This manuscript is a descriptive review and does not yet meet the Journal's requirements and expectations for a review paper. I propose that the authors include a 'sufficient but not necessary' phrase and pathways to back it up. This will make the paper an analytical review, present a framework that is testable and falsifiable and elevate it to a conceptual syntheis review paper. Provide me with your analysis of my idea.

That's exactly the kind of **conceptual reframing** this paper needs—and it aligns very well with the journal's expectations.

Right now, your manuscript *implicitly* argues this, but making it **explicit, formal, and mechanistically grounded** would elevate it from descriptive to analytical.

🔑 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.

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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**

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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**

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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

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5. 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

---

6. Anti-inflammatory / Stress Pathway

- Exercise → ↓ chronic inflammation
- ↓ cortisol (long-term)
- Restores plasticity environment

This can:

- indirectly improve cognition
- without measurable BDNF change

🧩 Putting It Together (What You Should Explicitly Add)

Proposed Framework Paragraph (you can almost paste this)

> The relationship between exercise, BDNF, and cognition can be more accurately described using a “sufficient but not necessary” framework. Exercise-induced increases in BDNF are sufficient to promote synaptic plasticity and cognitive improvements through TrkB-mediated signaling pathways. However, BDNF is not necessary for these outcomes, as parallel mechanisms—including lactate signaling, neurotransmitter

modulation, increased cerebral blood flow, and endocannabinoid activity—can independently enhance cognitive function. This multi-pathway model explains why cognitive improvements are sometimes observed in the absence of measurable increases in circulating BDNF, and conversely, why elevated BDNF does not always translate into improved cognitive performance.

📊 Optional: Add a Simple Formalization (Very High Impact)

Even a minimal model would elevate rigor:

$$\text{Cognition} = f(P_{BDNF}, P_{lactate}, P_{neurotransmitters}, P_{vascular}, P_{context})$$

Where:

- P_{BDNF}: BDNF-dependent plasticity
- others = parallel pathways

Then state:

- P_{BDNF} is **sufficient but not necessary**
- Multiple terms can independently drive the output

🚀 Why This Significantly Improves Your Paper

This single addition:

✔️ Resolves contradictions in the literature

✔️ Challenges an implicit assumption (required by rubric)

✔️ Introduces a new conceptual model

✔️ Is mechanistically grounded

✔️ Leads to testable predictions

🔬 Bonus: Testable Predictions (Add This!)

To fully satisfy the rubric:

- Blocking BDNF (e.g., TrkB inhibition) will:

    - reduce **long-term structural plasticity**
    - but not eliminate **acute cognitive gains**
- High-lactate exercise (HIIT):
    - may improve cognition even when BDNF does not increase
- Individuals with Val66Met:
    - may rely more on **non-BDNF pathways**

🧾 Bottom Line

Yes—this is exactly the kind of **"above-and-beyond" conceptual leap** the journal is asking for.

But it only works if you:

- state it explicitly
- support it mechanistically
- and connect it to testable predictions

If you want, I can:

- integrate this into your **Discussion section seamlessly**, or
- rewrite your **Conclusion to center this framework**

both

Great—this is exactly the upgrade that will move the manuscript into the journal's "insight-generating" category. Below are **two ready-to-insert sections**:

✍️ 1. New Conceptual Framework Paragraph (Discussion Section)

(Place this near the end of Section 4, after discussing inconsistencies)

Writing

4.X A "Sufficient but Not Necessary" Framework for BDNF-Mediated Cognitive Effects

The relationship between exercise, brain-derived neurotrophic factor (BDNF), and cognition can be more accurately interpreted using a "sufficient but not necessary" framework. Exercise-induced increases in BDNF are sufficient to promote synaptic plasticity and support learning and memory through TrkB-mediated signaling pathways, including CREB, MAPK/ERK, and PI3K/AKT cascades. These pathways facilitate long-term potentiation, dendritic spine formation, and neuronal survival, all of which are critical for durable cognitive improvements.

However, BDNF is not necessary for cognitive enhancement, as multiple parallel mechanisms activated by exercise can independently improve cognitive function. For example, exercise-induced lactate production has been shown to correlate with memory improvements independent of BDNF changes, suggesting a metabolically mediated pathway for neural enhancement. Additionally, increases in cerebral blood flow, neurotransmitter modulation (e.g., dopamine and norepinephrine), endocannabinoid signaling, and reductions in neuroinflammation can each enhance cognitive performance without requiring measurable increases in circulating BDNF.

This multi-pathway model resolves a key inconsistency in the literature: cognitive improvements are sometimes observed in the absence of BDNF increases, while elevated BDNF does not always translate into measurable cognitive gains. Rather than assuming a linear causal relationship, these findings support a model in which BDNF acts as one of several parallel and interacting contributors to cognitive enhancement. In this framework, BDNF may function as a permissive or amplifying factor for structural plasticity, particularly over longer timescales, while other pathways may dominate short-term or task-specific cognitive improvements.

Formally, cognitive outcomes can be conceptualized as a function of multiple interacting pathways:

Cognition = f(P_BDNF, P_lactate, P_neurotransmitter, P_vascular, P_context)

where each term represents a distinct biological mechanism influenced by exercise. Under this model, P_BDNF is sufficient to drive cognitive improvements but not necessary, as other pathways can independently produce similar outcomes. This reframing shifts the interpretation of exercise-cognition research from a single-mediator model to a distributed systems perspective, providing a more coherent explanation for variability across studies.

🧾 2. Rewritten Conclusion (Centered on Your Framework)

(Replace your current conclusion with this upgraded version)

Writing

5. Conclusion

Brain-derived neurotrophic factor (BDNF) plays a central role in neuroplasticity and cognitive development during childhood and adolescence, supporting synaptic growth, dendritic branching, and neuronal survival. While physical activity consistently influences BDNF levels, the relationship between exercise-induced BDNF changes and cognitive outcomes is complex, variable, and often non-linear. Evidence across youth populations demonstrates that increases in circulating BDNF do not uniformly correspond to improvements in learning or memory, and conversely, cognitive gains can occur in the absence of detectable BDNF changes.

To reconcile these findings, this review proposes a “sufficient but not necessary” framework for interpreting the role of BDNF in exercise-induced cognitive enhancement. Within this model, BDNF-dependent pathways are sufficient to support neuroplasticity and long-term cognitive improvements, particularly through structural and synaptic adaptations. However, BDNF is not

required for cognitive gains, as parallel mechanisms—including lactate signaling, neurotransmitter modulation, vascular adaptations, endocannabinoid activity, and reductions in inflammation—can independently enhance cognitive function. This multi-pathway perspective explains the observed dissociation between BDNF changes and cognitive outcomes and highlights the limitations of treating BDNF as a singular causal mediator.

Importantly, this framework suggests that cognitive improvements following exercise are context-dependent, shaped by interactions between biological pathways, developmental stage, genetic variation, and environmental factors such as diet, sleep, and stress. Rather than seeking a single biomarker to explain exercise-induced cognitive benefits, future research should adopt integrative approaches that capture the dynamic interplay among these systems.

To advance the field, future studies should move beyond correlational designs and employ multimodal, mechanistically informed approaches. These include: (1) simultaneous measurement of peripheral and central markers of neuroplasticity (e.g., serum BDNF, neuroimaging, and cognitive performance), (2) experimental designs that isolate pathway-specific contributions (e.g., lactate-driven vs. BDNF-mediated effects), and (3) stratification by genetic factors such as the BDNF Val66Met polymorphism. Additionally, longitudinal and intervention-based studies should aim to identify threshold effects, nonlinear dynamics, and critical developmental windows during which exercise most effectively enhances cognitive outcomes.

In summary, exercise remains a powerful and accessible tool for supporting cognitive development in youth, but its effects are mediated by a network of interacting biological mechanisms rather than a single pathway. Recognizing BDNF as sufficient but not necessary for cognitive enhancement provides a more precise and mechanistically grounded framework for understanding how physical activity shapes the developing brain, and offers a foundation for designing more targeted and effective interventions.

🚀 What This Accomplishes (Why This Will Impress Reviewers)

With these additions, your manuscript now:

✔️ Explicitly challenges an implicit assumption

✔️ Introduces a new conceptual model

✔️ Resolves contradictions in the literature

✔️ Provides mechanistic grounding

✔️ Suggests concrete, testable research directions

👉 This directly satisfies the journal’s requirement to:

> “extract/extrapolate information… and propose a new way of thinking”

If you want one more step up, I can also:

- add a **figure concept (diagram of pathways)**
- or a **short "Incorrect Assumptions in the Field" section** (very high impact for this journal)

both

Perfect—these two additions will push the manuscript firmly into the journal's "above-and-beyond" category.

Below are **(1) a figure concept you can implement** and **(2) a high-impact "Incorrect Assumptions" section** that explicitly meets the rubric.

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

(You can label this as Figure 3 in your manuscript)

Writing

Figure 3. Multi-Pathway Model of Exercise-Induced Cognitive Enhancement

Concept:
A systems-level diagram illustrating that exercise influences cognition through multiple parallel and interacting biological pathways, rather than a single linear BDNF-mediated mechanism.

Structure of the figure:

Left panel: Input

- Box: *Exercise*
    - Sub-labels:
        - Intensity
        - Duration
        - Modality (aerobic, resistance, HIIT)

Middle panel: Parallel Pathways (5–6 arrows emerging from Exercise)

1. **BDNF-Dependent Pathway**
    - Exercise → ↑ BDNF → TrkB activation → CREB/MAPK/PI3K-Akt → synaptic plasticity (LTP, dendritic growth)
2. **Metabolic (Lactate) Pathway**
    - Exercise → ↑ lactate → BBB transport → neuronal signaling → memory enhancement
3. **Neurotransmitter Pathway**
    - Exercise → ↑ dopamine / norepinephrine / serotonin → attention & executive function
4. **Vascular Pathway**

    - Exercise → ↑ cerebral blood flow & angiogenesis → improved oxygen/glucose delivery
5. **Endocannabinoid Pathway**
    - Exercise → ↑ endocannabinoids → synaptic modulation & mood regulation
6. **Anti-inflammatory / Stress Pathway**
    - Exercise → ↓ chronic inflammation & cortisol → improved plasticity environment

Right panel: Output

- Box: *Cognitive Outcomes*
    - Executive function
    - Working memory
    - Learning efficiency
    - Memory consolidation

Overlay element (critical):

- Label across pathways:
    - "BDNF = sufficient but not necessary pathway"

Optional modifiers (top or bottom):

- Age / developmental stage
- Genetics (Val66Met)
- Sleep / diet / stress

These act as *modulators* of pathway strength.

Caption (important for reviewers):
This figure illustrates a distributed, multi-pathway model in which BDNF represents one sufficient—but not necessary—mechanism linking exercise to cognitive outcomes. The model explains why cognitive improvements may occur independently of measurable changes in circulating BDNF and highlights the role of parallel biological systems.

⚠️ 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)

Writing

X. Incorrect Implicit Assumptions in Current Literature

Despite extensive research on exercise, brain-derived neurotrophic factor (BDNF), and cognition, several implicit assumptions continue to shape interpretation of findings. These assumptions are often not explicitly stated, yet they influence experimental design, data interpretation, and

conclusions. Identifying and revising these assumptions is critical for resolving inconsistencies in the literature.

Assumption 1: BDNF is a Direct Causal Mediator of Cognitive Improvement

A common assumption is that increases in BDNF directly cause improvements in learning and memory. However, evidence reviewed in this manuscript demonstrates that this relationship is not consistently observed. Cognitive improvements can occur without measurable increases in circulating BDNF, and conversely, elevated BDNF does not always produce detectable cognitive gains. This suggests that BDNF may function as a permissive or modulatory factor that supports neuroplasticity, rather than as a sole or rate-limiting driver of cognitive performance.

Assumption 2: Peripheral BDNF Reflects Central Nervous System Activity

Many studies rely on serum or plasma BDNF as a proxy for brain BDNF activity. However, circulating BDNF is influenced by peripheral sources such as platelets, skeletal muscle, and vascular endothelium, and is sensitive to methodological factors including blood processing and time of measurement. As a result, peripheral BDNF measurements may not accurately reflect central neurotrophic activity, limiting their interpretability in studies of cognition.

Assumption 3: The Exercise–BDNF–Cognition Relationship is Linear

The prevailing model assumes a linear relationship in which increases in exercise lead to proportional increases in BDNF, which in turn produce proportional improvements in cognition. However, empirical findings suggest a non-linear and context-dependent relationship, with threshold effects, saturation, and variability across individuals and developmental stages. This non-linearity may arise from interactions among multiple biological pathways and moderating variables such as age, fitness level, and genetic variation.

Assumption 4: BDNF is the Primary Mechanism Linking Exercise to Cognition

The focus on BDNF as the central mediator has overshadowed alternative mechanisms through which exercise may influence cognitive function. Emerging evidence highlights the roles of lactate signaling, neurotransmitter modulation, vascular adaptations, endocannabinoid activity, and inflammatory regulation as parallel contributors to cognitive enhancement. These pathways can operate independently of BDNF, challenging the notion of a single dominant mechanism.

Implications for Future Research

Revising these assumptions necessitates a shift toward multi-pathway, systems-level models of exercise-induced cognitive enhancement. Future studies should move beyond single-biomarker approaches and instead integrate multiple physiological, neurobiological, and behavioral measures. Experimental designs should also aim to isolate pathway-specific contributions and test non-linear and interaction effects, rather than assuming uniform or direct relationships.

By explicitly addressing these assumptions, researchers can develop more accurate models of how exercise influences cognitive development and better interpret the variability observed across studies.

🚀 Why These Two Additions Are High-Impact

Together, they do something most student reviews do **not**:

✔️ Make implicit assumptions explicit (journal requirement)

✔️ Replace a linear model with a systems model

✔️ Provide a visual + conceptual synthesis

✔️ Generate testable hypotheses

✔️ Elevate the paper from "review" → "framework paper"

🧾 Final Advice (Strategic)

If you include:

- the **"sufficient but not necessary" framework**
- this **assumptions section**
- and the **figure**

👉 Your paper will likely be perceived as:

> "thoughtful, integrative, and conceptually original"

—which is exactly what the journal is screening for.

If you want, I can also:

- sketch the **actual figure diagram (clean layout you can recreate in PowerPoint)**
- or add a **short mathematical model paragraph** to further strengthen rigor

both

Excellent—these two additions will give your paper a **clear visual identity + quantitative backbone**, which is exactly what reviewers look for.

🧩 1. Clean Figure Layout (Ready to Recreate in PowerPoint / BioRender)

Use this as a **direct blueprint**.

Writing

Figure 3. Multi-Pathway Model of Exercise-Induced Cognitive Enhancement

Layout: Horizontal flow (left → right)

LEFT COLUMN (Input)

[Box 1: EXERCISE]

- Intensity (low / moderate / high)
- Duration (acute vs chronic)
- Modality (aerobic, resistance, HIIT)

Draw **5–6 arrows** from this box into the middle column.

MIDDLE COLUMN (Parallel Pathways)

Arrange these as **stacked boxes (vertical alignment)**:

[Box 2A: BDNF-Dependent Pathway]
Exercise → ↑ BDNF → TrkB → CREB / MAPK / PI3K-Akt
→ Synaptic plasticity (LTP, dendritic growth)

[Box 2B: Lactate Pathway]
Exercise → ↑ Lactate → BBB transport → neuronal signaling
→ Memory enhancement

[Box 2C: Neurotransmitter Pathway]
Exercise → ↑ Dopamine / Norepinephrine / Serotonin
→ Attention / executive function

[Box 2D: Vascular Pathway]
Exercise → ↑ Cerebral blood flow / angiogenesis
→ ↑ Oxygen & glucose delivery

[Box 2E: Endocannabinoid Pathway]
Exercise → ↑ Endocannabinoids
→ Synaptic modulation / mood

[Box 2F: Anti-inflammatory Pathway]
Exercise → ↓ Inflammation / cortisol

→ Improved neural environment

RIGHT COLUMN (Output)

[Box 3: COGNITIVE OUTCOMES]

- Executive function
- Working memory
- Learning efficiency
- Memory consolidation

All pathway boxes point → this box.

CRITICAL OVERLAY (this is what makes your figure novel)

Across the **BDNF pathway only**, add a label:

👉 **"Sufficient but Not Necessary"**

Optional: dashed arrows from other pathways labeled:
👉 "BDNF-independent routes"

MODULATORS (top or bottom of figure)

Add a horizontal bar:

Modifiers:

- Age / developmental stage
- Genetics (Val66Met)
- Fitness level
- Sleep / diet / stress

Draw light arrows from this bar to all pathway boxes.

CAPTION (important for reviewers)

This figure presents a distributed systems model in which exercise influences cognition through multiple parallel biological pathways. BDNF represents a sufficient—but not necessary—mechanism, as cognitive improvements may arise through independent pathways such as lactate signaling, neurotransmitter modulation, and vascular adaptations. This framework explains inconsistencies in the relationship between circulating BDNF and cognitive outcomes observed across studies.

📐 2. Mathematical / Quantitative Framing Paragraph

(Insert at end of Discussion or just after your new framework section — this adds real rigor)

Writing

Quantitative Framework for Multi-Pathway Cognitive Modulation

To formalize the “sufficient but not necessary” framework, the relationship between exercise and cognition can be represented as a multi-factor function in which cognitive outcomes arise from the combined contributions of several partially independent biological pathways:

C = f(P_BDNF, P_lactate, P_neuro, P_vascular, P_endo, P_inflam; M)

where C represents cognitive performance, each P term represents the contribution of a specific pathway (BDNF-dependent plasticity, lactate signaling, neurotransmitter modulation, vascular adaptation, endocannabinoid signaling, and inflammatory regulation), and M represents moderating variables such as age, genetic variation, fitness level, sleep, and diet.

In this formulation, P_BDNF is sufficient but not necessary for increases in C. Formally, this implies:

$\partial C/\partial P\_BDNF > 0$, but C can increase even when $\Delta P\_BDNF \approx 0$

provided that other pathway contributions (e.g., P_lactate or P_neuro) increase. This structure naturally explains empirical observations in which cognitive improvements occur without measurable changes in circulating BDNF, as well as cases where elevated BDNF does not produce proportional cognitive gains.

Additionally, the function f is likely nonlinear, with threshold and saturation effects:

$C \approx \Sigma\ w\_i \cdot P\_i - \Sigma$ interaction terms

where weights w_i vary across individuals and developmental stages. For example, adolescents may exhibit higher weighting on plasticity-related pathways, whereas adults may require stronger or sustained inputs to achieve similar effects. Interaction terms capture synergistic or competitive effects among pathways, such as the interaction between sleep quality and inflammatory signaling or between exercise intensity and lactate production.

This quantitative framework shifts the interpretation of exercise-cognition relationships from a single-mediator model to a distributed systems model, enabling testable predictions about pathway dominance, individual variability, and nonlinear response dynamics.

🚀 Why These Two Additions Matter (Reviewer Perspective)

These are **high-signal upgrades**:

Figure:

- Makes your idea instantly understandable
- Signals conceptual originality
- Helps reviewers “see” your framework

Math paragraph:

- Demonstrates **analytical thinking**
- Moves beyond narrative review
- Introduces **testable structure**

🔬 Bonus (If You Want One Final Edge)

Add 1–2 sentences after the math:

> “This model predicts that interventions targeting different pathways (e.g., high-lactate vs moderate aerobic exercise) may produce similar cognitive outcomes through distinct mechanisms, a hypothesis that can be tested experimentally.”

🧾 Final Outcome

With everything you’ve now added:

- Framework ✅
- Assumptions critique ✅
- Mechanistic pathways ✅
- Figure ✅
- Quantitative model ✅

👉 This is no longer a standard review—it’s a **conceptual synthesis paper**, which is exactly what the journal wants.