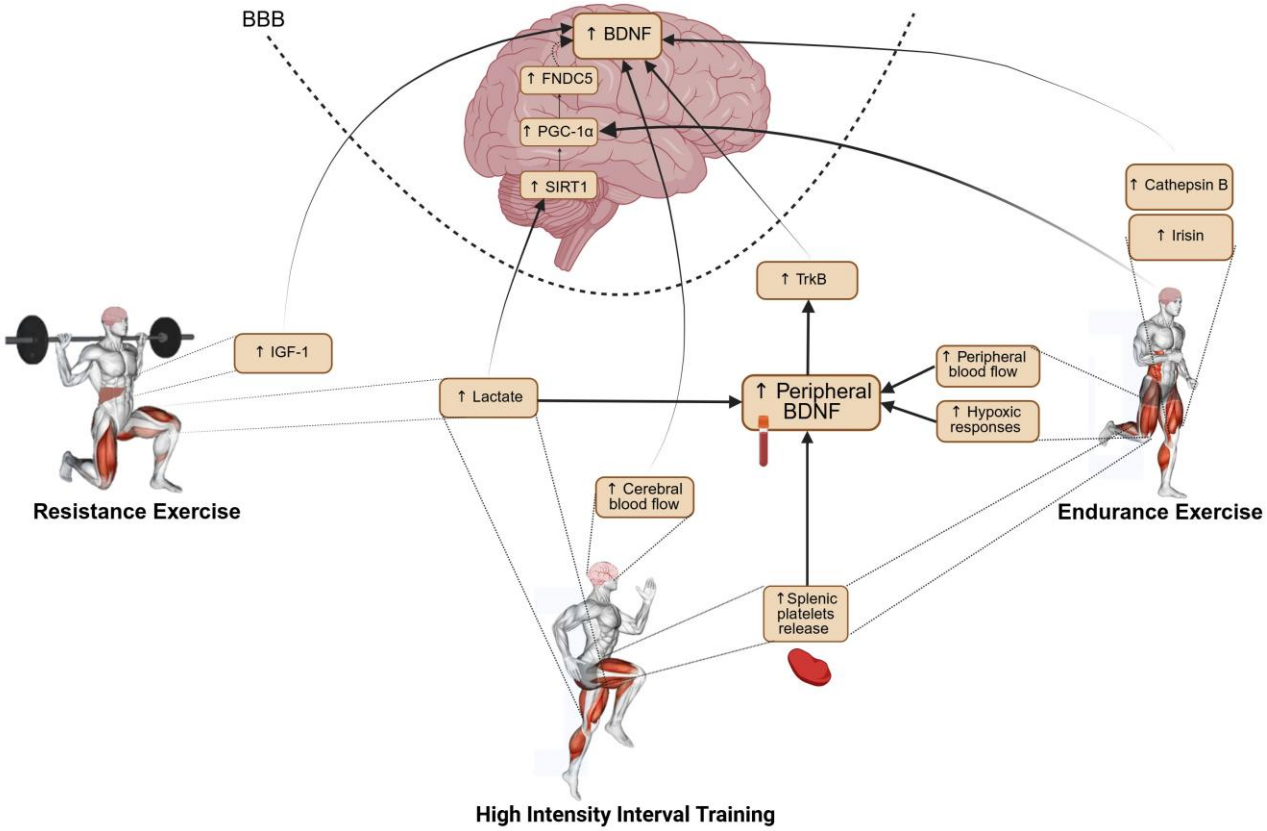

Figure 1. Exercise-Induced Mechanisms Driving Peripheral and Central BDNF Signaling. Different mechanisms are involved in three exercise modalities (endurance, high-intensity interval training, and resistance), leading to increased peripheral or cerebral BDNF levels. During resistance exercise, lactate production, depending on the intensity, triggers 1) the activation of the SIRT1–PGC-1α–FNDC5 pathway, which enhances brain BDNF levels, and 2) the activation of tropomyosin receptor kinase B (TrkB) by elevated peripheral BDNF levels, also stimulating brain BDNF production. Additionally, resistance exercise promotes the synthesis of insulin-like growth factor-1 (IGF-1) from the liver, which crosses the blood-brain barrier (BBB) and enhances brain BDNF levels. In response to high-intensity interval training, splenic platelet release increases, enhancing both platelet number and BDNF content and release, thereby activating TrkB and, consequently, increasing brain BDNF production. Additionally, the same lactate pathway previously described becomes active. Finally, improved cerebral blood flow directly raises brain BDNF levels. Regarding endurance exercise, increased splenic platelet release, hypoxic response, and peripheral blood flow lead to higher peripheral BDNF levels, which activate TrkB and, consequently, brain BDNF production. Additionally, endurance exercise stimulates muscle production of irisin and cathepsin B, which, when crossing the BBB, increase brain BDNF levels. Created with BioRender.com

Nevertheless, the beneficial impact of endurance exercise is well documented in neurodegenerative and neuropsychiatric conditions [96], as well as among older people [97], who are particularly vulnerable to cognitive decline. Consequently, endurance exercise interventions may not only enhance cognitive performance but also serve as a preventative role against neurodegenerative diseases, particularly in middle-aged adults, where

cognitive decline is believed to commence. Despite the growing body of literature, studies directly examining the effects of BDNF-mediated endurance interventions on cognitive performance remain limited. Nonetheless, several examples demonstrate the impact of aerobic exercise on brain function in middle-aged and older adult populations. Regarding chronic protocols, Erickson and colleagues conducted a trial involving moderate-intensity treadmill walking (three days/week) in adults aged 55 to 80 years [76]. At the end of the one-year intervention, participants in the endurance exercise group exhibited a 2% increase in hippocampal volume, which positively correlated with improvements in spatial memory.

Furthermore, although lower levels of serum BDNF were significantly associated with smaller hippocampal volumes and poorer memory, regardless of participant age, no significant changes in serum BDNF levels were observed. Moreover, Leckie et al. [98] examined the effects of aerobic training on executive function and serum BDNF levels in 90 older adults (mean age, 67 ± 6 years; 59 women and 33 men). Participants were randomly assigned to either a no-exercise control or a one-year intervention involving walking three days per week for 40 minutes at 60-75% of their maximum heart rate reserve (HRmax). Notably, individuals over 65 years in the walking group exhibited an approximate 25% increase in serum BDNF, which was significantly correlated with improvements in executive function and task-switching performance. Moreover, the mediating effect of BDNF on task-switching performance was significant only among participants older than 71 years, suggesting that moderate-intensity activities such as walking may yield greater cognitive benefits for adults over 70. Similarly, Nilsson et al. [47] reported that in healthy older adults (65–75 years), a 12-week intervention consisting of a 30-minute session per week at 65–75% of individual HRmax led to increased plasma BDNF levels, as well as improved performance on the n-back and running span task. In contrast, Xi Li and colleagues [99] found that in 29 physically inactive older adults (mean age, 64.8 ± 3.9 years), a 12-week vigorous-intensity continuous training protocol (25 minutes at 70% of VO_2 max, three times per week) increased serum BDNF levels but did not yield measurable improvements in cognitive performance.

It is noteworthy that global cognition was assessed using the Montreal Cognitive Assessment (MoCA) in this study, which may have limited sensitivity in detecting exercise-induced cognitive changes in a cognitively normal population. Regarding acute effects, Wheeler et al. [100] observed that a single bout of moderate-intensity treadmill walking (65–75% HRmax) enhanced serum BDNF levels and improved working memory or executive function in older adults. Encouraging results were also reported by Hakansson et al. [101], who recruited 19 healthy older adults (65-85 years of age). Each participant completed a single session comprising three different interventions: 35 minutes of moderate-intensity whole-body aerobic exercise, 35 minutes of cognitive training, and 35 minutes of mindfulness practice.

Blood samples were collected for BDNF analysis immediately before, immediately after, and at 20 min and 60 min post-intervention. Results showed that aerobic exercise induced a rapid and significant rise in circulating BDNF levels (+17%; $p = 0.004$), whereas cognitive training and mindfulness did not produce significant changes. Interestingly, the increase in BDNF following exercise was strongly correlated with working memory performance ($r = 0.89$; $p = 0.02$). In contrast, Tsai et al. [102] demonstrated that while a 30-minute bout of moderate-intensity aerobic exercise (65–75% HRmax) increased serum BDNF levels in sixty-six older adults with mild cognitive impairment, no corresponding improvements were observed in performance on the Flanker test. However, the cognitive health status of the participants could have affected their performance. In summary, aerobic exercise appears to stimulate BDNF production through multiple physiological and molecular pathways, with both chronic and acute exercise interventions exhibiting potential benefits for cognitive function, particularly in memory and executive function. Nevertheless, variations in exercise modality, intensity, and duration, as well as the sensitivity of cognitive assessments or the health status of the subjects, may influence the correlation between increased BDNF levels and observed outcomes.

HIIT and its influence on cognition and BDNF

HIIT has been widely recognised as an efficient method to enhance BDNF levels and cognitive performance across different populations. Elevated serum concentrations of BDNF have been observed following HIIT, which has been attributed to increased BDNF synthesis in the brain [103]. One proposed mechanism is the improvement of cerebral blood flow, as neuronal BDNF production and release are dependent on physical activity [104] (Fig. 1). Additionally, circulating BDNF can also activate TrkB, stimulating the vascular endothelium to produce additional BDNF [105].

Moreover, HIIT promotes platelet activation, which increases both platelet count and the BDNF content per platelet, contributing to the pool of bioavailable BDNF [106, 107] (Fig. 1). Exercise intensity has been linked to the lactate pathway, a key factor in brain metabolism [108]. For example, in both animal and human studies, acute HIIT enhances brain lactate concentration, initiating a cascade that stimulates BDNF expression via activation of the SIRT1 and PGC1α signalling pathways [109, 110]

(Fig. 1). Furthermore, exercise-induced hypoxia and muscle microdamage may elicit a rapid rise in circulating BDNF [111]. Finally, the hyperthermia resulting from vigorous exercise can increase BBB permeability, potentially facilitating the transport of neuronally produced BDNF into the periphery [107] (Fig. 1). Regarding the intervention, Buzdagli and colleagues [112] reported a more pronounced increase in BDNF following HIIT (85-100% of VO_2 max) compared with moderate-intensity continuous exercise (MICE, 65% of VO_2 max). This finding may be attributed to differences in lactate metabolism. In young athletes, serum BDNF levels were found to be significantly higher in the HIIT group (5.65 ± 1.79 ng/mL) than in both the control group (1.24 ± 0.54 ng/mL) and the MICE group (3.38 ± 1.29 ng/mL) when measured immediately after exercise.

Furthermore, both HIIT and MICE improved cognitive performance, as demonstrated by Stroop test outcomes, although HIIT was superior in terms of reaction time and error rates on incongruent tasks. Despite consistent reports of HIIT-induced increases in BDNF levels [113, 114], research incorporating HIIT interventions, BDNF measurements, and cognitive performance assessments in healthy middle-aged to older adults is scarce and inconclusive. For example, Xi Li and colleagues [99] found that a 12-week HIIT protocol (consisting of 25 minutes per session with alternating 3-minute bouts at 90% intensity and 3-minute recovery periods, performed three times per week) increased serum BDNF levels in 29 physically inactive older adults (mean age 64.8 ± 3.9 years), yet this did not result in measurable improvements in cognitive performance as assessed by the MoCA. Similarly, de Lima et al. [115] compared HIIT (85–100% intensity) with moderate-intensity continuous training (MICT, 60–75% intensity) in middle-aged, overweight adults and observed that an 8-week exercise program produced positive cognitive effects regardless of the exercise intensity.

Although BDNF levels increased, Spearman correlation analysis did not reveal significant associations between BDNF changes and cognitive improvements. Additionally, Tsai et al. [116] compared a 30-minute acute HIIT protocol (1 minute at 70–75% heart rate reserve with 2 minutes of active recovery) with a MICE (50–55% HRR) intervention in 21 healthy late middle-aged and older adults (mean age 60.62 ± 4.96 years). Although HIIT increased BDNF levels, the pre- to post-intervention changes in BDNF were not correlated with changes in neurocognitive performance. Despite the beneficial effect of HIIT in increasing BDNF levels among this category of subjects, the effects on improving cognitive performance remain controversial. However, supporting HIIT intervention, a longitudinal study [117] compared the effect of three different 6-month exercise regimens on hippocampal-dependent cognition in healthy elderly individuals. Participants aged 65-85 with no cognitive deficits were randomly assigned to one of three exercise interventions (low-intensity training (LIT), medium-intensity training (MIT), and HIIT). Each participant attended 72 supervised exercise sessions over a 6-month period, with a total of 151 participants completing all sessions. Cognitive testing for hippocampal performance was conducted monthly, along with blood collection, and continued for up to five years following the initiation of the study. After six months, only the HIIT group displayed significant improvement in hippocampal function, as measured by paired associative learning (PAL). HIIT-mediated changes in the BDNF correlated with improved hippocampal-dependent cognitive ability.

These findings suggest that HIIT significantly improves and prolongs the hippocampal-dependent cognitive health of aged individuals. However, further studies are needed to investigate whether acute and chronic HIIT interventions are effective in enhancing both BDNF and cognitive performance. Additionally, it is worth noting that it is still unclear whether the potential benefit can be attributed to the intensity of the exercise or the intermittent nature of the HIIT protocol.

Resistance exercise and its influence on cognition and BDNF

The mechanisms underlying improvement in BDNF following a resistance intervention are not fully understood. One proposed mechanism involves lactate, which plays a crucial role in long-term memory formation by acting as an alternative energy source for the brain, particularly when glucose availability is prioritized for active muscles during exercise [118] (Fig. 1). Insulin-like growth factor-1 (IGF-1) is another critical factor that interacts with BDNF to support neuroplasticity, with significant consequences for learning and memory. While IGF-1 is primarily synthesized in the liver, animal studies suggest that it can cross the BBB and influence CNS processes [119, 120] (Fig. 1). These findings suggest that IGF-1 may be essential for BDNF mRNA expression in the hippocampus, and its deficiency could impair cognitive processes such as working memory and recall.

Recent meta-analyses of studies involving supervised exercise programs of at least four weeks' duration have shown improvements in cognitive domains, including executive function, memory, and working memory[86, 87]. In young to middle-aged adults, benefits on executive function have also been observed even after a single or acute bout of resistance exercise [121, 122]. Moreover, resistance training can increase peripheral levels of BDNF. Yarrow et al. [123] found that five weeks of

traditional and eccentric-enhanced progressive resistance training intervention resulted in increased serum BDNF response. Additionally, Marston et al. [124] investigated the effects of two resistance training protocols: a "strength" protocol (5 × 5 repetitions at 5RM with 3 minutes of rest between sets) and a "hypertrophy" protocol (3 × 10 repetitions at 10RM with 1 minute of rest between sets). Although both protocols were matched for work and volume, only the hypertrophy condition elicited a significant immediate increase in serum BDNF levels (13 %). This protocol also produced higher blood lactate concentrations compared with the strength protocol, indicating a greater metabolic demand and a more pronounced cardiovascular and sympathetic nervous system response. However, research on the relationship between BDNF release through resistance training and cognitive performance remains limited. Castaño et al. [125] examined the effects of traditional resistance training (TRT) and resistance training combined with cognitive tasks (RT + CT) in 30 community-dwelling older adults, who were randomly assigned to either TRT (mean age 70.0 ± 8.1 years; 25% men) or RT + CT (mean age 66.3 ± 4.6 years; 31% men). Both groups underwent a similar resistance training regimen twice a week for 16 weeks, with the RT+CT group simultaneously engaging in verbal fluency tasks during resistance exercises. The intervention consisted of eight resistance exercises, performed in two to three sets of eight to fifteen repetitions at 60%-70% of one-repetition maximum (1RM).

Cognitive assessments measured verbal fluency, dual-task performance, short-term memory, executive function, visual attention, and task switching. Findings revealed that RT+CT, but not TRT alone, led to significant improvements in cognition, semantic and phonological verbal fluency, and plasma BDNF levels. However, the study acknowledged two key limitations: (1) the lack of a control group may have led to an overestimation or underestimation of treatment effects, and (2) physiological mechanisms underlying the correlation between BDNF levels and cognitive improvement remain unclear. On the other hand, Fragala et al. [126] found that six weeks of resistance training, performed twice a week, were likely beneficial for improving spatial awareness and visual and physical reaction times, which showed improvements of 40.0%, 14.6%, and 14.0%, respectively. However, circulating BDNF did not show significant changes with resistance exercise training. The absence of significant changes in resting circulating BDNF may be attributable to the timing of measurement, as BDNF was assessed in fasting and resting conditions before and after the six-week intervention.

Recent evidence suggests that circulating changes may be more transient, lasting only 20 minutes post-exercise, and are dependent on exercise intensity [127]. As highlighted by previous studies, research on the interplay between resistance exercise, BDNF release, and cognitive function remains inconclusive, particularly in middle-aged to older populations. Further research is needed to elucidate the precise physiological and molecular mechanisms by which resistance training influences BDNF levels and cognitive outcomes.

Ketogenic diet and Intermittent fasting and their influence on BDNF and cognition

Diet interventions have traditionally been viewed as a source of energy and a building material for the body. Nowadays, its role in maintaining brain health and functionality is starting to be recognized [128]. Particularly, the ketogenic diet and intermittent fasting have been proposed as potential strategies to enhance BDNF levels and cognitive function. The ketogenic diet (KD) is a dietary strategy characterized by high fat intake, adequate protein consumption, and a marked restriction of carbohydrates, which is insufficient to meet typical metabolic demands [129]. Under conditions of prolonged fasting or severe carbohydrate restriction (typically 20/30 g d-1 or 5% of total daily energy intake), hepatic glycogen stores become depleted. As a result, glucose availability declines to levels that are inadequate to sustain normal fat oxidation through the Krebs cycle or to meet the energetic requirements of the brain and CNS [130].

Regarding the CNS, because free fatty acids are unable to cross the BBB, they cannot be used as an energy source; therefore, glucose remains the primary energy substrate for the brain. During KD, lipolysis is stimulated massively, leading to the release of free fatty acids from adipose tissue into the circulation. These fatty acids are transported to the liver, where they are converted into the ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (β-HB), with acetone produced as a volatile byproduct. The subsequent metabolic state, known as ketosis, is a well-established physiological condition. In this condition, energy for the CNS is supplied by the ketone bodies (KBs), which are generated via a process called ketogenesis from acetyl-CoA and occur mainly in the liver mitochondrial matrix. KD has been proposed as a possible therapy for neurological disorders such as epilepsy, Alzheimer's disease, and Parkinson's disease. This is because KBs have been shown to exert neuroprotective effects by enhancing ATP production, reducing reactive oxygen species generation, and promoting mitochondrial biogenesis, processes that may support synaptic function and neuronal resilience. In addition, KD-induced increases in polyunsaturated fatty

acid synthesis may contribute to the modulation of neuronal membrane excitability [131]. The ketosis state, in which the liver converts fats into ketones, is linked with BDNF upregulation in humans and animals [132]. Ketones are particularly of interest in cognition processes because they become the preferred fuel for the brain during fasting periods. Particularly, β-HB serves as a signaling molecule that upregulates BDNF expression in neurons, thereby improving synaptic plasticity [133–135].

A recent study showed that a ketogenic diet protocol was associated with a significant, yet transient, increase in serum BDNF from 78 pg/mL to 92 pg/mL after two weeks in a sample (n = 35, aged 30–45) [136]. However, levels returned to baseline levels after 12 weeks. Ketosis has been shown to increase BDNF production, which is implicated in the modulation of neuron proliferation, migration, neurite outgrowth, synaptic plasticity, and survival [137]. Furthermore, the authors also found a positive association between Δβ-HB and ΔBDNF after adjusting for energy intake. In addition, BDNF expression could be increased after an intraventricular infusion of β-HB [138]. Thus, the increased level of blood β-HB reached during a ketogenic diet may explain the increased BDNF in the KD group [139]. Indeed, in humans, KD has been shown to increase BDNF levels, likely via β-HB regulation [140], which is also associated with substantial improvements in cognitive function [136]. However, further studies will aim to investigate the correlation between cognitive performance and BDNF mediated by the KD. On the other hand, intermittent fasting (IF) is a form of restrictive eating in which individuals alternate between periods of voluntary fasting and feeding throughout the day. As with KD, IF can induce a state of ketosis, consequently triggering all the previously explained mechanisms. An IF cycle of 16 hours fasting and 8 hours feeding has been shown to increase hippocampal neurogenesis in mice, a relationship thought to be mediated by mechanisms involving Notch 1 signaling [141].

Moreover, several studies in animal models have demonstrated the effectiveness of intermittent fasting in increasing both BDNF levels and cognitive performance [142]. Regarding human studies, a systematic review [143] indicated that the effects of intermittent fasting on cognitive performance are controversial and depend on the type of fasting regimen (e.g., alternate-day fasting or time-restricted eating). Notably, none of the studies included in that review assessed changes in BDNF. Conversely, another systematic review [144] investigating the effects of time-restricted eating and intermittent fasting on cognitive function in older adults reported positive results across various studies, although no BDNF assessments were conducted. The available evidence suggests that intermittent fasting may have beneficial effects on both cognitive performance and BDNF levels. Consequently, further studies are necessary to investigate the correlation between cognitive performance and BDNF mediated by intermittent fasting.

Conclusion

Mounting evidence consistently indicates that BDNF supports neuroplasticity, synaptic function, and neuronal survival, thereby maintaining cognitive performance throughout life. Exercise modalities, such as endurance, HIIT, and resistance training, have demonstrated the ability to increase peripheral BDNF levels in serum and plasma, and to improve cognitive outcomes, often revealing a relationship between the increase in BDNF and cognitive performance. However, there are still inconsistencies regarding the strength and longevity of this relationship. The specifics of the exercise, including modality, intensity, duration, and rest periods, are crucial and must be defined and standardized. When assessing cognitive performance, it is important to consider the timing of the test, the total duration, the baseline cognitive level of the participants, and the characteristics of the assessment to ensure results are interpreted correctly. Likewise, dietary strategies such as ketogenic diets and intermittent fasting appear to increase BDNF availability, but evidence of resulting cognitive improvements remains limited.

Overall, variations in study design, populations (e.g., age-related and sex-related differences), intervention protocols, biospecimen types (serum vs. plasma), and timing of blood collection make it difficult to compare and interpret findings broadly. Translating molecular evidence of BDNF modulation into clinically meaningful outcomes remains a critical challenge in aging research. While exercise- and diet-based interventions consistently induce increases in peripheral BDNF levels, robust evidence directly linking these changes to long-term cognitive benefits, such as the prevention or slowing of age-related cognitive decline and dementia, is still limited. Nonetheless, longitudinal studies [76, 98, 117] suggest that sustained engagement in physical exercise may promote chronic upregulation of BDNF, accompanied by improvements in cognitive performance and a reduced risk of cognitive decline and dementia. However, future research should focus on standardized methods, long-term studies, and multi-faceted approaches that combine neuroimaging, molecular biomarkers, and neuropsychological tests to better understand how lifestyle interventions influence BDNF and cognition. For example, fMRI could be implemented as measures of brain volume, cortical thickness, hippocampal size, and white matter integrity, metrics that are fundamental indicators of neuroplasticity and are predictive of

cognitive decline across aging and neurodegenerative conditions [145].

Moreover, CSF analyses could represent one of the most direct approaches for assessing CNS–derived biomarkers. Unlike serum or plasma, CSF is in closer contact with the brain parenchyma and more accurately reflects molecular processes related to synaptic function, neuroplasticity, and neurodegeneration. For example, reduced CSF BDNF was associated with age-related cognitive decline, suggesting a potential mechanism that may contribute in part to cognitive decline in older individuals [146]. Ultimately, understanding the mechanisms by which exercise and diet modulate BDNF will guide targeted, non-drug strategies to maintain or improve cognitive health throughout life, especially in aging populations at risk for neurodegenerative and psychiatric disorders. However, the present focus on lifestyle-related interventions necessarily excludes pharmacological factors that also influence BDNF signaling and cognitive outcomes. This limitation of the current framework should be considered in future research, where integrated approaches combining behavioral, nutritional, and pharmacological perspectives may provide a more comprehensive understanding of BDNF modulation and its clinical relevance.

References

[1] Maisonpierre PC, Belluscio L, Friedman B, Alderson RF, Wiegand SJ, Furth ME, et al. (1990). NT-3, BDNF, and NGF in the developing rat nervous system: Parallel as well as reciprocal patterns of expression. Neuron, 5:501–509.

[2] Lewin GR, Barde YA (1996). Physiology of the neurotrophins. Annu Rev Neurosci, 19:289–317.

[3] Huang EJ, Reichardt LF (2001). Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci, 24:677–736.

[4] Bonni A, Brunet A, West AE, Datta SR, Takasu MA, Greenberg ME (1999). Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms. Science, 286:1358–1362.

[5] Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Grãos MM, et al. (2005). Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ, 12:1329–1343.

[6] Deogracias R, Yazdani M, Dekkers MPJ, Guy J, Ionescu MCS, Vogt KE, et al. (2012). Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. Proc Natl Acad Sci U S A, 109:14230–14235.

[7] Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, et al. (2009). Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat Med, 15:331–337.

[8] Bramham CR, Messaoudi E (2005). BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol, 76:99–125.

[9] Yoshii A, Constantine-Paton M (2010). Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. Dev Neurobiol, 70:304–322.

[10] Reichardt LF (2006). Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci, 361:1545–1564.

[11] Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, et al. (2006). Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci, 24:1850–1856.

[12] Smith PA (2014). BDNF: no gain without pain? Neuroscience, 283:107–123.

[13] Lu B, Nagappan G, Guan X, Nathan PJ, Wren P (2013). BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci, 14:401–416.

[14] Nicastri CM, McFeeley BM, Simon SS, Ledreux A, Håkansson K, Granholm A-C, et al. (2022). BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults. Alzheimers Dement (N Y), 8:e12337.

[15] Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. (2014). Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol, 10:634–642.

[16] Radecki DT, Brown LM, Martinez J, Teyler TJ (2005). BDNF protects against stress-induced impairments in spatial learning and memory and LTP. Hippocampus, 15:246–253.

[17] Bathina S, Das UN (2015). Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci, 11:1164–1178.

[18] Castrén E, Hen R (2013). Neuronal plasticity and antidepressant actions. Trends Neurosci, 36:259–267.

[19] Brigadski T, Leßmann V (2020). The physiology of regulated BDNF release. Cell Tissue Res, 382:15–45.

[20] Sleiman SF, Henry J, Al-Haddad R, El Hayek L, Abou Haidar E, Stringer T, et al. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. Elife, 5:e15092.

[21] Colucci-D'Amato L, Speranza L, Volpicelli F (2020). Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. Int J Mol Sci, 21:7777.

[22] Piepmeier A, Etnier J (2014). Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance. Journal of Sport and Health Science. doi: 10.1016/j.jshs.2014.11.001.

[23] Foltran RB, Diaz SL (2016). BDNF isoforms: a round trip ticket between neurogenesis and serotonin? J Neurochem, 138:204–221.
[24] Pang PT, Nagappan G, Guo W, Lu B (2016). Extracellular and intracellular cleavages of proBDNF required at two distinct stages of late-phase LTP. NPJ Sci Learn, 1:16003.
[25] Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG, et al. (2001). Biosynthesis and Post-translational Processing of the Precursor to Brain-derived Neurotrophic Factor*. Journal of Biological Chemistry, 276:12660–12666.
[26] Lee R, Kermani P, Teng KK, Hempstead BL (2001). Regulation of cell survival by secreted proneurotrophins. Science, 294:1945–1948.
[27] Barde Y-A (2025). The physiopathology of brain-derived neurotrophic factor. Physiological Reviews, 105:2073–2140.
[28] Mizui T, Ishikawa Y, Kumanogoh H, Kojima M (2016). Neurobiological actions by three distinct subtypes of brain-derived neurotrophic factor: Multi-ligand model of growth factor signaling. Pharmacol Res, 105:93–98.
[29] Woo NH, Teng HK, Siao C-J, Chiaruttini C, Pang PT, Milner TA, et al. (2005). Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci, 8:1069–1077.
[30] Gentry JJ, Barker PA, Carter BD (2004). The p75 neurotrophin receptor: multiple interactors and numerous functions. Prog Brain Res, 146:25–39.
[31] Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, et al. (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci, 25:5455–5463.
[32] Poo MM (2001). Neurotrophins as synaptic modulators. Nat Rev Neurosci, 2:24–32.
[33] Boyd JG, Gordon T (2001). The neurotrophin receptors, trkB and p75, differentially regulate motor axonal regeneration. J Neurobiol, 49:314–325.
[34] Wang Y, Liang J, Xu B, Yang J, Wu Z, Cheng L (2024). TrkB/BDNF signaling pathway and its small molecular agonists in CNS injury. Life Sciences, 336:122282.
[35] Volosin M, Song W, Almeida RD, Kaplan DR, Hempstead BL, Friedman WJ (2006). Interaction of survival and death signaling in basal forebrain neurons: roles of neurotrophins and proneurotrophins. J Neurosci, 26:7756–7766.
[36] Avwenagha O, Campbell G, Bird MM (2003). The outgrowth response of the axons of developing and regenerating rat retinal ganglion cells in vitro to neurotrophin treatment. J Neurocytol, 32:1055–1075.
[37] Kim H, Li Q, Hempstead BL, Madri JA (2004). Paracrine and autocrine functions of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in brain-derived endothelial cells. J Biol Chem, 279:33538–33546.
[38] Lessmann V, Gottmann K, Malcangio M (2003). Neurotrophin secretion: current facts and future prospects. Progress in Neurobiology, 69:341–374.
[39] McAllister AK (1999). Subplate neurons: a missing link among neurotrophins, activity, and ocular dominance plasticity? Proc Natl Acad Sci U S A, 96:13600–13602.
[40] Zagrebelsky M, Holz A, Dechant G, Barde Y-A, Bonhoeffer T, Korte M (2005). The p75 Neurotrophin Receptor Negatively Modulates Dendrite Complexity and Spine Density in Hippocampal Neurons. J Neurosci, 25:9989–9999.
[41] Binder DK, Scharfman HE (2004). Brain-derived neurotrophic factor. Growth Factors, 22:123–131.
[42] Edelmann E, Lessmann V, Brigadski T (2014). Pre- and postsynaptic twists in BDNF secretion and action in synaptic plasticity. Neuropharmacology, 76 Pt C:610–627.
[43] Radka SF, Holst PA, Fritsche M, Altar CA (1996). Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain Res, 709:122–301.
[44] Klein AB, Williamson R, Santini MA, Clemmensen C, Ettrup A, Rios M, et al. (2011). Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J Neuropsychopharmacol, 14:347–353.
[45] Chacón-Fernández P, Säuberli K, Colzani M, Moreau T, Ghevaert C, Barde Y-A (2016). Brain-derived Neurotrophic Factor in Megakaryocytes*♦. Journal of Biological Chemistry, 291:9872–9881.
[46] Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Exp Physiol, 94:1062–1069.
[47] Nilsson J, Ekblom Ö, Ekblom M, Lebedev A, Tarassova O, Moberg M, et al. (2020). Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. Sci Rep, 10:4395.
[48] Tarassova O, Ekblom MM, Moberg M, Lövdén M, Nilsson J (2020). Peripheral BDNF Response to Physical and Cognitive Exercise and Its Association With Cardiorespiratory Fitness in Healthy Older Adults. Front Physiol, 11:1080.
[49] Le Blanc J, Fleury S, Boukhatem I, Bélanger J-C, Welman M, Lordkipanidzé M (2020). Platelets Selectively Regulate the Release of BDNF, But Not That of Its Precursor Protein, proBDNF. Front Immunol, 11:575607.
[50] Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, et al. (2002). Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost, 87:728–734.
[51] Sartorius A, Hellweg R, Litzke J, Vogt M, Dormann C, Vollmayr B, et al. (2009). Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. Pharmacopsychiatry, 42:270–276.
[52] Want A, Morgan JE, Barde YA (2023). Brain-derived neurotrophic factor measurements in mouse serum and plasma using a sensitive and specific enzyme-linked immunosorbent assay. Sci Rep, 13:7740.

[53] Pardridge WM, Kang YS, Buciak JL (1994). Transport of human recombinant brain-derived neurotrophic factor (BDNF) through the rat blood-brain barrier in vivo using vector-mediated peptide drug delivery. Pharm Res, 11:738–746.

[54] Yamamoto H, Gurney ME (1990). Human platelets contain brain-derived neurotrophic factor. J Neurosci, 10:3469–3478.

[55] Radka SF, Holst PA, Fritsche M, Altar CA (1996). Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain Res, 709:122–301.

[56] Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. (2011). Harnessing neuroplasticity for clinical applications. Brain, 134:1591–1609.

[57] Morris RG (1999). D.O. Hebb: The Organization of Behavior, Wiley: New York; 1949. Brain Res Bull, 50:437.

[58] El-Sayes J, Harasym D, Turco CV, Locke MB, Nelson AJ (2019). Exercise-Induced Neuroplasticity: A Mechanistic Model and Prospects for Promoting Plasticity. Neuroscientist, 25:65–85.

[59] Park DC, Bischof GN (2011). Chapter 7 - Neuroplasticity, Aging, and Cognitive Function. In: Schaie KW, Willis SL, editors Handbook of the Psychology of Aging (Seventh Edition). San Diego: Academic Press, 109–119.

[60] Zenke F, Agnes EJ, Gerstner W (2015). Diverse synaptic plasticity mechanisms orchestrated to form and retrieve memories in spiking neural networks. Nat Commun, 6:6922.

[61] Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A, 104:5638–5643.

[62] Erickson CA, Barnes CA (2003). The neurobiology of memory changes in normal aging. Exp Gerontol, 38:61–69.

[63] Mattson MP, Maudsley S, Martin B (2004). BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci, 27:589–594.

[64] Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, et al. (2005). The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiology of Aging, 26:115–123.

[65] Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, et al. (2014). A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. Front Aging Neurosci, 6:69.

[66] Salthouse TA (2019). Trajectories of normal cognitive aging. Psychol Aging, 34:17–24.

[67] Ferreira D, Machado A, Molina Y, Nieto A, Correia R, Westman E, et al. (2017). Cognitive Variability during Middle-Age: Possible Association with Neurodegeneration and Cognitive Reserve. Front Aging Neurosci, 9:188.

[68] Ji L, Zhang H, Potter GG, Zang Y-F, Steffens DC, Guo H, et al. (2017). Multiple Neuroimaging Measures for Examining Exercise-induced Neuroplasticity in Older Adults: A Quasi-experimental Study. Front Aging Neurosci, 9:102.

[69] Stern Y (2009). Cognitive reserve. Neuropsychologia, 47:2015–2028.

[70] Schaeverbeke JM, Gabel S, Meersmans K, Luckett ES, De Meyer S, Adamczuk K, et al. (2021). Baseline cognition is the best predictor of 4-year cognitive change in cognitively intact older adults. Alzheimers Res Ther, 13:75.

[71] Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RC-M (2019). Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. Int J Mol Sci, 20:257.

[72] Khalil H, Alomari MA, Khabour OF, Al-Hieshan A, Bajwa JA (2016). Relationship of circulatory BDNF with cognitive deficits in people with Parkinson's disease. Journal of the Neurological Sciences, 362:217–220.

[73] AMERICAN COLLEGE OF SPORTS MEDICINE WRT ACSM's Guidelines for Exercise Testing and Prescription EIGHTH EDITION. 2019.

[74] Mielniczek M, Aune TK (2025). The Effect of High-Intensity Interval Training (HIIT) on Brain-Derived Neurotrophic Factor Levels (BNDF): A Systematic Review. Brain Sciences, 15:34.

[75] McArdle W, Katch F, Katch V Exercise Physiology: Nutrition, Energy, and Human Performance. 2010.

[76] Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. (2011). Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A, 108:3017–3022.

[77] Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. (1999). Ageing, fitness and neurocognitive function. Nature, 400:418–419.

[78] Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat HW, Shigeoka JW, et al. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiology of Aging, 5:35–42.

[79] Hassmén P, Koivula N (1997). Mood, physical working capacity and cognitive performance in the elderly as related to physical activity. Aging Clin Exp Res, 9:136–142.

[80] Williams P, Lord SR (1997). Effects of group exercise on cognitive functioning and mood in older women. Australian and New Zealand Journal of Public Health, 21:45–52.

[81] Hill RD, Storandt M, Malley M (1993). The Impact of Long-term Exercise Training on Psychological Function in Older Adults. Journal of Gerontology, 48:P12–P17.

[82] Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A, 101:3316–3321.

[83] Nanda B, Balde J, Manjunatha S (2013). The Acute Effects of a Single Bout of Moderate-intensity Aerobic Exercise on Cognitive Functions in Healthy Adult Males. J Clin Diagn Res, 7:1883–1885.

[84] Statton MA, Encarnacion M, Celnik P, Bastian AJ (2015). A Single Bout of Moderate Aerobic Exercise Improves Motor Skill Acquisition. PLoS One, 10:e0141393.

[85] Leahy AA, Mavilidi MF, Smith JJ, Hillman CH, Eather N, Barker D, et al. (2020). Review of High-Intensity Interval Training for Cognitive and Mental Health in Youth. Medicine & Science in Sports & Exercise, 52:2224–2234.

[86] Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br J Sports Med, 52:154–160.

[87] Falck RS, Davis JC, Best JR, Crockett RA, Liu-Ambrose T (2019). Impact of exercise training on physical and cognitive function among older adults: a systematic review and meta-analysis. Neurobiol Aging, 79:119–130.

[88] Alves CR, Gualano B, Takao PP, Avakian P, Fernandes RM, Morine D, et al. (2012). Effects of acute physical exercise on executive functions: a comparison between aerobic and strength exercise. J Sport Exerc Psychol, 34:539–549.

[89] Curtis R, Blades A, Moris JM, Koh Y (2024). Changes in brain-derived neurotropic factor following aerobic exercise. Sport Sci Health, 20:1153–1167.

[90] Monnier A, Prigent-Tessier A, Quirié A, Bertrand N, Savary S, Gondcaille C, et al. (2017). Brain-derived neurotrophic factor of the cerebral microvasculature: a forgotten and nitric oxide-dependent contributor of brain-derived neurotrophic factor in the brain. Acta Physiologica, 219:790–802.

[91] Brunelli A, Dimauro I, Sgrò P, Emerenziani GP, Magi F, Baldari C, et al. (2012). Acute exercise modulates BDNF and pro-BDNF protein content in immune cells. Medicine and Science in Sports and Exercise, 44:1871–1880.

[92] Helan M, Aravamudan B, Hartman WR, Thompson MA, Johnson BD, Pabelick CM, et al. (2014). BDNF secretion by human pulmonary artery endothelial cells in response to hypoxia. Journal of Molecular and Cellular Cardiology, 68:89–97.

[93] Kojima D, Nakamura T, Banno M, Umemoto Y, Kinoshita T, Ishida Y, et al. (2018). Head-out immersion in hot water increases serum BDNF in healthy males. International Journal of Hyperthermia, 34:834–839.

[94] Jinhong KE, Bo W (2022). Effects of aerobic exercise on memory and its neurobiological mechanism. Advances in Psychological Science, 30:115.

[95] Yang X, Li M-Y, Yan C-Y, Xiao Z-J, Jiang W-Q, Wang X-Y, et al. (2020). [Research progress on chemical composition and pharmacological effects of Periplocae Cortex and predictive analysis on Q-marker]. Zhongguo Zhong Yao Za Zhi, 45:2772–2783.

[96] Oyovwi MO, Ogenma UT, Onyenweny A (2025). Exploring the impact of exercise-induced BDNF on neuroplasticity in neurodegenerative and neuropsychiatric conditions. Mol Biol Rep, 52:140.

[97] Best JR, Chiu BK, Liang Hsu C, Nagamatsu LS, Liu-Ambrose T (2015). 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, 21:745–756.

[98] Leckie RL, Oberlin LE, Voss MW, Prakash RS, Szabo-Reed A, Chaddock-Heyman L, et al. (2014). BDNF mediates improvements in executive function following a 1-year exercise intervention. Front Hum Neurosci. doi: 10.3389/fnhum.2014.00985.

[99] Li X, Han T, Zou X, Zhang H, Feng W, Wang H, et al. (2021). Long-term high-intensity interval training increases serum neurotrophic factors in elderly overweight and obese Chinese adults. Eur J Appl Physiol, 121:2773–2785.

[100] Wheeler MJ, Green DJ, Ellis KA, Cerin E, Heinonen I, Naylor LH, et al. (2020). Distinct effects of acute exercise and breaks in sitting on working memory and executive function in older adults: a three-arm, randomised cross-over trial to evaluate the effects of exercise with and without breaks in sitting on cognition. Br J Sports Med, 54:776–781.

[101] Håkansson K, Ledreux A, Daffner K, Terjestam Y, Bergman P, Carlsson R, et al. (2017). BDNF Responses in Healthy Older Persons to 35 Minutes of Physical Exercise, Cognitive Training, and Mindfulness: Associations with Working Memory Function. Journal of Alzheimer's Disease, 55:645–657.

[102] Tsai C-L, Ukropec J, Ukropcová B, Pai M-C (2018). An acute bout of aerobic or strength exercise specifically modifies circulating exerkine levels and neurocognitive functions in elderly individuals with mild cognitive impairment. Neuroimage Clin, 17:272–284.

[103] Jiménez-Maldonado A, Rentería I, García-Suárez PC, Moncada-Jiménez J, Freire-Royes LF (2018). The Impact of High-Intensity Interval Training on Brain Derived Neurotrophic Factor in Brain: A Mini-Review. Front Neurosci. doi: 10.3389/fnins.2018.00839.

[104] Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. (2010). Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol, 298:R372-377.

[105] Meuchel LW, Thompson MA, Cassivi SD, Pabelick CM, Prakash YS (2011). Neurotrophins induce nitric oxide generation in human pulmonary artery endothelial cells. Cardiovascular Research, 91:668–676.

[106] Serra-Mill&agrave M, s (2016). Are the changes in the peripheral brain-derived neurotrophic factor levels due to platelet activation? World Journal of Psychiatry, 6:84–101.

[107] Walsh JJ, Tschakovsky ME (2018). Exercise and circulating BDNF: Mechanisms of release and implications for the design of exercise interventions. Appl Physiol Nutr Metab, 43:1095–1104.

[108] Müller P, Duderstadt Y, Lessmann V, Müller NG (2020). Lactate and BDNF: Key Mediators of Exercise Induced Neuroplasticity? Journal of Clinical Medicine, 9:1136.

[109] El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, et al. (2019). Lactate Mediates the Effects of Exercise on Learning and Memory through SIRT1-Dependent Activation of Hippocampal Brain-Derived Neurotrophic Factor (BDNF). J Neurosci, 39:2369–2382.

[110] Reycraft JT, Islam H, Townsend LK, Hayward GC, Hazell TJ, Macpherson REK (2020). Exercise Intensity and Recovery on Circulating Brain-derived Neurotrophic Factor. Med Sci Sports Exerc, 52:1210–1217.

[111] Jiménez-Maldonado A, Rentería I, García-Suárez PC, Moncada-Jiménez J, Freire-Royes LF (2018). The Impact of High-Intensity Interval Training on Brain Derived Neurotrophic Factor in Brain: A Mini-Review. Front Neurosci, 12:839.

[112] Buzdagli Y, Ozan M, Baygutalp N, Oget F, Karayigit R, Yuce N, et al. (2024). The effect of high-intensity intermittent and moderate-intensity continuous exercises on neurobiological markers and cognitive performance. BMC Sports Sci Med Rehabil, 16:39.

[113] Mielniczek M, Aune TK (2025). The Effect of High-Intensity Interval Training (HIIT) on Brain-Derived Neurotrophic Factor Levels (BNDF): A Systematic Review. Brain Sciences, 15:34.

[114] Rodríguez-Gutiérrez E, Torres-Costoso A, Saz-Lara A, Bizzozero-Peroni B, Guzmán-Pavón MJ, Sánchez-López M, et al. (2024). Effectiveness of high-intensity interval training on peripheral brain-derived neurotrophic factor in adults: A systematic review and network meta-analysis. Scandinavian Journal of Medicine & Science in Sports, 34:e14496.

[115] de Lima NS, De Sousa RAL, Amorim FT, Gripp F, Diniz E Magalhães CO, Henrique Pinto S, et al. (2022). Moderate-intensity continuous training and high-intensity interval training improve cognition, and BDNF levels of middle-aged overweight men. Metab Brain Dis, 37:463–471.

[116] Tsai C-L, Pan C-Y, Tseng Y-T, Chen F-C, Chang Y-C, Wang T-C (2021). Acute effects of high-intensity interval training and moderate-intensity continuous exercise on BDNF and irisin levels and neurocognitive performance in late middle-aged and older adults. Behav Brain Res, 413:113472.

[117] Blackmore DG, Schaumberg MA, Ziaei M, Belford S, To XV, O'Keeffe I, et al. (2024). Long-Term Improvement in Hippocampal-Dependent Learning Ability in Healthy, Aged Individuals Following High Intensity Interval Training. Aging Dis. doi: 10.14336/AD.2024.0642.

[118] Baumgartner NW, Belbis MD, Kargl C, Holmes MJ, Gavin TP, Hirai DM, et al. (2024). Acute Effects of High-Intensity Resistance Exercise on Recognition of Relational Memory, Lactate, and Serum and Plasma Brain-Derived Neurotrophic Factor. Journal of Strength & Conditioning Research. doi: 10.1519/JSC.0000000000004851.

[119] Cotman CW, Berchtold NC, Christie L-A (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci, 30:464–472.

[120] Cotman CW, Berchtold NC (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci, 25:295–301.

[121] Alves CR, Gualano B, Takao PP, Avakian P, Fernandes RM, Morine D, et al. (2012). Effects of acute physical exercise on executive functions: a comparison between aerobic and strength exercise. J Sport Exerc Psychol, 34:539–549.

[122] Dunsky A, Abu-Rukun M, Tsuk S, Dwolatzky T, Carasso R, Netz Y (2017). The effects of a resistance vs. an aerobic single session on attention and executive functioning in adults. PLoS One, 12:e0176092.

[123] Yarrow JF, White LJ, McCoy SC, Borst SE (2010). Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). Neurosci Lett, 479:161–165.

[124] Marston KJ, Newton MJ, Brown BM, Rainey-Smith SR, Bird S, Martins RN, et al. (2017). Intense resistance exercise increases peripheral brain-derived neurotrophic factor. Journal of Science and Medicine in Sport, 20:899–903.

[125] Castaño LAA, Castillo de Lima V, Barbieri JF, de Lucena EGP, Gáspari AF, Arai H, et al. (2022). Resistance Training Combined With Cognitive Training Increases Brain Derived Neurotrophic Factor and Improves Cognitive Function in Healthy Older Adults. Front Psychol, 13:870561.

[126] Fragala MS, Beyer KS, Jajtner AR, Townsend JR, Pruna GJ, Boone CH, et al. (2014). Resistance Exercise May Improve Spatial Awareness and Visual Reaction in Older Adults. Journal of Strength and Conditioning Research, 28:2079–2087.

[127] Walsh EI, Smith L, Northey J, Rattray B, Cherbuin N (2020). Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage. Ageing Research Reviews, 60:101044.

[128] Gómez-Pinilla F (2008). Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci, 9:568–578.

[129] Paoli A, Bianco A, Grimaldi KA (2015). The Ketogenic Diet and Sport: A Possible Marriage? Exerc Sport Sci Rev, 43:153–162.

[130] Paoli A, Tinsley G, Bianco A, Moro T (2019). The Influence of Meal Frequency and Timing on Health in Humans: The Role of Fasting. Nutrients, 11:719.

[131] Paoli A, Rubini A, Volek JS, Grimaldi KA (2013). Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr, 67:789–796.

[132] Maalouf M, Rho JM, Mattson MP (2009). The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res Rev, 59:293–315.

[133] Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A (2018). Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci, 19:63–80.

[134] Hood DA, Tryon LD, Carter HN, Kim Y, Chen CCW (2016). Unravelling the mechanisms regulating muscle mitochondrial biogenesis. Biochem J, 473:2295–2314.
[135] Hu E, Du H, Zhu X, Wang L, Shang S, Wu X, et al. (2018). Beta-hydroxybutyrate Promotes the Expression of BDNF in Hippocampal Neurons under Adequate Glucose Supply. Neuroscience, 386:315–325.
[136] Mohorko N, Černelič-Bizjak M, Poklar-Vatovec T, Grom G, Kenig S, Petelin A, et al. (2019). Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. Nutr Res, 62:64–77.
[137] Koppel SJ, Swerdlow RH (2018). Neuroketotherapeutics: A modern review of a century-old therapy. Neurochem Int, 117:114–125.
[138] El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, et al. (2019). Lactate Mediates the Effects of Exercise on Learning and Memory through SIRT1-Dependent Activation of Hippocampal Brain-Derived Neurotrophic Factor (BDNF). J Neurosci, 39:2369–2382.
[139] Paoli A, Cenci L, Pompei P, Sahin N, Bianco A, Neri M, et al. (2021). Effects of Two Months of Very Low Carbohydrate Ketogenic Diet on Body Composition, Muscle Strength, Muscle Area, and Blood Parameters in Competitive Natural Body Builders. Nutrients, 13:374.
[140] Marosi K, Kim SW, Moehl K, Scheibye-Knudsen M, Cheng A, Cutler R, et al. (2016). 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. J Neurochem, 139:769–781.
[141] Baik S-H, Rajeev V, Fann DY-W, Jo D-G, Arumugam TV (2020). Intermittent fasting increases adult hippocampal neurogenesis. Brain Behav, 10:e01444.
[142] Seidler K, Barrow M (2022). Intermittent fasting and cognitive performance - Targeting BDNF as potential strategy to optimise brain health. Front Neuroendocrinol, 65:100971.
[143] Alkurd R, Mahrous L, Zeb F, Khan MA, Alhaj H, Khraiwesh HM, et al. (2024). Effect of Calorie Restriction and Intermittent Fasting Regimens on Brain-Derived Neurotrophic Factor Levels and Cognitive Function in Humans: A Systematic Review. Medicina, 60:191.
[144] Sharifi S, Rostami F, Babaei Khorzoughi K, Rahmati M (2024). Effect of time-restricted eating and intermittent fasting on cognitive function and mental health in older adults: A systematic review. Prev Med Rep, 42:102757.
[145] Chen G, McKay NS, Gordon BA, Joseph-Mathurin N, Liu J, Schindler SE, et al. (2025). Baseline and longitudinal changes in cortical thickness and hippocampal volume predict cognitive decline. J Alzheimers Dis, 106:1452–1462.
[146] Li G, Peskind ER, Millard SP, Chi P, Sokal I, Yu C-E, et al. (2009). Cerebrospinal Fluid Concentration of Brain-Derived Neurotrophic Factor and Cognitive Function in Non-Demented Subjects. PLoS One, 4:e5424.