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Evaluating exercise-induced changes in BDNF and cognitive development in children and adolescents: A multi-pathway operationalized framework

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Abstract
Brain-Derived Neurotrophic Factor (BDNF) supports synaptic plasticity, neurogenesis, and cognitive function, with higher levels often linked to improved memory and neural health. Exercise has gained attention as a practical approach to modulating BDNF and enhancing cognitive health in children and adolescents. However, this relationship is complex, non-linear, and often not explained by a single causal pathway. This review proposes that BDNF is sufficient but not necessary for cognitive improvements, since multiple parallel biological mechanisms can independently support learning and memory. Improvements in cognitive processes from exercise are not always proportional to changes in circulating BDNF; instead, other BDNF-independent mechanisms, such as lactate signaling, cerebral blood flow, neurotransmitter modulation, endocannabinoid activity, and anti-inflammatory effects, may also contribute to modulate cognitive function. These variables raise important questions about the consistency of exercise-induced BDNF changes and their translation into meaningful cognitive improvements, particularly in areas like memory and executive function. This framework helps explain inconsistencies in the literature and highlights the need for a more integrative mechanistic understanding of how exercise influences cognition. This review develops a multi-pathway operationalized model linking exercise to cognition, incorporating measurable biomarkers and generating falsifiable predictions across acute and chronic exercise conditions. Evidence on the effects of exercise on BDNF and cognition in children and adolescents is synthesized to evaluate whether exercise-induced BDNF changes translate into meaningful cognitive improvements, while identifying key research gaps and directions for future research within a multi-pathway framework.These findings also support a future framework in which exercise prescriptions may be mechanistically tailored to selectively recruit pathways such as BDNF signaling for targeted modulation of specific cognitive domains and temporal cognitive objectives.

Keywords
Brain-Derived Neurotrophic Factor (BDNF), Exercise, Neuroplasticity, Executive function, Adolescence, Cognitive development, Hippocampal plasticity, Multi-pathway neurobiology, Exercise-mediated cognition, Cognitive-selective exercise prescription

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1. Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a key neurotrophin involved in neurogenesis, synaptic plasticity, and cognitive function. Its role in learning and memory has been well established, with increased BDNF expression consistently linked to enhanced memory retention and neural health. Understanding this relationship between BDNF levels and cognitive development is particularly important in children and adolescents. During brain development, BDNF supports the survival of peripheral sensory neurons and influences dendritic branching (1, 2), which are both crucial for effective neuronal communication (Figure 1). BDNF also plays a central role in modulating synaptic plasticity, a fundamental process underlying learning and memory. BDNF exerts these effects by binding to the tyrosine kinase B (TrkB) receptor on neurons, triggering intracellular signaling cascades that strengthen synaptic connections.

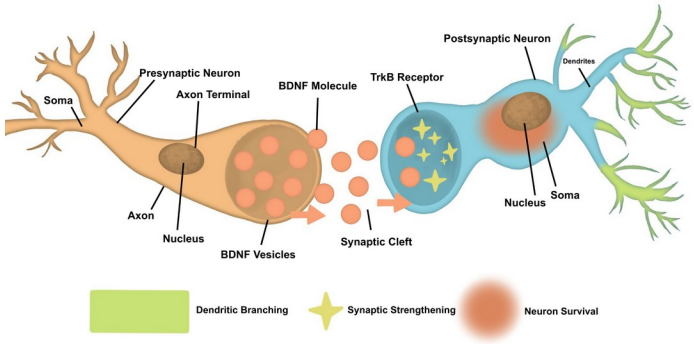

Figure 1. BDNF signaling at the synapse. The presynaptic neuron releases BDNF-containing vesicles into the synaptic cleft, where BDNF binds TrkB receptors on the postsynaptic neuron. This triggers signaling pathways that strengthen synaptic connections, promote dendritic spine growth, and enhance neuronal survival.

Physical activity has long been recognized as a powerful modulator of bodily health, yet its effects on cognition remain incompletely understood in youth. By influencing cognitive function and neural plasticity, regular exercise promotes improvements in learning, memory, and executive function by supporting neuronal growth and synaptic connectivity (3). Among the molecular mediators of these effects, BDNF plays a crucial role, linking physical activity to improved neural function and adaptability. Importantly, BDNF is commonly measured in serum or plasma; however, these measures yield inconsistent results due to platelet activation during clotting and are not directly comparable across studies (2). There are many factors that affect the relationship among exercise, BDNF, and cognition. These include exercise type (aerobic, resistance, and high-intensity interval training), intensity, duration, frequency, age, sex, fitness level, and genetic variation. Notably, acute increases in BDNF serum levels do not always correlate to measurable cognitive outcomes (4). This inconsistency suggests that

the relationship between exercise, BDNF, and cognition may not follow a single linear pathway. Instead, BDNF increases caused by exercise may be sufficient to support cognitive improvements, but may not be necessary, since cognitive benefits can arise through multiple parallel neurobiological mechanisms. In addition to BDNF-mediated plasticity, exercise influences cognition through multiple other pathways: metabolic, vascular, neurochemical, and inflammatory mechanisms. Some studies suggest that BDNF may instead promote structural changes in the brain, contributing to overall health benefits (5). These findings indicate that while exercise is a promising tool for improving cognition in youth, the consistency of BDNF-related cognitive gains and the mechanisms underlying them remain unclear.

Studies of exercise effects on BDNF and cognition show both consistent patterns and substantial variability across populations. For instance, age significantly influences the BDNF response to exercise. While some studies in adults report significant or sustained changes in BDNF levels, research in children more consistently reports cognitive improvements following physical activity (6). Genetic variation also modulates this relationship (7). Specifically, individuals carrying the Met66 variant of the BDNF gene, which is associated with reduced activity-dependent BDNF secretion, often experience greater cognitive benefits from exercise than those with the more common Val66 allele (6). These findings suggest that individuals with lower activity-dependent BDNF may be more responsive to exercise-induced benefits (6). Interestingly, cognitive improvements can occur even when BDNF levels do not increase, potentially because BDNF influences not only memory and cognitive processes but also structural brain changes. For example, elevated BDNF levels are associated with increased hippocampal volume, and aerobic exercise has been shown to enlarge this region (8, 9). However, increases in hippocampal volume are not necessarily accompanied by proportional improvements in spatial memory (9), suggesting that BDNF may play a more protective or structural role rather than directly enhancing memory performance.

Although numerous studies have examined the relationship between exercise, BDNF, and cognitive function, much of the existing research focuses mainly on specific populations or conditions, such as healthy adults, individuals with depression, or patients with neurodegenerative diseases (2, 3, 10). Compared to studies in adult populations, few studies have examined the relationship between physical activity and BDNF in children and adolescents. Furthermore, there are inconsistencies in exercise protocols, including differences in exercise type, intensity, duration, and frequency of intervention, which lead to inconsistent findings. Consequently, it remains unclear whether these results generalize across varying age groups, sexes, and genetic backgrounds, limiting our understanding of BDNF’s role in cognitive development.

To address these gaps, this review not only examines BDNF's role in cognitive processes and how different types and intensities of exercise influence its levels, but also proposes a framework where BDNF is sufficient but not necessary for exercise-induced cognitive improvements. By synthesizing evidence across molecular, physiological, and behavioral pathways, this review aims to explain the

inconsistencies in the literature and provide a testable, multi-pathway model of how exercise enhances cognition in children and adolescents.

2. Implicit assumptions in current exercise-BDNF-cognition research

Despite decades of research on exercise, BDNF, and cognition, several implicit assumptions appear to persist across literature and continue to shape how findings are interpreted. Although often unstated, these assumptions influence study design, data interpretation, and conclusions, potentially contributing to discrepancies across the literature. Consequently, addressing these assumptions is essential for developing more accurate models of exercise-induced cognitive enhancement.

One common assumption is that increases in BDNF directly mediate improvements in learning and memory. However, findings from emerging studies demonstrate that this relationship is inconsistent; cognitive improvements can occur without measurable changes in circulating BDNF, and increases in BDNF levels do not always translate into measurable cognitive gains (5, 7). This suggests that BDNF may function as more of a permissive or modulatory factor supporting neuroplasticity, rather than a singular causal driver of cognitive performance.

Another common assumption is that peripheral BDNF accurately reflects the central nervous system activity. In reality, circulating BDNF reflects contributions from multiple peripheral tissues, including vascular tissue and other non-neuronal sources, since BDNF is widely expressed outside the central nervous system (1). Furthermore, skeletal muscle may influence BDNF-related signaling within the neuromuscular system in an activity-dependent manner (11). Consequently, peripheral BDNF may not reliably represent brain-level neurotrophic activity.

Furthermore, although it is often assumed that increases in exercise lead to proportional increases in BDNF and subsequent cognitive improvements linearly, this presumption may be overly simplistic. Instead, a non-linear, context-dependent relationship characterized by variability across individuals, developmental stages, and individual differences is more plausible and likely contributes to this complexity (3).

Finally, the focus on BDNF as the primary mechanism linking exercise to cognition may overlook other important biological pathways. Findings from new studies emphasize the role of lactate signaling, neurotransmitter modulation, cerebral blood flow, endocannabinoid activity, and inflammatory regulation in cognitive function (3, 5, 7).

Revising these assumptions supports a shift toward a multi-pathway, systems-level model of exercise-induced cognitive enhancement. Instead of relying on a single biomarker explanation, future research should integrate multiple physiological and neurobiological measures and consider interaction effects across systems.

3. Biological role of BDNF in learning and adolescent neurodevelopment

BDNF plays a central role in supporting neurogenesis, synaptic plasticity, and cognitive function by promoting neuronal growth, strengthening synaptic connections, and facilitating communication between neurons. This role is especially pronounced during

childhood and adolescence, periods of rapid brain development when BDNF most significantly influences neuronal growth, mood, and neural plasticity most significantly. By supporting dendritic branching, synapse formation, and long-term potentiation, BDNF optimizes neural communication, ultimately facilitating the acquisition and retention of new information. Understanding this biological role provides essential context for exploring how exercise-induced changes in BDNF may influence learning outcomes in children and adolescents.

3.1 BDNF as a central regulator of synaptic plasticity and cognitive function

Synaptic plasticity, the ability of synapses to strengthen or weaken over time, is significantly influenced by the presence of neurotrophins. In the hippocampus, BDNF strengthens synaptic connections critical for memory formation, spatial navigation, and emotional processing (11). BDNF is a key regulator of long-term potentiation (LTP), a cellular mechanism underlying learning and memory, by enhancing synaptic transmission and supporting activity-dependent synaptic strengthening (12). BDNF also promotes dendritic spine formation and maturation, increasing both the number and stability of synaptic connections (12). This increase in synaptic connections further assists the communication between neurons and memory consolidation. Together, these processes mediated by BDNF support efficient neuronal communication and are critical for learning, memory consolidation, and cognitive development.

BDNF functions by binding to the TrkB receptor; this receptor activates intracellular signaling cascades, such as the cAMP Response Element Binding (CREB) and CREB-binding protein (CBP), to promote protein synthesis essential for gene transcription, synaptic maintenance, plasticity, and neuronal survival and function. These pathways linked to BDNF also influence other cognitive processes. BDNF's role in learning and memory has been well documented, with increased BDNF expression consistently linked to enhanced memory retention and neural health (13, 14). While primarily expressed in the brain, BDNF is also present in the gut and other tissues.

Beyond the nervous system, BDNF contributes to cardiovascular health and angiogenesis (the formation of new blood vessels). It supports the survival of endothelial and cardiac cells through TrkB-mediated activation of the extracellular signal-regulated kinase / mitogen-activated protein kinase (ERK/MAPK) and phosphatidyl inositol-3 kinase /protein kinase B (PI3K/AKT) pathways. The latter also stimulates nitric oxide production, promoting vasodilation and cardiovascular protection. In contrast, BDNF binding to the low-affinity neurotrophin receptor P75 (p75^NTR) receptor can induce apoptosis and inhibit angiogenesis. Animal studies have demonstrated that both BDNF and neurotrophin-3 (NT-3) are vital for proper cardiovascular development (1, 15).

At the molecular level, BDNF is part of the neurotrophin family, which includes nerve growth factor (NGF), neurotrophins (NT-3, NT-4/5, and NT-6), sharing approximately 50% amino acid similarity with these proteins. BDNF is synthesized as a precursor protein (pro-BDNF) and enzymatically cleaved into its mature, active form for activity-dependent release. In humans, BDNF mRNA expression is tissue-specific, with predominant expression in

the brain. Notably, BDNF mRNA levels peak postnatally and decline with age (1, 2).

During brain development, BDNF supports the survival of peripheral sensory neurons and influences dendritic branching; both of which are critical for effective neuronal communication (1, 2). In synaptic plasticity, a fundamental process underlying learning and memory, BDNF acts both pre-and post-synaptically to support neurotransmitter release and synaptic strength. This process is largely mediated by N-Methyl-D-Aspartate receptor (NMDA) receptors, which regulate calcium influx essential for LTP. BDNF facilitates the removal of the magnesium block from NMDA receptors, enhancing calcium entry and promoting LTP, which is key to memory consolidation. Disruption in BDNF or TrkB receptor activity impairs these mechanisms, underscoring BDNF's essential role in cognitive function (1, 7). While these mechanisms emphasize BDNF's central role in synaptic plasticity and cognitive function, they also only represent one pathway through which cognitive improvements can occur, as explored in later sections.

3.2 The role of BDNF in adolescent neuroplasticity

Adolescence is a critical developmental period characterized by changes in brain structure and function, especially in the prefrontal cortex, hippocampus, and other cortical regions (16, 17). During this period, white matter volume continues to increase. This growth improves signal conduction, supports memory retention, and strengthens executive function (18, 19).

Additionally, grey matter undergoes synaptic pruning, during which neural circuits for cognitive processes and memory are refined. These changes coincide with heightened neural plasticity, causing the adolescent brain to become more vulnerable to environmental stressors, such as social stress and drug exposure (20, 21), yet simultaneously more responsive to positive experiences like learning opportunities (22).

BDNF is a critical molecular mediator in this plasticity. By binding to TrkB receptors, BDNF activates CREB/CBP pathways that support neuron growth, synapse formation, and the development of prefrontal and hippocampal circuits (13, 14). Dynamic regulation of BDNF during adolescence ensures the adaptation of neurons to both internal and external influences. Dysregulation of BDNF or TrkB, as observed in conditions like Alzheimer's disease, has been linked to impaired neuronal health and cognitive function, highlighting the importance of proper BDNF signaling (19, 23, 24).

External factors during adolescence can have lasting effects on brain development. Social stress, for example, has been shown in rodent studies to affect adolescent brains differently than adult brains (25-28). Adolescent rats exposed to repeated bouts of social stress display altered prefrontal cortex activation (26, 28), changes in exploratory behavior (26, 27), and reduced recovery compared to adults (28). These findings demonstrate that this developmental period is sensitive to external stressors. Similarly, in human studies, genetic variation in BDNF, particularly the Val66Met polymorphism, can interact with environmental influences and factors to impact brain structure, including cortical thickness and surface area (29). This further illustrates how BDNF

contributes to individual differences in adolescent brain development.

In this context, adolescence is a period of cognitive development and growth, with continued improvements in working memory, inhibition, and cognitive flexibility (30, 31). Lifespan studies of autobiographical memory show that adults recall a disproportionate number of memories from their adolescence and early adulthood compared with other life periods (32). This pattern is commonly referred to as the "reminiscence bump" (32, 33), and this difference suggests that memories formed during adolescence are retained more distinctly later in life. However, environmental influences can either support or disrupt these development processes (20-22). Exposure to substances such as cannabis during adolescence may impair neuronal maturation and interfere with prefrontal cortex development, resulting in negative long-term cognitive effects (21, 34). On the other hand, supportive social environments, which interact with adolescents' heightened neuroplasticity to shape brain networks involved in learning, can enhance learning outcomes (35). Furthermore, targeted cognitive training can also induce neural changes in circuits underlying cognitive control and memory performance, demonstrating experience-dependent plasticity (36). Together, these findings illustrate how adolescence is a developmental window characterized by both vulnerability and opportunity, with BDNF playing a central role in shaping neural circuitry, cognitive function, and resilience. This heightened plasticity further suggests that multiple biological pathways, including but not limited to BDNF signaling, may contribute to cognitive development during adolescence.

3.3 Limitations of circulating BDNF as a biomarker of brain function

While BDNF is primarily produced in the brain, it can also be found in the blood, termed as circulating BDNF (37, 38). Circulating BDNF is released from peripheral tissues such as platelets, skeletal muscle, and the vascular endothelium (39, 40), and its levels can be measured in serum or plasma. Serum BDNF is commonly measured using enzyme-linked immunosorbent assay (ELISA), and its levels are influenced by factors such as exercise type, intensity, duration, age, sex, and fitness level. These measurements are often used in human research because directly sampling BDNF from the brain is invasive and not feasible (41).

While circulating BDNF provides a practical way of measuring BDNF activity, it has several limitations as a biomarker of central neural function (41). Understanding these limitations is crucial because many studies rely on peripheral BDNF measurements to make inferences about brain function and cognitive function. Circulating BDNF levels may not accurately reflect central BDNF concentrations because peripheral tissues may contribute to total blood BDNF (42); consequently, changes in blood levels may not necessarily indicate changes in the brain. Additionally, circulating BDNF can fluctuate based on factors unrelated to brain function, such as exercise, diet, stress, time of day, and platelet count (43). Finally, methods of blood collection, processing, and storage can also affect measured BDNF levels, introducing additional variability (42). Together, these factors highlight that while peripheral BDNF is a convenient measure, caution is necessary when interpreting it as a direct marker of neural activity or cognitive function.

These limitations are especially relevant when interpreting studies examining the effects of exercise on BDNF. Many exercise studies report increases in circulating BDNF following aerobic or resistance training (3, 44) and suggest potential benefits for cognition and brain health (9, 45). However, it is important to recognize that changes in blood BDNF may not fully capture changes in the brain, and observed associations with cognitive performance may reflect a combination of central and peripheral effects (41). Researchers must therefore interpret circulating BDNF data with caution and consider additional measures, such as neuroimaging or cognitive testing, to better understand how exercise influences neural function. When interpreting studies linking circulating BDNF to cognitive outcomes, considering these limitations is imperative since discrepancies between peripheral and central BDNF may contribute to the inconsistent relationship observed between BDNF levels and cognitive performance.

4. Exercise-induced changes in BDNF

Emerging research emphasizes that both acute and chronic exercise can influence BDNF levels (46-48). However, multiple factors influence the magnitude and duration of BDNF responses, including the type, intensity, and duration of exercise, as well as individual characteristics such as age, sex, fitness level, and genetic variation like the BDNF Val66Met polymorphism (29, 44, 49). Understanding how these variables interact and affect BDNF is essential for interpreting exercise studies and for designing interventions aimed at optimizing cognitive outcomes in adolescents. Still, exercise-induced changes in BDNF should not be interpreted as the only mechanism underlying cognitive benefits; multiple parallel physiological pathways may independently contribute to these effects.

4.1 Acute vs chronic exercise effects on BDNF and cognitive function

Exercise can influence BDNF levels in both the short and long term (51). The type of response often depends on whether the exercise is acute, a single session, or chronic, repeated over weeks or months (50, 51). Acute bouts of exercise, such as a single session of aerobic activity, typically produces transient increases in circulating BDNF (51). Acute BDNF increases are often more pronounced in sedentary or depressed individuals, though these responses do not always accumulate over time with long-term training (2, 7, 44). These temporary spikes are thought to result from immediate activity-dependent release from skeletal muscle and platelets, with exercise-induced thrombocytosis (EIT) contributing to the surge as splenic contractions release BDNF-rich platelets into circulation (52, 53). These transient increases may support short-term improvements in attention, learning, and memory consolidation (54). However, the effects of a single session are typically brief, returning to baseline within minutes to hours after exercise ends (54, 55).

In contrast to the brief spikes seen from acute exercise, chronic exercise, defined as repeated physical training over an extended period, can produce sustained elevations in both circulating and central BDNF (56). Regular exercise appears to enhance baseline BDNF expression, promote structural brain changes such as increased hippocampal volume, and support lasting improvements in cognitive performance (9). Mechanistically, these increases likely arise from BDNF release across multiple tissues, including the brain, skeletal muscle, and

platelets, with the majority of circulating BDNF stored in splenic platelets for gradual release into the bloodstream (52, 55, 58). These sustained increases likely result from neural and peripheral adaptations, better blood flow, and enhanced brain metabolism (52). Emerging research further shows that long-term exercise significantly increases BDNF levels, especially in studies with larger sample sizes (44, 59). However, further large-scale randomized trials are needed to reduce heterogeneity and better clarify effect sizes.

Identifying the difference between acute and chronic effects is critical for interpreting exercise studies. While acute BDNF spikes may contribute to immediate cognitive benefits (51), only long-term exercise appears capable of inducing lasting neuroplastic changes. This recognition helps clarify why some studies observe immediate improvements in learning or memory after a single workout (60), whereas others require sustained training to detect structural or functional changes in the brain (61). Nevertheless, while both acute and chronic exercise can influence BDNF, cognitive benefits may occur independently of the magnitude of these changes, supporting multi-pathway models of exercise-induced neuroplasticity.

4.2 Exercise parameters affecting BDNF levels

The effects of exercise on BDNF levels are influenced by multiple parameters, including exercise type, intensity, total amount, and duration (11, 49, 61). Aerobic exercise, including running or cycling, has been consistently shown to increase circulating BDNF, both acutely and with chronic training (3, 4, 57). Acute aerobic exercise produces temporary elevations in serum or plasma BDNF that return to baseline within minutes to hours (3, 50, 62), while chronic aerobic training has been associated with higher baseline BDNF levels in some populations, especially at moderate-to-vigorous intensities (9, 59). These effects are likely due to increased cardiovascular demand, elevated cerebral blood flow, changes in neurotransmitter activity, shifts in arousal levels, structural remodeling in the brain, and metabolic signaling that supports the release of BDNF during aerobic activity (49, 58).

Additionally, resistance training can also elevate BDNF levels; although findings are less consistent across studies (59). Certain studies report increases in circulating BDNF from acute bouts of exercise, especially when high volume or moderate-to-high intensity protocols are used (63). On the other hand, other studies find minimal or no changes, especially with low-intensity or short duration sessions (64). This variability may reflect differences in training volume, intensity, or recovery periods; it also relates to the predominately anaerobic nature of resistance exercise and its shorter, intermittent bouts of exertion (63). These shorter bouts may produce temporary BDNF responses rather than continuous aerobic exercise (3, 50). Resistance exercise may also increase lactate production, another suggested mediator of the release of BDNF, though the effect appears less obvious than observed in aerobic or high-intensity interval training (HIIT) (65).

Furthermore, HIIT, which combines elements of both aerobic and anaerobic exercise, has been associated with pronounced acute increases in circulating BDNF (66). Several studies demonstrate that brief periods of high-intensity exercise may strongly stimulate neurotrophin release (4, 60). These brief sessions of high-

intensity exercise elicit larger immediate BDNF responses than moderate continuous exercise (53, 60); this is likely due to the increased metabolic and cardiovascular stress that strongly activates the sympathetic nervous system and increases catecholamine release. As a result, these signals stimulate BDNF transcription and activity-dependent release at the synapse (4, 61). Moreover, these processes engage signaling pathways such as MAPK/ERK, PI3K/AKT, and CREB. These signaling cascades promote synaptic plasticity, dendritic branching, and long-term potentiation, all of which are essential for learning and memory (12-14). However, HIIT does not always increase BDNF levels; still, it is correlated to improved physical function, reduced depression, and enhanced quality of life (15). Notably, exercise-induced hippocampal enlargement has been correlated with BDNF serum levels, supporting the hypothesis that BDNF may mediate some of the neuroplastic benefits of physical activity (9) (Figure 2).

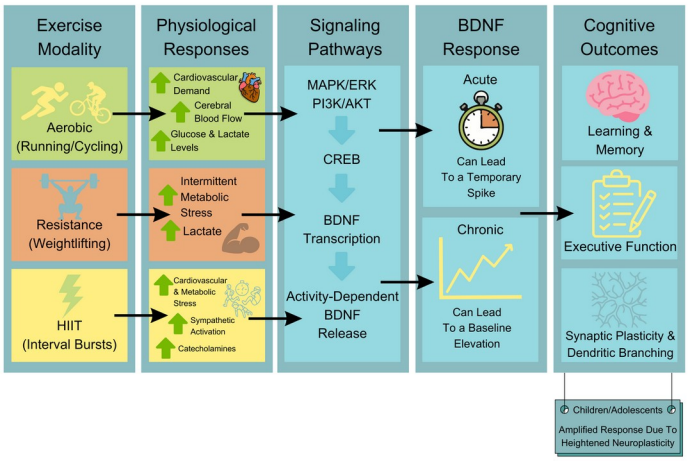

Figure 2. Exercise modality (Aerobic, Resistance, and HIIT) causes specific physiological stressors, such as increased lactate and catecholamine release, which trigger the MAPK/ERK, PI3K/AKT, and CREB signaling pathways. These intracellular cascades drive activity-dependent BDNF transcription, ultimately resulting in both acute spikes and chronic baseline elevations that are associated with improvements in learning outcomes, working memory, executive function, synaptic plasticity, and dendritic branching. Youth may exhibit higher levels of responsiveness due to their heightened neuroplasticity during development.

In addition to modality, exercise intensity appears to play a key role. Emerging research suggests that significant increases in BDNF levels require a threshold of exercise intensity. Higher-intensity exercise produces larger acute BDNF responses than moderate or light intensities, likely due to the greater metabolic stress and sympathetic nervous system activation required to exceed the threshold for significant BDNF release (53, 67). Vigorous exercise is often necessary to exceed the threshold for significant neurotrophin release (4, 5, 44, 53). Duration and frequency also influence BDNF responses: single sessions of exercise can acutely and temporarily elevate BDNF serum levels (51), whereas repeated exercise sessions over months can enhance baseline BDNF expression and support structural and functional adaptations in the brain (56, 64). These mechanisms may be amplified

in children and adolescents due to heightened neuroplasticity, potentially suggesting that high-intensity aerobic or HIIT interventions are especially effective in supporting executive function, working memory, and learning outcomes in youth. These effects may reflect overlapping physiological systems beyond BDNF alone. This reinforces the idea that cognitive benefits of exercise are not exclusively mediated by BDNF. A better understanding of how factors such as exercise type, intensity, duration, and frequency can help design interventions for maximizing cognitive benefits in adolescents and other populations. Although these exercise modalities differ in their influence on BDNF, they may also affect outcomes through additional mechanisms. These include metabolic, vascular, and neurochemical pathways that are not fully captured by peripheral BDNF levels.

4.3 Individual differences in exercise-induced BDNF changes

The response of BDNF to exercise is also influenced by individual characteristics, including age, sex, fitness level, and genetic factors. Age significantly influences the BDNF responses, especially in children and adolescents (68). While many adult studies report no significant or sustained changes in BDNF levels, research in children shows cognitive improvements following physical activity (6). This difference is likely due to heightened neuroplasticity during periods of cognitive development (45, 64). This heightened responsiveness suggests that interventions in youth may be especially effective for promoting learning and other cognitive processes. However, this age-related difference is not consistent across studies (64, 69), suggesting that factors such as exercise type, intensity, and duration may substantially influence BDNF levels across different populations.

BDNF responses to exercise also vary between males and females. Emerging research reveals that females may display a higher level of BDNF responsiveness to physical activity, potentially due to hormonal influences due to the sex hormone estrogen (70). Estrogen interacts with neurotrophic pathways, potentially enhancing synaptic plasticity and growth factor expression (71, 72). Still, the effect of sex differences on exercise-induced BDNF varies across studies, as different factors like age, hormonal state, fitness level, and exercise protocol appear to shape the response (64).

Baseline fitness level is another key factor in BDNF responses to exercise. Some research observes that individuals with higher cardiorespiratory fitness tend to exhibit greater acute and chronic BDNF responses to exercise, as well as enhanced cognitive outcomes (74); this likely reflects more efficient cardiovascular and metabolic support for neural activity and neuroplasticity. In contrast, other studies have found weaker or even inverse relationships between baseline fitness and resting BDNF (75), and fitness has been shown to relate to cognitive outcomes independent of acute BDNF changes (76), indicating complex relationships between physical activity, neurobiology, and cognition.

Genetic variation also modulates the relationship between exercise and BDNF. Specifically, individuals carrying the Met66 variant of the BDNF gene, which is associated with reduced activity-dependent BDNF secretion, often experience greater cognitive

benefits from exercise than those with the more common Val66 allele (73). These findings suggest that those with lower baseline BDNF levels may be more responsive to exercise-induced benefits such as learning and memory (6, 7).

Overall, these findings underscore that BDNF responses from exercise are highly individualized. In adolescents, considering age, sex, fitness level, and genetic variation is crucial for designing interventions that maximize both neurotrophic and cognitive benefits. These individual differences further highlight the notion that while BDNF does contribute to exercise-induced neuroplasticity, it is neither a necessary nor exclusive predictor of cognitive outcomes.

5. Role of BDNF in cognitive development and learning in children and adolescents

While emerging research demonstrates that exercise can regulate BDNF levels, the extent to which these changes can translate into improvements in learning and memory remains an area of ongoing debate in the literature (61). Exercise-induced increases in BDNF are often interpreted as a direct link between physical activity and cognitive function (59); however, a growing body of literature reveals variability in cognitive outcomes (77). In certain studies, acute or chronic exercise correlates with measurable improvements in memory retention and learning outcomes (6, 9), whereas in other studies, cognitive benefits still occur without increases in BDNF serum (2, 7). This variability in cognitive outcomes demonstrates that BDNF is one of several contributing mechanisms rather than the only mediator of exercise-induced cognitive benefits.

Rather than assuming a direct relationship between exercise-induced BDNF changes and cognitive performance, current research indicates that this link is highly dependent on different factors. These include exercise parameters, study designs, and individual characteristics. Cognitive outcomes vary substantially across developmental stages, with children and adolescents often showing patterns that differ from adults (6, 10). Accordingly, the following subsections examine evidence from adolescent and pediatric studies, compare these findings with adult research, and examine circumstances in which cognitive benefits occur independently of measurable BDNF changes.

5.1 Evidence from adolescent and pediatric studies

Changes in BDNF caused by exercise have been linked to learning, memory, and executive function in children and adolescents (6), but the evidence is complex and occasionally contradictory. Several studies indicate that both acute and chronic physical activity can improve cognitive function in youth (Table 1). For instance, a six-week study tested the effects of HIIT in children by comparing exercise with non-physical activities such as trivia and computer games and assessing cognitive control and working memory (6). The HIIT group demonstrated significantly greater improvements in cognitive control and working memory, especially in children carrying the BDNF Val66Met allele (6). These results demonstrate that both exercise characteristics and genetic variation influence individual differences in BDNF responsiveness and cognitive gains. The cognitive improvements observed in youth may stem from both BDNF-dependent and BDNF-independent pathways,

depending on exercise parameters and individual characteristics.

Regular aerobic exercise improved executive function in school-aged children (69). Additionally, exercise consistently increased circulating BDNF in adolescents; however, cognitive outcomes differed between individuals (64). Together, these studies suggest that heightened neuroplasticity during youth may amplify the cognitive benefits of exercise relative to adults. This pattern supports a non-linear relationship between BDNF and cognition, in which BDNF changes are sufficient to cause cognitive improvements but not required for them to occur.

Table 1. Summary of exercise intervention studies on BDNF and cognition in youth and older populations.

Study	Sample Size	Age	Population	Exercise Type	Intensity	Duration	BDNF Change
Moreau et al., 2017	34	7-13 years	Healthy children	HIIT-style motor-cognitive training	High	6 weeks	Not directly measured
Key Findings:High-intensity training significantly improved executive function compared to placebo control; intensity was critical for cognitive gains.							
Latomme et al., 2022	100+ (cross-sectional sample)	8-12 years	Healthy children	Habitual physical activity (accelerometry measured)	Moderate to vigorous	Observational	No significant mediation effect
Key Findings: BDNF did not significantly mediate the relationship between physical activity and executive functioning in this sample.							
Ballester-Ferrer et al., 2022	40	18-30 years	Health young adults	Acute aerobic exercise	Moderate to high	Single session	Increased acutely
Key Findings: Memory improvements were associated with lactate, not BDNF polymorphism or sex differences.							
Marin Bosch et al., 2021	20	20-35 years	Healthy males	Cycling (aerobic)	Moderate	30 minutes (single session)	Increased acutely
Key Findings: A single moderate session increased BDNF and improved memory; endocannabinoids also increased.							
Walsh et al., 2016	30	60-75 years	Healthy older adults	Lower-body resistance training	Moderate	Acute and 12 weeks	Increased acutely
Key Findings: Resistance training increased neurotrophic growth factors; acute BDNF increases observed, chronic changes less consistent.							
Murack et al., 2023	Animal study (rodent sample; multiple groups)	Pubertal (adolescent rats)	Male and female rats	Environmental enrichment (not structured exercise; enriched housing with physical/cognitive stimulation)	N/A	Chronic exposure during puberty	
Key Findings: Environmental enrichment during puberty altered neuroplasticity markers. It buffered inflammatory (LPS-induced) reductions in BDNF and PSD-95 expression, suggesting puberty is a sensitive window for environmental modulation of brain plasticity.							
Currie et al., 2009	30-40	18-35 years	Healthy men and women	Cardiorespiratory fitness assessment & habitual physical activity (observational)	Fitness-based (VO_2max levels)	Cross-sectional	Higher fitness associated with higher resting BDNF
Key Findings: Individuals with greater cardiorespiratory fitness demonstrated higher serum BDNF levels. Habitual physical activity and aerobic fitness were positively associated with circulating BDNF, suggesting chronic fitness adaptations may influence baseline BDNF.							

Nevertheless, the effects of exercise on BDNF levels and cognition are inconsistent across all studies. Some trials result in significant increases in BDNF following exercise without

measurable improvements in memory or executive function (7, 54), while others display cognitive gains without detectable BDNF changes (10, 55). This contrast suggests that the relationship between BDNF and cognitive outcomes is nonlinear: increases in circulating BDNF do not always correspond to proportional improvements in learning or executive function. Such variability may arise from the complex interplay of exercise parameters, including type, intensity, duration, and frequency, and how these factors influence the magnitude and timing of BDNF responses (49, 61). Together, these findings support the idea that BDNF may be sufficient, but not necessary, for exercise-induced cognitive improvements. These outcomes may be regulated by multiple pathways, including metabolic, vascular, and neurochemical mechanisms such as lactate signaling, increased cerebral blood flow, and neurotransmitter modulation, which can independently affect cognitive performance (7, 9, 58). The developmental stage also plays a major role: the increased neuroplasticity that adolescents possess may potentially cause greater cognitive benefits of exercise-induced benefits compared to adults, but this effect differs based on the maturation of the prefrontal cortex and hippocampus (64). Furthermore, adolescents and children differ from adults in baseline neuroplasticity, synaptic density, and hormone profiles, which can also influence increases in BDNF serum levels and the translation of these changes into functional improvements (64, 85, 86). Individual differences in characteristics such as fitness level (75), sex (70, 74), and genetic variation, particularly the BDNF Val66Met polymorphism (29, 73), additionally affect BDNF responsiveness to exercise.

Furthermore, task specificity also plays a role in the link between exercise-induced BDNF and learning and memory. Cognitive gains are more prominent and consistently observed in executive functions that involve working memory, inhibitory control, and cognitive flexibility; on the other hand, effects on episodic memory or long-term memory retention are more unpredictable (6, 7). This tendency suggests that BDNF-mediated neuroplasticity preferentially supports certain neural circuits or cognitive domains during adolescence, likely involving the development of the prefrontal cortex and the hippocampus (17-19).

Overall, while there is clear evidence regarding how physical activity can positively influence BDNF and cognition in youth populations, there are also inconsistencies that highlight the need for careful consideration of exercise parameters, developmental timing, and individual differences. Research indicates that the interaction between exercise-induced BDNF and learning in youth is context-dependent, rather than strictly linear or uniform.

5.2 Comparison with adult and aging populations

Exercise-induced BDNF responses observed in adolescents cannot be directly generalized to apply to adult or older populations. This is due to differences in neurodevelopment, baseline neuroplasticity, and physiology, with studies supporting that adolescence is a critical period of brain development (16, 18, 19). Two focused areas of these changes are in the prefrontal cortex and the hippocampus, which supports synaptic plasticity and learning ability (18, 19).

Accordingly, recent studies suggest that older adults display lower baseline neuroplasticity

and weaker responsiveness to interventions designed to stimulate plasticity, reflecting age-related declines in neural function (81-83). Adults also display declines in hippocampal volume and executive function, which potentially limits the magnitude of cognitive benefits induced by BDNF (9, 45, 56). The differences that are linked with age potentially stem from structural and molecular changes, including declines in synaptic density, impaired neurogenesis, and disrupted receptor signaling pathways. These changes reduce BDNF-mediated synaptic plasticity in older adults compared to adolescents (2, 49, 59). These developmental differences further suggest that the correlation between exercise and cognition cannot be fully explained through BDNF alone; rather, it likely reflects multiple interacting biological systems that vary across the lifespan. The impact of exercise on cognitive and neurotrophic processes and structures varies across developmental stages (49, 59). Findings from studies focused on youth indicate that even acute exercise can have meaningful cognitive benefits, especially in learning and memory, which depend on synaptic plasticity mediated by BDNF (6, 68). In contrast, findings from studies focused on adult and older populations indicate that comparable increases in circulating BDNF and associated cognitive benefits require larger exercise volumes, longer intervention durations, or higher levels of training intensity (2). From a mechanistic perspective, slower BDNF responses in adults may be caused by age-related declines in activity-dependent BDNF release, mitochondrial efficiency, and cellular signaling cascades required for synaptic potentiation (1, 2, 81). However, substantial differences exist within adult BDNF responses; outcomes are strongly influenced by age, baseline fitness, sex, and the type of exercise intervention, with some cases displaying minimal changes in BDNF and other cognitive processes despite regular physical activity (49, 59).

Notably, whereas children and adolescents may exhibit rapid and substantial improvements in cognitive function and processes following exercise, adult and older populations often require greater volumes, more sustained training, and high-intensity programs to produce similar BDNF levels and cognitive benefits (2, 6). This finding underscores age as a major contributor to exercise-induced BDNF on cognition, though age-related differences do not follow a consistent pattern across cognitive domains. To summarize, this evidence highlights the need for a careful consideration of age, neurodevelopmental stage, and individual differences when interpreting BDNF-related outcomes, especially when comparing youth and adult populations.

5.3 Confounding factors affecting exercise-induced BDNF changes and their impact on learning and memory in adolescents

Interpreting exercise-BDNF relationships also warrants considering lifestyle and environmental factors that independently modulate BDNF levels and may interact with exercise effects. These include diet quality, physiological stress, sleep patterns, and screen time (87-90) (Figure 3). Each factor can influence BDNF and the cognitive processes it controls, potentially enhancing or weakening the effects of physical activity on learning and memory during childhood and adolescence (64, 86). Accounting for these non-exercise influences is necessary for separating the effects from physical activity from other influences and for understanding the cognitive processes driven by BDNF. These factors emphasize the idea that

BDNF is embedded within a broader physiological and environmental system influencing cognition, rather than acting as the sole regulator.

Beyond exercise, diet is a key lifestyle factor that can influence BDNF levels and cognitive function during childhood and adolescence. Emerging research suggests that specific nutrients and diet quality can influence neurotrophic signaling, learning, and memory (91). For instance, omega-3 polyunsaturated fatty acids consistently seem to have a direct relationship with BDNF serum levels, which supports synaptic plasticity and cognitive development during childhood and adolescence (92). A growing body of literature further supports that higher consumption of omega-3 fatty acids correlates with higher levels of circulating BDNF, implying that diet influences essential cognitive processes, like learning and memory (87, 92).

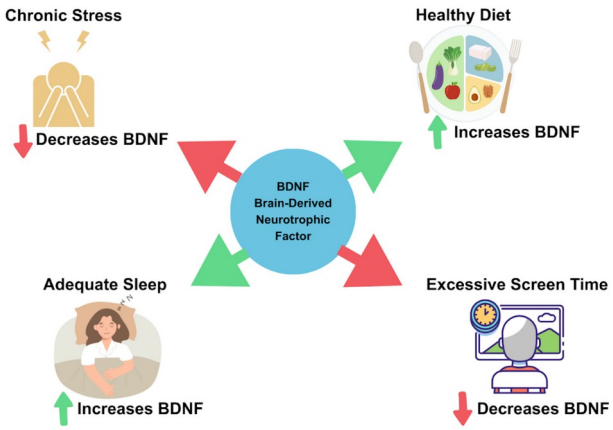

Figure 3. Beyond physical activity, factors such as diet quality, psychological stress, sleep patterns, and screen time influence BDNF signaling during childhood and adolescence.

Furthermore, studies indicate that overall diet also has a substantial impact on BDNF and cognitive outcomes. Diets rich in fruits, vegetables, whole grains, and lean proteins are associated with better academic performance and higher cognitive function in children and adolescents; however, diets full of saturated fats, added sugars, and processed foods were linked with negative learning outcomes (91, 93). These findings suggest that diet regulates BDNF and cognitive processes, not only by specific nutrients like omega-3s, but also through the combined effects of a diverse and balanced diet.

Recent studies investigate psychological stress as another critical factor that influences BDNF, especially in youth (94). Early-life and chronic stress can disrupt BDNF signaling through the activation of the hypothalamic-pituitary-adrenal axis and prolonged glucocorticoid exposure, suppressing BDNF transcription and impairing synaptic plasticity (88). Furthermore, findings from animal and human studies indicate that reductions in BDNF caused by stress may affect neural development in brain regions involved with learning, memory, and the regulation of emotions, such as the hippocampus and the prefrontal cortex (88).

Still, the correlation between BDNF and stress is not always consistent. The timing, duration, and the severity of stress exposure shapes this relationship. Acute stress may temporarily change BDNF levels, whereas chronic or early-life stress appears to consistently reduce BDNF expression and impairs cognitive outcomes (88). This is especially relevant during childhood and adolescence due to heightened neural plasticity and environmental sensitivity (19).

Additionally, sleep interacts closely with stress to influence BDNF. Sleep deprivation or disruption can intensify stress effects on neuroplasticity, ultimately reducing BDNF availability (89). For example, in adolescents and young adults, sleep disruptions caused by high levels of stress have been linked to lower levels of circulating BDNF compared to stress alone (96). Furthermore, findings from studies focused on high-risk young adults demonstrate that sufficient sleep has the potential to buffer reductions in BDNF caused by stress, while poor sleep intensifies these effects (88, 89).

On a mechanistic level, disturbances in sleep may impair BDNF signaling through multiple pathways: dysregulated glucocorticoid rhythms, heightened inflammatory signaling, and disruptions to synaptic homeostasis (96-98). Higher levels of cortisol and pro-inflammatory cytokines caused by sleep deprivation can further hinder processes necessary for learning and memory in developing brains, such as BDNF transcription and synaptic plasticity (89, 95, 99, 100). These findings highlight that in youth, stress and sleep do not operate independently; rather, their combined effects critically influence BDNF-mediated neuroplasticity during key periods of neurodevelopment.

Furthermore, screen time has also become an area of interest when determining factors that influence BDNF and its related cognitive outcomes in childhood and adolescence. In a youth study with obesity, longer amounts of recreational screen time were found to be directly linked with lower levels of circulating BDNF, even after accounting for factors such as physical activity and body composition (90). Since BDNF supports synaptic plasticity, memory, and executive function, lower BDNF levels correlated with high amounts of screen exposure may reflect or contribute to less optimal neurodevelopmental outcomes, especially in individuals at risk for metabolic or cognitive challenges. Although the exact mechanisms remain unclear, sedentary behavior may suppress neurotrophic signaling dependent on physical activity and reduce time spent on physical and cognitive activities that improve BDNF expression (101). These findings highlight that behavioral patterns like screen use, not just exercise, diet, sleep, and stress, can be important determinants of BDNF and cognitive health during developmental periods.

In summary, BDNF-mediated neuroplasticity during childhood and adolescence is shaped by more than just exercise: diet quality, stress exposure, sleep patterns, and screen time all influence BDNF levels and the cognitive processes it supports. Specifically, a balanced diet promotes neurotrophic signaling, whereas chronic stress and disrupted sleep can suppress BDNF and impair synaptic plasticity. Moreover, excessive screen time may further reduce BDNF availability by limiting engagement in active and cognitively stimulating behaviors. Together, these results reveal a dynamic interplay of lifestyle and environmental factors that influence BDNF-related cognitive

development in youth, beyond the effects of exercise examined in this review. These findings reinforce a multi-pathway model in which BDNF contributes to, but does not exclusively determine, exercise-induced cognitive outcomes in youth.

5.4 A "sufficient but not necessary" framework for BDNF-mediated cognitive effects

The relationship between exercise, BDNF, and cognition can be more accurately interpreted using a "sufficient but not necessary" framework. In this model, exercise-induced increases in BDNF are sufficient to support cognitive improvements through TrkB-mediated signaling pathways, including CREB, MAPK/ERK, and PI3K/AKT cascades. These pathways contribute to long-term potentiation, dendritic spine formation, and neuronal survival (13, 14). All of these effects are essential for synaptic plasticity, learning, and overall improvements in cognition.

Even so, BDNF is not necessary for cognitive benefits to occur. Multiple parallel mechanisms activated by exercise can independently support cognitive function: lactate signaling, increased cerebral blood flow, neurotransmitter modulation (such as dopamine and norepinephrine), endocannabinoid activity, and reductions in neuroinflammation (5, 54, 58, 65) (Figure 4). Each pathway, individually or together, can contribute to improvements in attention, memory, and executive function without measurable increases in circulating BDNF.

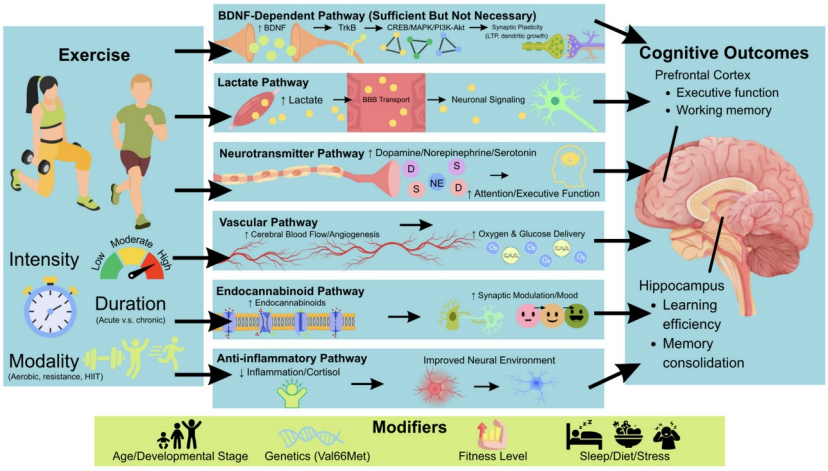

Figure 4. This figure illustrates a distributed systems model in which exercise influences cognition through multiple biological pathways beyond BDNF (lactate signaling, neurotransmitter modulation, vascular adaptations, endocannabinoid activity, and anti-inflammatory processes), helping explain inconsistencies in the relationship between circulating BDNF and cognitive outcomes observed across studies.

This multi-pathway model helps explain a key inconsistency in literature: cognitive improvements are sometimes observed without changes in BDNF, and higher levels of BDNF do not always correspond to better cognitive performance. Rather than demonstrating a linear causal correlation, these findings display a distributed systems framework in which BDNF

is only one of several interacting contributors to improved cognitive function. In this context, BDNF may act as a permissive or amplifying factor for structural plasticity, especially over longer periods of time, while other pathways may better support short-term or task-specific cognitive effects.

This framework can be formalized mathematically, as described below.

5.4.1 *Quantitative model of the framework*

$$C = f\left(P_{BDNF},\ P_{lactate},\ P_{neurotransmitter},\ P_{vascular},\ P_{endocannabinoid},\ P_{inflammatory};\ M\right)$$

where C represents cognitive outcomes, each P term represents the contribution of a specific mechanism influenced by exercise (BDNF-dependent plasticity, lactate signaling, neurotransmitter modulation, vascular adaptation, endocannabinoid signaling, and inflammatory regulation), and M represents the individual variables such as age, genetic variation, fitness level, sleep, and diet. In this model, P_{BDNF} is sufficient but not necessary for increases in C. Formally, this implies: $\frac{\partial C}{\partial P_{BDNF}} > 0$, but C can increase even when $\Delta P_{BDNF} \approx 0$ provided that other pathways increase. This framework allows improvements to occur through alternative pathways when BDNF responses are minimal, explaining why cognitive improvements occur without measurable changes in circulating BDNF and when higher levels of serum BDNF do not produce proportional cognitive gains.

In addition, the function f is likely nonlinear, exhibiting threshold effects, in which a minimum level of pathway activation is required to elicit measurable cognitive changes, and saturation effects, in which further increases in pathway activity produce diminishing returns in cognitive performance. A mathematical representation is

$$C(M) \approx \left(\sum_{i=1}^{N} w_i P_i\right) + \left(\sum_{i=1}^{N} \sum_{j=i+1}^{N} \alpha_{ij} P_i P_j\right)$$

where weights w_i vary across individuals and developmental stages, and interaction terms α_{ij} represent connecting or competitive effects among pathways. For example, adolescents may demonstrate higher weighting on plasticity-related pathways, whereas adults may require more sustained inputs to achieve similar effects. Interaction terms may also reflect relationships such as sleep quality, inflammatory signaling, exercise intensity, and lactate production.

This quantitative framework shifts the interpretation of the relationship between exercise and cognition from a single-mediator model to a multipathway model. This framework allows for testable predictions about pathway dominance, individual variability, and nonlinear response dynamics.

5.4.2 *Operationalization of the multi-pathway model*

To operationalize the proposed multi-pathway framework, Table 2 summarizes pathway-

specific mechanisms linking exercise and cognitive outcomes, along with associated biomarkers, measurement strategies, and predicted effects under acute high-intensity and chronic low-intensity exercise conditions.

Table 2. Multi-pathway mechanisms linking exercise to cognitive outcomes: predicted effects, biomarkers, and measurement strategies.

Pathway	Acute High-Intensity Exercise	Chronic Low-Intensity Exercise	Key Biomarkers	Measurement Methods
BDNF-dependent plasticity	Modest acute facilitation of encoding; transient BDNF elevation	Strong long-term gains (memory, hippocampal plasticity)	Serum/plasma BDNF	ELISA; MRI (hippocampal volume); fMRI (memory tasks)
Reduced BDNF signaling (Val66Met)	Preserved acute gains via non-BDNF pathways; weak BDNF-cognition correlation	Variable/attenuated long-term plasticity	BDNF Val66Met polymorphism genotype; BDNF levels	Genotyping (PCR); ELISA; cognitive testing
Lactate signaling	Strong acute enhancement (attention, executive function); correlates with lactate	Minimal sustained contribution	Blood lactate (mmol/L)	Finger-prick lactate assay; post-exercise cognition
Neurotransmitter modulation (DA/NE/5-HT)	Strong acute improvements (attention, processing speed)	Moderate baseline improvements via arousal/mood	Plasma catecholamines (indirect)	EEG (P300); reaction-time tasks; blood assays
Cerebral blood flow/vascular	Moderate acute gains via increased perfusion	Strong chronic gains (angiogenesis, efficiency)	Cerebral blood flow (CBF); VO_2 max	fMRI (CBF); Doppler ultrasound; CPET
Anti-inflammatory/stress regulation	Minimal acute effect	Significant long-term support via improved neural environment	CRP, IL-6, cortisol	Blood cytokine panels; salivary cortisol
Endocannabionoid system	Acute mood/stress improvements; indirect cognitive benefits	Moderate sustained effects via stress buffering	Anandamide (AEA), 2-AG	Blood assays; mood–cognition correlation
Metabolic/mitochondrial efficiency	Limited immediate effect	Strong support for sustained cognitive performance	PGC-1α (proxy), metabolic markers	VO_2 max; endurance testing; metabolic panels
Myokine signaling (e.g., irisin)	Possible acute modulation (less characterized)	Supports long-term neuroplasticity and metabolic adaptation	Irisin, IL-6 (context-dependent)	Blood assays; longitudinal cognition

This table summarizes predicted pathway-specific contributions to cognitive outcomes under acute high-intensity and chronic low-intensity exercise conditions. Each pathway is linked to measurable biomarkers: circulating BDNF (ELISA) and hippocampal structure/function (MRI/fMRI); genotype via BDNF Val66Met polymorphism; blood lactate (post-exercise); catecholamines or EEG proxies (neurotransmission); cerebral blood flow and VO_2 max (vascular); cytokines and cortisol (inflammatory/stress); endocannabinoids (AEA, 2-AG); and metabolic or myokine markers (e.g., PGC-1α, irisin). Cognitive outcomes are

assessed using standardized tasks (e.g., n-back, Stroop, memory recall) at baseline, acute, and post-intervention timepoints.

Values represent predicted, not definitive, relationships within a multi-pathway framework and may vary by genotype, fitness, and protocol. For empirical testing, studies should be powered to detect moderate effects (e.g., Cohen's $d \approx 0.5$; power = 0.8), typically requiring ~ 25–30 participants per group in genotype-stratified designs.

5.4.3 *Mechanistic basis of non-BDNF pathways*

The BDNF-dependent pathway is a primary pathway linking exercise to cognitive benefits. However, additional pathways, such as lactate signaling, neurotransmitter modulation, vascular adaptations, endocannabinoid activity, and anti-inflammatory processes, can independently contribute to cognitive outcomes (102-106).

Lactate, traditionally seen as a metabolic byproduct, has demonstrated that it functions as a signaling molecule capable of crossing the blood-brain barrier and supporting neuronal energy metabolism and gene expression, particularly during high-intensity exercise (2, 107). Similarly, exercise-induced neurotransmitter modulation, including dopamine, serotonin, and norepinephrine, can acutely boost attention, mood, and executive function independent of structural plasticity (103). Vascular adaptations, such as increased cerebral blood flow and angiogenesis, further improve cognitive performance by improving oxygen and nutrient delivery to neural tissue (104). In addition, endocannabinoid signaling contributes to stress regulation and affective state, indirectly influencing cognitive function (105), and reductions in systemic inflammation also supports a more favorable neural environment for cognitive outcomes (106).

Within this framework, these mechanisms relate to the non-BDNF pathway terms

$$\left(P_{lactate},\ P_{neurotransmitter},\ P_{vascular},\ P_{endocannabinoid},\ P_{inflammatory}\right)$$

and provide other biologically possible routes through which cognitive improvements may occur in the absence of significant changes in BDNF.

5.4.4 *Testable predictions*

This framework creates several experimentally testable and falsifiable predictions. Building on the operationalized model (Table 2), the following predictions can be evaluated empirically.

Acute–chronic pathway dissociation is expected to emerge across exercise conditions. Acute high-intensity exercise will produce cognitive improvements that correlate more strongly with non-BDNF pathways, particularly blood lactate levels. In contrast, chronic low-intensity exercise will show stronger associations with BDNF-dependent markers such as circulating BDNF, hippocampal structural changes, or functional adaptations.

Genotype-dependent variability is predicted in BDNF-related responses. Individuals carrying the BDNF Val66Met polymorphism will show preserved cognitive improvements following high-intensity exercise despite reduced activity-

dependent BDNF secretion, with weaker correlations between BDNF levels and cognitive outcomes compared to non-carriers.

Temporal dissociation between acute and long-term effects is expected. Cognitive improvements observed immediately following exercise will not require sustained increases in BDNF and will instead reflect rapid-acting pathways, such as lactate or neurotransmitter modulation. Long-term cognitive gains will align more closely with structural and plasticity-related changes associated with BDNF.

A failure condition of the framework is defined by BDNF exclusivity. The multi-pathway framework would be challenged if cognitive improvements consistently correlate only with BDNF across both acute and chronic conditions, or if individuals with reduced BDNF signaling fail to exhibit cognitive gains despite activation of alternative pathways.

5.4.5 *Perspectives: toward precision exercise prescriptions for targeted cognitive modulation*

Current models of exercise-induced cognitive enhancement often treat exercise as a generalized intervention that uniformly improves cognition through broad physiological benefits. However, emerging evidence suggests that distinct exercise parameters may preferentially recruit different neurobiological pathways, resulting in selective modulation of specific cognitive domains rather than a uniform global cognitive response. This raises the possibility that exercise prescriptions could eventually be tailored to produce targeted neurocognitive outcomes through controlled activation of particular mechanistic mediators.

One important implication of this framework is that different cognitive domains may depend on partially distinct biological substrates. Executive functions such as working memory, inhibitory control, and cognitive flexibility appear particularly dependent on activity-dependent neuroplasticity involving hippocampal and prefrontal cortical circuits. In these contexts, increases in Brain-Derived Neurotrophic Factor may play a disproportionately important mechanistic role relative to other exercise-induced physiological responses. Consequently, exercise paradigms designed to maximize transient or chronic BDNF elevation may preferentially enhance these executive domains. In contrast, other forms of cognition, such as sustained attention, processing speed, or mood-associated cognitive performance, may depend more strongly on alternative mechanisms including cerebral perfusion, catecholaminergic modulation, inflammatory regulation, or metabolic stabilization. Therefore, future frameworks should avoid treating all exercise-induced physiological responses as equally relevant to all cognitive outcomes.

This perspective also suggests that exercise interventions could potentially be stratified according to the desired cognitive objective. For example, if the primary goal is enhancement of working memory or cognitive flexibility, higher-intensity aerobic or interval-based protocols capable of producing substantial lactate accumulation and downstream BDNF induction may be preferable. Conversely, if the objective is sustained low-fatigue cognitive performance, emotional regulation, or long-term adherence, lower-intensity continuous exercise emphasizing vascular, autonomic, or anti-inflammatory adaptations may be more

appropriate. Such distinctions may help explain inconsistencies across exercise-cognition studies in which heterogeneous exercise paradigms are frequently grouped together despite likely engaging different biological pathways.

Another important future direction involves genetic stratification. Variability in exercise responsiveness may partly arise from polymorphisms affecting neuroplasticity-related pathways, including variants associated with activity-dependent BDNF secretion. Individuals with greater intrinsic sensitivity to BDNF-mediated plasticity may exhibit stronger executive-function responses to vigorous exercise protocols, whereas others may derive greater benefit through alternative pathways such as cerebrovascular or metabolic adaptations. As a result, future exercise-cognition studies may benefit from integrating genetic, metabolic, and physiological profiling to better characterize inter-individual variability in neurocognitive outcomes.

The temporal dimension of exercise-induced cognitive enhancement also warrants further investigation. Acute and chronic cognitive objectives may require fundamentally different exercise architectures. Acute goals, such as improving performance during examinations, testing, or cognitively demanding tasks, may benefit from transient increases in BDNF, lactate signaling, catecholaminergic activation, and arousal generated by carefully timed threshold-sensitive high-intensity interval exercise. In contrast, chronic objectives such as neuroprotection, healthy aging, or long-term executive-function enhancement likely depend on repeated cumulative adaptations involving synaptic plasticity, angiogenesis, inflammatory modulation, and structural remodeling. Distinguishing between transient state-dependent cognitive enhancement and long-term trait-level neuroadaptation may therefore improve both mechanistic clarity and experimental design.

Collectively, these perspectives support a transition from viewing exercise as a nonspecific cognitive enhancer toward a more mechanistically targeted framework in which exercise parameters are intentionally designed to recruit specific biological pathways for specific cognitive outcomes. Under such a model, exercise could potentially function as a programmable neuromodulatory intervention rather than a singular homogeneous stimulus. However, substantial experimental validation remains necessary before precise cognitive "engineering" through exercise can be reliably achieved. Future studies should therefore prioritize mechanistic isolation, biomarker-guided validation, genotype-stratified analysis, and standardized cognitive phenotyping to determine whether selective pathway-biased exercise prescriptions can reproducibly and causally modulate distinct cognitive domains.

6. Conclusion

BDNF plays a key role in neuroplasticity and cognitive development during childhood and adolescence supporting synaptic growth, dendritic branching, and neuronal survival. Physical activity has been shown to influence BDNF levels; however, its relationship with cognitive outcomes is complex, influenced by several lifestyle and environmental factors, and often non-linear. Across youth studies, increases in circulating BDNF do not consistently correspond to improvements in learning or memory, and cognitive gains may also occur in the absence of measurable changes in BDNF.

To reconcile these findings, this review proposes a "sufficient but not necessary" model for interpreting the role of BDNF in exercise-induced cognitive benefits. Within this framework, BDNF-mediated pathways are sufficient to support neuroplasticity and long-term cognitive improvements through mechanisms such as synaptic strengthening and structural adaptation. However, BDNF is not required for cognitive gains. Multiple parallel mechanisms activated by exercise, such as lactate signaling, neurotransmitter modulation, cerebral blood flow adaptations, endocannabinoid activity, and reductions in inflammation, can also independently contribute to cognitive function. This new multi-pathway perspective helps bridge the gaps between the variability between peripheral BDNF changes and cognitive outcomes. Ultimately, this shows the limitation of treating BDNF as the sole mediator of cognitive performance.

Critically, this work formalizes an operationalized and falsifiable model of exercise-induced cognition, defined through measurable biomarkers across multiple biological systems. The accompanying framework (Table 2) specifies pathway-specific biomarkers and predicted differential activation patterns across acute versus chronic exercise conditions. This structure enables direct empirical testing, including pathway dissociation, genotype-dependent effects (e.g., BDNF Val66Met), and nonlinear biomarker–cognition relationships.

Cognitive responses to exercise are therefore context-dependent. They are shaped by interactions between biological pathways, developmental stages, genetic variation, and environmental factors. Exercise may ultimately be developed into a precision neuromodulatory intervention in which exercise architecture, intensity, timing, and individual biological variability are strategically optimized to produce selective and potentially programmable cognitive outcomes. Instead of relying on a single biomarker to explain exercise-induced cognitive benefits, future research should adopt integrative approaches that capture the coordinated activity of multiple systems.

Future studies should move beyond correlational designs and incorporate mechanistically informed, multimodal approaches. A simultaneous assessment of peripheral and central markers of neuroplasticity (such as combining measurements of circulating BDNF, neuroimaging, and cognitive testing), experimental designs that isolate pathway-specific mechanisms and stratification by genetic factors like the BDNF Val66Met polymorphism. Longitudinal and intervention-based studies are also needed to clarify nonlinear effects and identify more specific developmental windows of heightened sensitivity to exercise.

In summary, exercise is a powerful modulator of cognitive development in youth, but its effects are best understood as emerging from a network of interacting biological systems rather than a single pathway. Recognizing BDNF as sufficient but not necessary for cognitive enhancement provides a more accurate and mechanistically grounded framework for interpreting the relationship between exercise and cognition. Ultimately, this framework may guide the development of more targeted and effective interventions.

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