Peer-Review

Kim, Annabelle J, and Sally Zeidan. 2026. "Evaluating Exercise-Induced Changes in BDNF and Cognitive Development in Children and Adolescents: A Multi-Pathway Operationalized Framework." *Journal of High School Science* 10 (2): 206–42. https://doi.org/10.64336/001c.161949.

This is a good descriptive review but it does not meet the Journal's expectations for an analytical review paper as seen here; https://jhss.scholasticahq.com/for-authors, review papers.
However, if you can add a 'sufficient but not necessary' trajectory to the paper, it will elevate it from a pure descriptive review to an analytical review - in which case, it will satisfy the Journal's expectations (see chat gpt file attached).
The attached chatgpt file is self-explanatory. If you can seamlessly integrate it with your manuscript's content, I will be happy to review the revised manuscript again.

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Reviewer 1's Comments

This is a good descriptive review but it does not meet the Journal's expectations for an analytical review paper as seen here; https://jhss.scholasticahq.com/for-authors, review papers. However, if you can add a 'sufficient but not necessary' trajectory to the paper, it will elevate it from a pure descriptive review to an analytical review - in which case, it will satisfy the Journal's expectations (see chat gpt file attached). The attached chatgpt file is self-explanatory. If you can seamlessly integrate it with your manuscript's content, I will be happy to review the revised manuscript again.

Revision: In the revised manuscript, we have integrated a "sufficient but not necessary" analytical framework throughout the discussion to transition the paper from a descriptive review to an analytical review. This model has been seamlessly incorporated into the interpretation of exercise-induced BDNF changes and cognitive outcomes, alongside existing multi-pathway evidence, to better explain inconsistencies in the literature and align with the journal's expectations for analytical synthesis. In-depth revisions are listed below in accordance with the file.

1. Comment 1 (ChatGPT File)

🔑 Core Idea: "BDNF is Sufficient but Not Necessary"

Clean formulation (what you should explicitly state): Exercise-induced increases in BDNF are sufficient to support cognitive improvements under certain conditions, but are not necessary, as cognitive gains can arise through BDNF-independent pathways.

This directly explains your central paradox:

• BDNF ↑ without cognition ↑

• cognition ↑ without BDNF ↑

🧠 Why This Works Conceptually

You are essentially proposing a non-unique causal pathway model: Instead of:

Exercise → BDNF → Cognition You propose:

Exercise → {BDNF-dependent pathways} → Cognition →
{BDNF-independent pathways} → Cognition

This is a major upgrade in causal reasoning and fits the journal's "non-obvious insight" requirement.

🔬 Mechanistic Pathways to Back It Up: To make this convincing, you need to anchor it in biology, not just logic.

1. BDNF-Dependent Pathway (Sufficient Arm) This is the classical mechanism:

Pathway:

• Exercise → ↑ neuronal activity • → ↑ BDNF expression

• → TrkB activation

•

• → CREB / MAPK / PI3K-Akt signaling

• → synaptic plasticity (LTP, dendritic growth)

• → improved learning/memory
This is already well described in your manuscript
👉 Interpretation:
• If this pathway is strongly activated → cognitive gains can occur
✔️ Sufficient
2. Lactate-Mediated Pathway (BDNF-Independent) You already cite this indirectly (very important):
- Exercise → ↑ lactate
- Lactate crosses BBB
- Acts as signaling molecule (HCAR1 receptor)
- Enhances neuronal excitability and plasticity

Critically:
- Some studies show memory improvements tied to lactate, not BDNF

👉 Interpretation:
✔️ Cognitive improvement WITHOUT BDNF change
→ Not necessary

3. Cerebral Blood Flow / Angiogenesis Pathway
- Exercise → ↑ cerebral blood flow
- ↑ oxygen + glucose delivery
- ↑ vascular remodeling
- Improved neural efficiency

This can enhance cognition:
- independent of immediate BDNF fluctuations

4. Neurotransmitter Modulation
- Exercise → ↑ dopamine, norepinephrine, serotonin
- Improves:
- attention
- executive function
- mood

These can directly enhance cognitive task performance
→ even without structural plasticity

Endocannabinoid System You briefly mention this:
- Exercise → ↑ endocannabinoids
- Modulate:
- synaptic plasticity
- mood
- stress

Shown to correlate with memory improvements alongside BDNF—but not dependent on it

5. Anti-inflammatory / Stress Pathway
- Exercise → ↓ chronic inflammation
- ↓ cortisol (long-term)
- Restores plasticity environment This can:
- indirectly improve cognition
- without measurable BDNF change

Revision (Abstract): Replaced “However, this relationship is complex and influenced by factors such as exercise type, intensity, duration, as well as individual differences in age, sex, fitness, and genetics. These variables raise important questions about the consistency of exercise-induced BDNF increases and their translation into meaningful cognitive improvements, particularly in areas like memory and executive function. Critically, the cognitive benefits of exercise are not always proportional to changes in circulating BDNF, suggesting that central BDNF or other neurobiological mechanisms may modulate these cognitive gains. Overall, these findings reveal inconsistencies in the translation of BDNF changes into measurable cognitive gains and highlight gaps in mechanistic understanding. This review summarizes the evidence on how exercise influences BDNF and cognition in children and adolescents, examines whether exercise-induced BDNF changes translate into meaningful cognitive improvements, and identifies the research gaps and directions for future research” with “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, as 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 better 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 literature and highlights the need for a more integrative mechanistic understanding of how exercise influences cognition. This review summarizes the evidence on how exercise influences BDNF and cognition in children and adolescents, examines whether exercise-induced BDNF changes translate into meaningful cognitive improvements, and identifies the research gaps and directions for future research based on a multi-pathway model.”

Revision (Paragraph 2 in Introduction): Added “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 are not 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.” after “Notably, acute increases in BDNF serum levels do not always correlate to measurable cognitive outcomes (4).”

Revision (Paragraph 5 in Introduction): Replaced “To address these gaps, this review examines BDNF's role in cognitive processes, how different types and intensities of exercise influence its levels, and whether exercise-induced BDNF changes translate to meaningful improvements in memory retention and learning in children and adolescents.” with “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 literature and provide a testable, multi-pathway model of how exercise enhances cognition in children and adolescents.”

Revision (Paragraph 1 in Section 3.1): Cut “This communication is essential for learning and memory processes” for redundancy.

Revision (Paragraph 5 in Section 3.1): Added “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." at the end of the paragraph.
Revision (Paragraph 4 in Section 3.2): Added "This heightened plasticity further suggests that multiple biological pathways, including but not limited to BDNF signaling, may contribute to cognitive development during adolescence." at the end of the paragraph.
Revision (Paragraph 3 in Section 3.3): Added "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." at the end of the paragraph.
Revision (Paragraph 1 in Section 4): Added " 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." at the end of the introduction paragraph.
Revision (Paragraph 3 in Section 4.1): Added "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." at the end of the paragraph.
Revision (Paragraph 4 in Section 4.2): Added "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." and "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."
Revision (Paragraph 5 in Section 4.3): Added "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."
Revision (Paragraph 1 in Section 5): Added "This variability in cognitive outcomes demonstrates that BDNF is one of several contributing mechanisms rather than the only mediator of exercise-induced cognitive benefits."
Revision (Paragraph 1 in Section 5.1): Added "The cognitive improvements observed in youth may stem from both BDNF-dependent and BDNF-independent pathways, depending on exercise parameters and individual characteristics."

Revision (Paragraph 2 in Section 5.1): Added "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."

Revision (Paragraph 3 in Section 5.1): Replaced "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. These inconsistencies may reflect 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)" with 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)."

Revision (Paragraph 1 in Section 5.2): Added “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.”

Revision (Paragraph 1 in Section 5.3): Added “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.”

Revision (Paragraph 9 in Section 5.3): Added “These findings reinforce a multi-pathway model in which BDNF contributes to, but does not exclusively determine, exercise-induced cognitive outcomes in youth.”

Revision (Title): Changed title from “Exercise-Induced Changes in BDNF and Cognitive Development in Children and Adolescents” to “Evaluating Exercise-Induced Changes in BDNF and Cognitive Development in Children and Adolescents: A Multi-Pathway Framework”

2. Comment 2, 3 (ChatGPT File)

✍️ 1. New Conceptual Framework Paragraph (Discussion Section)

📐 2. Mathematical / Quantitative Framing Paragraph (Insert at end of Discussion or just after your new framework section — this adds real rigor)

Revision (added Section 5.4): Added “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. 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.” **Revision (added subsection 5.4.1 Quantitative Model of the Sufficient But Not Necessary Framework):**

Added “C=f(PBDNF, Plactate, Pneurotransmitter, Pvascular, Pendocannabinoid, Pinflammatory | M) 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. 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, PBDNF is sufficient but not necessary for increases in C. Formally, this implies: CPBDNF>0, but C can increase even when PBDNF0 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: Ci=1wiPi+ jiαijPiJj where weights wi vary across individuals and developmental stages, and interaction terms αijrepresent 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."

Revision (added subsection 5.4.2): Added "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, 103, 104, 105, 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 (PBDNF, Plactate, Pneurotransmitter, Pvascular, Pendocannabinoid, Pinflammatory) and provide other biologically possible routes through which cognitive improvements may occur in the absence of significant changes in BDNF."

3. Comment 4 (ChatGPT File)

🗒️ 2. Rewritten Conclusion (Centered on Your Framework) (Replace your current conclusion with this upgraded version

Revision (Conclusion): Replaced "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 and influenced by several lifestyle and environmental factors. While certain findings from youth studies indicate that exercise can improve executive function and working memory, particularly in children carrying the BDNF Val66Met Met allele, increases in circulating BDNF do not consistently correlate with measurable cognitive benefits. Some studies report cognitive improvements without detectable BDNF changes, while others find increases in BDNF without significant learning outcomes. This inconsistency suggests that BDNF may support cognition indirectly by fostering neuroplasticity, rather than acting as a direct regulator of cognitive performance. Furthermore, current findings suggest that lifestyle factors beyond exercise, including diet quality, sleep patterns, stress, and screen time, also regulate BDNF and cognitive outcomes. Physical activity alone, although helpful, is not sufficient to optimize neurodevelopment. Overall, these findings emphasize the need for comprehensive, multifactorial, and individualized interventions to maximize neurodevelopment in youth. Overall,

exercise-induced increases in BDNF are sufficient to support cognitive improvements under certain conditions, but are not necessary, as cognitive gains can arise through BDNF-independent pathways; improved cognition can occur through BDNF-independent pathways such as metabolic signaling, neurotransmitter modulation, and vascular or structural brain changes. This explains why some studies display increases in BDNF without measurable cognitive benefits, while others report cognitive improvements without detectable changes in BDNF. Future research should employ longitudinal studies, measure both peripheral and central BDNF using neuroimaging and cognitive testing, and assess age-related BDNF changes. By accounting for both genetic and external influences, interventions can more effectively target plasticity mediated by BDNF to support cognitive development in youth." with "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. Notably, cognitive responses to exercise are context-dependent. They are shaped by interactions between biological pathways, developmental stages, genetic variation, and environmental factors. 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."

4. Comment 5 (ChatGPT File)

⚠️ 2. New Section: Incorrect Implicit Assumptions in Current Literature (Place this at the end of the Introduction or as a short standalone section before Section 4—this is VERY high impact for this journal)

Revision (added Section 2 after Introduction): Added "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 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, as 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 accurate 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."

5. Comment 6 (ChatGPT File)

🔬 Bonus: Testable Predictions (Add This!)

Revision (added Section 5.4.3): Added "5.4.3 Testable Predictions This framework creates several experimentally testable predictions. Inhibiting BDNF signaling, such as TrkB inhibition, would be expected to reduce long-term structural plasticity while not fully eliminating acute cognitive improvements following exercise. In addition,
high-lactate exercise modalities, like high-intensity interval training (HIIT), may still improve cognition despite the absence of significant increases in BDNF. Ultimately, this supports the notion that other metabolic and neurotransmitter pathways are involved.
Furthermore, individuals carrying the Val66Met polymorphism may demonstrate reduced BDNF secretion; therefore, they may rely more heavily on non-BDNF mechanisms to achieve cognitive gains."

6. Comment 7 (ChatGPT File)

📊 1. Figure Concept: Multi-Pathway Model of Exercise-Induced Cognitive Enhancement

Revision (added figure and caption): Added Figure 4 and this caption "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."

Reviewer 2's Comments

Please verify that all links to the references point to the correct source.

Revision: References were checked for credibility and working links.

The authors must disclose and acknowledge any assistance received in the preparation of this manuscript, including but not limited to editorial, technical, analytical, or writing support. All such contributions must be clearly stated in the Acknowledgments section.
Revision: Added Acknowledgements section: "I would like to express my sincere gratitude to Sally Zeidan for her mentorship and guidance throughout this research project, including her role as co-author. I am also grateful to Asad Mustafa for his careful proofreading and constructive suggestions, which improved the clarity of this work. Finally, I would like to acknowledge the Lumiere Research program for providing the initial framework and opportunity to begin this project, as well as for connecting me with Sally Zeidan."

Include enough recent references along with foundational ones. Ensure references directly support your claims. Avoid "padding." Use credible sources (peer-reviewed journals, reputable books, official reports).
Revision: The manuscript was checked to include additional recent peer-reviewed sources alongside foundational references. All citations directly support the associated claims. Redundant or indirectly relevant references were removed to reduce citation "padding" and improve clarity and precision.

Verify that you have used past perfect tense and third person throughout the manuscript wherever applicable.
Revision: The manuscript was reviewed and ensured consistent use of third-person voice and appropriate past perfect tense where applicable throughout the text.

Thank you for addressing my comments. My remaining comment relates to a summary operationalization in the form of a table that also includes measurable evidence in the form of biomarkers, as well as predictions that encompass falsifiablity. Please include the table and legend; as well as the predictions in the manuscript at an appropriate place. Please also update the abstract and conclusion as necessary to specifically include an operationalized model with measurable biomarkes and a falsifiable design.
Please see attached file.

Reviewer 1's Comments
Thank you for addressing my comments. My remaining comment relates to a summary operationalization in the form of a table that also includes measurable evidence in the form of biomarkers, as well as predictions that encompass falsifiablity. Please include the table and legend; as well as the predictions in the manuscript at an appropriate place. Please also update the abstract and conclusion as necessary to specifically include an operationalized model with measurable biomarkes and a falsifiable design. Please see attached file.
Revision (Section 5.4.2): Added "Section 5.4.2 Operationalization of the Multi-Pathway Model" and "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."
Revision (Section 5.4.3): Changed "5.4.2 Mechanistic Basis of Non-BDNF Pathways" to "5.4.3 Mechanistic Basis of Non-BDNF Pathways"
Revision (Section 5.4.4): Changed "5.4.3 Testable Predictions" to "5.4.4 Testable Predictions"
Revision (Section 5.4.2): Added "Table 2. Multi-pathway mechanisms linking exercise to cognitive outcomes: predicted effects, biomarkers, and measurement strategies."
Revision (Section 5.4.2): Added table legend (in file): "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 should be 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 approximately 25–30 participants per group in genotype-stratified designs."
Revision (Abstract): Added "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." before the last sentence in the abstract.
Revision (Abstract): Replaced "This review summarizes the evidence on how exercise influences BDNF and cognition in children and adolescents, examines whether exercise-induced BDNF changes translate into meaningful cognitive improvements, and identifies the research gaps and directions for future research based on a multi-pathway model." with "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" to avoid redundancy of "this review."
Revision (Conclusion): Added "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."

Thank you for addressing my coments. Accepted.