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The Mechanistic Pathways Linking Exercise to Neuroprotection and Mental Health: Construction and Elaboration of an Integrative Theoretical Model

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Abstract: Objective: This study proposes the Exercise–Neuroprotection–Mental Health (ENM) model, an integrative framework explaining how exercise enhances mental health through multilevel neurobiological mechanisms. **Methods:** Drawing on evidence related to exercise-induced neurotrophic factors, myokines, neuroplasticity, and emotion-related neural circuits, we synthesized current findings and developed mechanistic inferences following the pathway from physiological activation to molecular signaling, neuroplastic changes, neural-circuit modulation, and mental-health outcomes. **Results:** The ENM model suggests that exercise triggers peripheral activation leading to increased BDNF, irisin, and anti-inflammatory and antioxidant responses. These molecular changes enhance synaptic plasticity, neurogenesis, and network efficiency in the hippocampus and prefrontal cortex. At the circuit level, improved functioning of the PFC–amygdala emotion-regulation pathway, the hippocampus–HPA axis, and the VTA–NAc reward system contributes to better emotional stability, stress resilience, and motivation. The model yields testable hypotheses regarding the mediating role of BDNF, the involvement of the PFC–amygdala circuit in anxiolytic effects, the role of the VTA–NAc pathway in antidepressant effects, and myokines and inflammation as

intervention targets. **Conclusion:** The ENM model offers a coherent framework linking exercise to neuroprotection and mental-health improvement and provides theoretical guidance for targeted exercise prescriptions and future neuroimaging, biomarker, and clinical validation studies.

Keywords: Neuroprotection; Mental health; Neural plasticity; Neural circuits; Myokines; Theoretical model

Introduction

Mental health disorders have rapidly emerged as a major global public health challenge. According to recent analyses published in *The Lancet Psychiatry*[1], depression, anxiety, and stress-related disorders are steadily increasing among young people and individuals in high-pressure occupations, exerting profound impacts on cognitive functioning, social adaptation, and overall quality of life. Although pharmacological and psychological treatments offer certain benefits, their side effects, financial burden, and limited accessibility underscore the urgent need for safer, long-term, and self-manageable intervention strategies. Against this backdrop, exercise—an activity that simultaneously generates physiological and psychological benefits—has been increasingly recognized as a promising core approach for promoting mental health.

Recent advances in neuroscience indicate that exercise not only alters peripheral metabolic states but also elicits profound central nervous system responses, including upregulation of brain-derived neurotrophic factor (BDNF), suppression of inflammatory pathways, enhancement of brain plasticity

mediated by myokines such as irisin, and modulation of dopaminergic systems[2–5] . At the same time, neuroimaging studies demonstrate that exercise strengthens prefrontal cortical regulation of the amygdala, improves hippocampal sensitivity to stress feedback, and activates midbrain reward pathways, thereby contributing to greater emotional stability and stress resilience[6] . However, current explanations remain fragmented: the relationships among molecular alterations, cellular-level neuroplastic adaptations, and large-scale neural network dynamics have yet to be captured within a coherent and inferentially robust integrative framework.

Therefore, the central aim of this study is not merely to synthesize existing findings but to propose an integrated theoretical model—Exercise–Neuroprotection–Mental Health (ENM)—that mechanistically explains how exercise promotes neuroprotection and mental health. The ENM model seeks to elucidate how exercise influences emotion regulation, stress adaptation, and psychological functioning through a cascade of interconnected processes spanning molecular responses, neuroplasticity, and neural-circuit modulation. By articulating this model, the present study addresses a critical gap in the current literature—the absence of a comprehensive mechanistic chain linking exercise to mental health—and provides a theoretical foundation for the scientific, precise, and experimentally testable development of future exercise-based interventions[7,8].

1. Theoretical Foundations

The theoretical foundations of this study aim to establish a logically continuous biological pathway for the ENM model, beginning with exercise as an external stimulus and explaining how it sequentially induces molecular changes, modulates neuroplasticity, and optimizes large-scale brain networks. The following four sections correspond to the four key levels of the model.

1.1. Physiological Effects of Exercise: The External Trigger for Neural Adaptation

Exercise initially functions as a whole-body physiological activation that provides the trigger for subsequent central nervous system responses. Sustained or moderate-to-vigorous exercise induces metabolic alterations in peripheral organs—particularly skeletal muscle, the cardiovascular system, and the immune system—including increased glucose utilization, elevated lactate release, and enhanced mitochondrial function. These alterations are considered “front-end signals” that initiate central neural adjustments. During exercise, skeletal muscle releases a variety of signaling molecules capable of crossing the blood–brain barrier, forming a “muscle–brain communication axis” that constitutes a major starting point for neuroprotective responses[9] . Additionally, exercise-induced increases in heart rate and hemodynamic activity elevate cerebral blood flow, creating favorable metabolic conditions for synaptic plasticity and neuronal functioning[10] . Together, these physiological drivers represent the first triggering unit of the ENM model.

1.2. Molecular Mechanisms: Neurotrophic Factors, Myokines, and Inflammation/Oxidative-Stress Regulation

The second level of exercise-induced changes occurs at the molecular scale. BDNF is widely regarded as the core molecule through which exercise enhances neuroplasticity, directly regulating synaptogenesis, neuronal survival, and learning–memory functions. Evidence indicates that exercise increases BDNF expression via the CREB signaling pathway and strengthens its interaction with TrkB receptors[11]. Exercise also plays a crucial role in suppressing systemic inflammation. Under chronic stress, pro-inflammatory cytokines (e.g., TNF-α, IL-1β) impair neuroplasticity and contribute to emotional disturbances, whereas exercise can reduce neuroinflammation by inhibiting NF-κB signaling and increasing anti-inflammatory cytokines such as IL-10, thereby alleviating depressive tendencies[12] . Oxidative-stress regulation constitutes another major mechanism. Exercise enhances the activity of endogenous antioxidant enzymes (SOD, CAT), reduces free-radical-induced damage, and improves mitochondrial function—mechanisms collectively described as the core "endogenous neuroprotection system" of exercise[13] . These molecular-level responses form the theoretical basis of the ENM model's "molecular driving unit."

1.3. Neuroplasticity: Synaptic Remodeling and Adult Neurogenesis

Molecular alterations initiate neuroplastic changes at the cellular level. At the synaptic level, increased signaling from BDNF, irisin, and other molecules promotes dendritic spine formation, strengthens synaptic efficacy, and induces long-term potentiation—processes fundamental to emotional regulation and stress resilience. Exercise elicits marked synaptic remodeling in the hippocampus and prefrontal cortex, modifying input–output patterns within neuronal networks and enhancing neural-coding efficiency. At the neurogenesis level, the adult dentate gyrus retains a certain proliferative capacity of neural stem cells. Regular exercise can increase hippocampal neurogenesis by two- to three-fold, and these newly generated neurons contribute to learning, emotional regulation, and stress adaptation, forming a key mechanistic basis for exercise's antidepressant effects[14].

The central logic here is that molecular responses to exercise are not isolated events but jointly promote synaptic plasticity and neurogenesis, thereby building more resilient neural structures capable of supporting adaptive responses under stress.

1.4. Functional Logic of Emotional and Cognitive Neural Circuits ENM

The third layer of the ENM model focuses on large-scale neural circuits, which directly underlie observable emotional, motivational, and stress-related behaviors. The prefrontal cortex (PFC) exerts top-down regulatory control over the amygdala, a pathway regarded as the core emotion-stabilizing circuit. Exercise significantly strengthens PFC inhibitory control and reduces amygdala threat reactivity,

thereby decreasing anxiety tendencies.The hippocampus–hypothalamus–pituitary–adrenal (HPA) axis serves as the central stress-feedback system. Exercise has a bidirectional regulatory effect on this axis: by enhancing hippocampal plasticity, it improves negative-feedback sensitivity and effectively stabilizes cortisol fluctuations, which is essential for adaptive stress responses[15] .A third critical circuit is the midbrain dopaminergic reward system (VTA–NAc). Exercise increases the firing activity of dopamine neurons, heightens reward sensitivity, and counteracts anhedonia-like symptoms [16]. Thus, the theoretical basis at the circuit level illustrates how cellular-level neuroplastic adaptations expand into emotion-regulation networks, ultimately producing observable psychological improvements.

2. Construction of the Theoretical Model

2.1. Exercise Stimulation → Peripheral and Central Molecular Responses

As a whole-body physiological load, exercise immediately triggers coordinated responses across the muscular, endocrine, and immune systems. These peripheral signals subsequently reach the central nervous system, forming the first stage of neuroprotection. Substantial evidence indicates that moderate-intensity exercise significantly elevates the expression of neurotrophic molecules such as BDNF, IGF-1, and VEGF in both the bloodstream and specific brain regions[16] . Myokines released from skeletal muscle—such as irisin and cathepsin B—can cross the blood–brain barrier and directly influence gene expression within the hippocampus and prefrontal cortex[17] . In addition, exercise rapidly modulates peripheral inflammation by reducing levels of TNF-α, IL-1β, and CRP, thereby mitigating inflammatory load on the central nervous system[18] .

Importantly, these molecular changes do not occur in isolation but proceed in a coordinated, cross-system signaling cascade. For example, elevated irisin not only promotes BDNF gene expression but also activates the PGC-1α pathway to regulate mitochondrial metabolism, thereby enhancing neuronal energy supply. Thus, within the ENM model, exercise is conceptualized as the initiator of a "peripheral–central bidirectional signaling network," forming the molecular foundation for subsequent neuroplasticity.

2.2. Molecular Responses → Enhancement of Neuroplasticity

Once exercise-induced molecules reach the brain, their most direct effect is the enhancement of neuroplasticity, including strengthened synaptic plasticity, increased neurogenesis, and improved structural plasticity. The BDNF–TrkB pathway plays a central role by promoting dendritic spine formation and augmenting long-term potentiation (LTP), thereby improving neural coding efficiency in the hippocampus and prefrontal cortex[19] . Concurrently, exercise-induced VEGF and IGF-1 contribute to angiogenesis and progenitor cell proliferation within the hippocampus, providing metabolic support for the survival of newly formed neurons [20] .

Furthermore, exercise's ability to reduce oxidative stress and inflammation provides a more stable cellular environment for plasticity. Reduced oxidative damage improves membrane potential regulation and synaptic transmission efficiency, while attenuated inflammation prevents excessive microglial activation and subsequent neuronal injury[21] .

Based on these mechanisms, the ENM model posits that molecular responses serve as the biological mediators through which exercise enhances neuroplasticity, constituting a core pathway linking exercise to improved psychological function.

2.3. Neuroplasticity → Regulation of Neural Circuits

As synaptic efficiency increases and newly generated neurons integrate into existing networks, large-scale neural circuits undergo systematic functional adjustments. The ENM model focuses on three circuits closely associated with emotion and stress regulation:

1)Prefrontal cortex–amygdala (PFC–Amygdala) emotion-regulation pathway

2)Hippocampus–hypothalamus stress-feedback system (HPA axis)

3)Ventral tegmental area–nucleus accumbens (VTA–NAc) reward–motivation pathway

Enhanced synaptic plasticity within the PFC strengthens its top-down inhibitory control over the amygdala, thereby reducing exaggerated emotional reactivity and improving emotion-regulation efficiency[22] . Elevated hippocampal neurogenesis increases the sensitivity of negative feedback within the HPA axis, leading to more effective suppression of cortisol release and improved stress homeostasis. Plasticity-related changes within the dopaminergic system enhance reward sensitivity and motivational drive, helping alleviate anhedonia commonly observed in depressive states[23] .These findings suggest that neuroplastic adaptations propagate to the circuit level, enabling the brain to adopt a more stable and adaptive emotional-functional mode.

2.4. Neural-Circuit Regulation → Improvements in Mental Health

At the final level of the ENM model, circuit-level modulation manifests as observable improvements in mental health, including enhanced emotional stability, increased stress tolerance, reduced anxiety, and elevated motivation. Strengthened PFC–amygdala regulation is reflected in faster emotional recovery and lower emotional volatility; improved hippocampal regulation of the HPA axis increases psychological resilience under stress; and activation of the VTA–NAc reward pathway enhances positive affect and the capacity to experience pleasure in daily activities[24].

Crucially, these improvements do not stem from any single mechanism but from the coordinated effects across all preceding layers. Mental health outcomes within the ENM model therefore represent the cumulative expression of exercise-induced multisystem interactions. A schematic representation of the mechanism is shown in **Figure 1**.

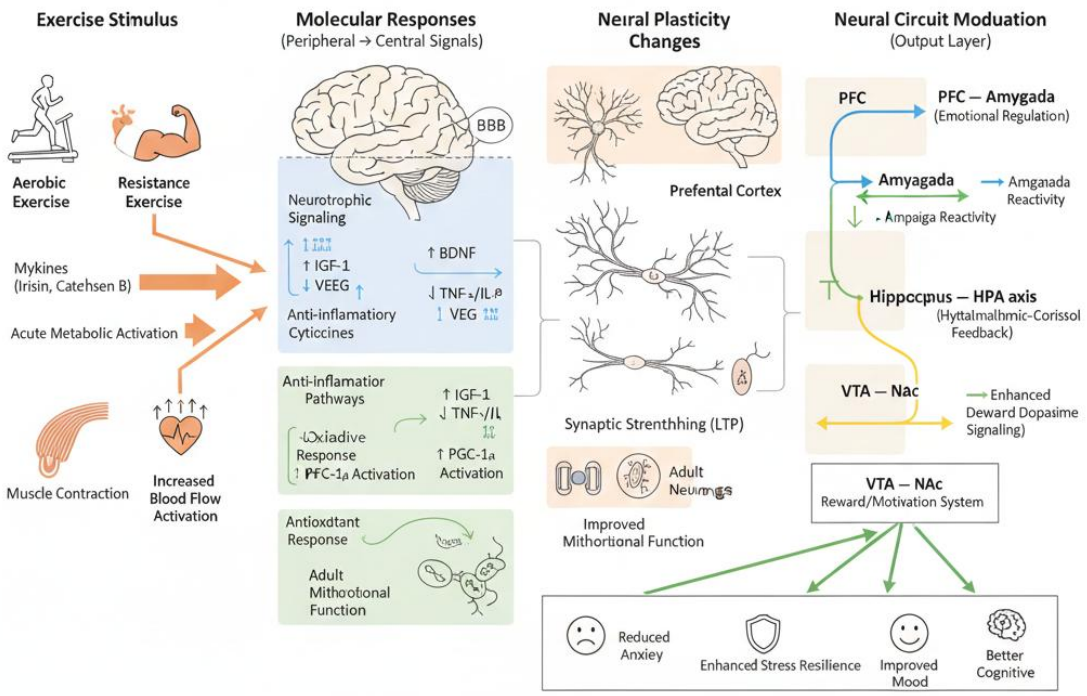

Figure 1. Mechanistic model of exercise-induced neuroprotection and mental-health enhancement (ENM model).

The model illustrates the multilevel pathway through which exercise promotes mental health, beginning with peripheral physiological stimulation and subsequent molecular signaling (e.g., increased BDNF and irisin, anti-inflammatory and antioxidant responses). These molecular changes enhance neuroplasticity—including synaptic plasticity, neurogenesis, and myelin remodeling—which in turn optimize key neural circuits such as the PFC–amygdala emotion-regulation pathway, the hippocampus–HPA-axis stress-feedback system, and the VTA–NAc reward circuit. Together, these adaptations contribute to improved emotional stability, stress resilience, and psychological well-being.

3. Theoretical Inferences

Following the construction of the ENM model, this study proposes a series of testable theoretical inferences to clarify how exercise influences mental health through molecular responses, neuroplastic remodeling, and neural-circuit regulation. These inferences are not derived from empirical data but are logically inferred from established findings in exercise physiology, neuroscience, and affective regulation. They serve as conceptual predictions that may guide future mechanistic experiments and intervention studies.

3.1. BDNF as a Mediator in Exercise-Induced Emotional Improvement

The exercise-induced increase in BDNF is hypothesized to play a central mediating role in emotional enhancement. Theoretically, elevated BDNF levels triggered by exercise should enhance hippocampal neurogenesis and synaptic plasticity in both the hippocampus and prefrontal cortex, thereby improving emotional stability and stress regulation. Longitudinal studies that examine the temporal sequence of exercise exposure, BDNF changes, and emotional outcomes may reveal that

BDNF occupies a mediating, rather than merely accompanying, position in the pathway linking exercise to emotional improvement[25].

3.2. Exercise May Reduce Anxiety by Strengthening the PFC–Amygdala Circuit

A core mechanism of anxiety involves hyperresponsivity of the amygdala to threat signals alongside insufficient prefrontal inhibitory control. The ENM model posits that exercise enhances the functional connectivity and regulatory capacity of the dorsolateral prefrontal cortex, thereby reducing amygdala-driven emotional reactivity and lowering anxiety. If future fMRI studies examine pre–post intervention changes in this circuit, they may verify the causal chain:exercise → enhanced PFC regulation → reduced amygdala activation → decreased anxiety.

3.3. Activation of the VTA–NAc Reward System May Contribute to Exercise's Antidepressant Effects

A hallmark neural mechanism of depression is reduced reward sensitivity within the midbrain dopaminergic system, leading to anhedonia. According to the ENM model, exercise may increase the firing rate of VTA dopamine neurons, enhance presynaptic dopamine availability, or increase receptor sensitivity within the NAc, thereby restoring reward responsiveness and counteracting depressive symptoms. This inference is directly testable using PET or fMRI techniques to quantify dopamine release following exercise

3.4. Myokines as Emerging Targets for Future Mental-Health Interventions

Exercise-induced myokines—such as irisin, cathepsin B, and the anti-inflammatory form of IL-6—may influence neuroplasticity or inflammatory states after crossing the blood–brain barrier, subsequently modulating emotional processes. The ENM model implies that even individuals unable to engage in moderate or high-intensity exercise might benefit from pharmacological or biological interventions that mimic these myokine pathways, achieving "exercise-like" neuroprotective and psychological effects. Thus, myokines represent promising future targets for mental-health applications[26,27].

3.5. Reduction in Inflammation May Be a Necessary Condition for Emotional Improvement

Individuals with elevated inflammatory markers (e.g., IL-1β, TNF-α, CRP) often exhibit impaired neuroplasticity and diminished emotional regulation. The ENM model suggests that exercise-induced anti-inflammatory effects may not be merely auxiliary but instead constitute an essential step in the pathway to emotional improvement. In other words, without a reduction in inflammation, the full emotional benefits of exercise may not occur. Longitudinal biomarker studies could empirically test the chain: exercise → reduced inflammation → enhanced neuroplasticity → improved emotion[28].

3.6. Restoration of HPA-Axis Feedback May Underlie Exercise-Induced Stress Resilience

Chronic stress leads to dysregulation of the HPA axis, producing excessive cortisol and impaired feedback control. The ENM model infers that exercise may restore feedback regulation by enhancing hippocampal sensitivity to cortisol, thereby improving stress adaptation. Even without experimental data, this pathway is logically predicted: if exercise enhances hippocampal function, then HPA-axis regulation should improve correspondingly, offering a measurable target for future research[29].

4. Discussion

The ENM model proposed in this study—linking *exercise → molecular modulation → neuroplasticity → neural-circuit regulation → mental health*—aims to explain how exercise promotes neuroprotection and psychological improvement through multilevel biological processes in the absence of pharmacological intervention. This discussion highlights the model's theoretical significance, its mechanistic innovations, potential applications, and directions for future research.

First, at the structural level, the model emphasizes that the mental-health benefits of exercise do not arise from a single mechanism but from coordinated interactions among peripheral and central pathways. This perspective aligns with the emerging "multiscale integration theory" in neuroscience, which posits that changes in psychological function are typically driven by the layered interplay of molecular, cellular, and circuit-level mechanisms[30] . By incorporating this perspective into exercise science, the ENM model helps clarify why exercise can, in some clinical settings, produce effects comparable to antidepressant medication[30] .

Second, the cross-level mechanistic chain proposed in this study fills a critical gap in existing literature. Current research on exercise-induced emotional or cognitive improvement often focuses on isolated mechanisms—such as BDNF upregulation[31] or modulation of the prefrontal–amygdala emotional circuit[32] . In contrast, the ENM model highlights the sequentiality and interdependence of mechanisms: molecular changes initiate neuroplastic adaptation, which then influences large-scale neural circuits. This "nested mechanistic logic" strengthens the biological plausibility of exercise's effects and provides a framework for future empirical work—such as longitudinal imaging studies to test the temporal relationships among molecular responses, circuit changes, and behavioral outcomes.

Third, in terms of application, the ENM model offers a theoretical basis for developing personalized exercise prescriptions. For instance, interventions targeting the PFC–amygdala emotion-regulation circuit may benefit from cognition-demanding exercises (e.g., coordination training). To enhance reward-system activation, rhythmic or feedback-rich exercise modalities such as high-intensity interval training (HIIT) or dance-based activities may be preferable. When the aim is to elevate BDNF or irisin levels, sustained moderate-to-high-intensity aerobic exercise may be the most effective option[33].

Additionally, the model suggests new avenues for biomarker development. Traditional biomarkers have focused primarily on inflammation (e.g., cytokines) or cortisol levels, whereas the ENM

framework highlights exercise-induced myokines—such as irisin—as potential predictors of mental-health improvement[34] . Future work may examine whether these peripheral factors can serve as indicators for monitoring exercise-intervention outcomes, offering more precise tools for clinical evaluation.

Despite its contributions, the model has limitations. As a theoretically derived framework, the ENM model requires empirical validation across multiple modalities. Key unresolved questions include: Do the multilevel mechanisms follow causal relationships? Do different exercise modalities elicit distinct patterns of neuroplasticity? Are molecular responses and emotional outcomes moderated by individual differences? These questions can be addressed in future research through animal models, longitudinal neuroimaging, electrophysiological studies, and multicenter randomized controlled trials.

Overall, the ENM model provides a novel integrative perspective for understanding how exercise influences mental health through multiscale neural mechanisms. With systematic experimental and clinical validation, it may serve as a theoretical foundation for guiding exercise-based interventions and advancing interdisciplinary research across exercise science, cognitive neuroscience, and psychiatry.

5. Conclusion

This study proposes the ENM model, an integrative framework explaining how exercise promotes neuroprotection and mental health through a multilevel biological pathway. The model outlines how exercise-triggered peripheral stimulation induces molecular signaling changes—such as increased BDNF and irisin, reduced inflammatory cytokines, and enhanced antioxidant activity—which subsequently facilitate synaptic plasticity, neurogenesis, and myelin remodeling. These adaptations, in turn, optimize key neural circuits, including the PFC–amygdala emotion-regulation pathway, the hippocampus–HPA-axis stress-feedback system, and the VTA–NAc reward circuit, ultimately enhancing emotional stability, stress resilience, and psychological well-being.

By articulating this sequential mechanism chain, the ENM model addresses the longstanding gap in explaining how exercise translates into mental-health benefits. Although empirical validation is still needed, the model provides theoretical guidance for designing targeted exercise prescriptions, identifying molecular and circuit-level intervention points, and developing personalized mental-health strategies. Future research using neuroimaging, longitudinal designs, and molecular assays will be essential for testing and refining this framework.

In summary, the ENM model offers a coherent and scalable explanation for the neural basis of exercise-induced mental-health benefits and provides a theoretical foundation for advancing precise and scientifically informed exercise-based interventions.

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