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The Role of BDNF as a Mediator of Neurobiological and Clinical Improvements in Parkinson's Disease Patients Following HIIT: A Comprehensive Review

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Abstract

Background. Parkinson's disease (PD) is characterized by progressive dopaminergic neurodegeneration and significantly reduced levels of Brain-Derived Neurotrophic Factor (BDNF). High-Intensity Interval Training (HIIT) has emerged as a critical non-pharmacological strategy to stimulate neuroplasticity via the muscle-brain axis.

Aim. This review evaluates the role of BDNF as the primary biological mediator of the neurobiological and clinical improvements observed in PD patients following HIIT interventions.

Material and methods. A structured analysis was performed on 28 scientific publications (2008–2026) sourced from PubMed. The methodology synthesized molecular signaling pathways with standardized clinical outcome measures.

Results. HIIT-induced elevations in blood lactate and irisin trigger the PGC-1α/BDNF pathway, crossing the blood-brain barrier to enhance mitochondrial quality control and neuronal survival. Clinical evidence demonstrates a 21.6% mean reduction in MDS-UPDRS Part III scores, alongside significant improvements in gait economy, executive functions, and respiratory mechanics. HIIT further mitigates depressive symptoms through BDNF-modulated neurotransmission.

Conclusions. BDNF is the central driver of the multi-systemic benefits associated with HIIT. Providing a more robust neurotrophic stimulus than moderate-intensity exercise, HIIT acts as a potent disease-modifying therapy. Early implementation of individualized HIIT protocols is essential for optimizing long-term psychomotor resilience.

Key words: HIIT, Parkinson's disease, BDNF, neuroplasticity, MDS-UPDRS, neurorehabilitation.

1. Introduction

Parkinson's disease (PD) currently stands as the second most prevalent neurodegenerative condition globally, posing a significant challenge to aging populations and healthcare systems. The core of its pathophysiology lies in the progressive and selective degeneration of dopaminergic neurons within the substantia nigra pars compacta, leading to a profound depletion of dopamine in the striatum. While the hallmark motor symptoms-bradykinesia, resting tremor, and muscular rigidity-dominate the clinical diagnosis, the disease is increasingly recognized for its heterogeneous non-motor spectrum, which includes executive dysfunction, depression, and respiratory impairment. Despite decades of research, the primary treatment remains symptomatic; pharmacological interventions like levodopa compensate for dopamine loss but do not provide substantial neuroprotection or halt the underlying apoptotic cascades [1, 2]. A critical factor emerging in the study of neural resilience is the role of neurotrophins, specifically Brain-Derived Neurotrophic Factor (BDNF). As a master regulator of synaptic plasticity, BDNF is essential for the survival, differentiation, and maintenance of dopaminergic neurons. Research indicates that patients with PD exhibit a chronic "trophic deficit," where systemic and central BDNF levels are significantly downregulated, correlating with both motor severity and cognitive decline [3]. Consequently, there is an urgent need to identify non-pharmacological strategies that can effectively upregulate BDNF expression to foster neuroplasticity and potentially modify the disease trajectory [4]. High-Intensity Interval Training (HIIT) has emerged as a promising therapeutic paradigm in this context. Characterized by alternating short bursts of near-maximal intensity exercise with periods of active or passive recovery, HIIT induces a unique physiological state of metabolic stress. This "hormetic" stimulus

is thought to be more effective than traditional moderate-intensity continuous training (MICT) in activating the muscle-brain axis. Specifically, the acute elevation of blood lactate and the release of myokines, such as irisin, are believed to cross the blood-brain barrier, subsequently triggering the molecular machinery responsible for BDNF synthesis in the hippocampus and striatum [5]. Despite the growing body of literature, a comprehensive synthesis focusing on BDNF as the primary mediator of clinical and psychomotor improvements in PD is still needed to optimize rehabilitation protocols.

Research Objective.

The aim of this narrative review is to evaluate the role of BDNF as a key mediator of the neurobiological and clinical improvements observed in patients with Parkinson's disease following high-intensity interval training (HIIT) interventions.

Research Problems.

1. Does the intensity of HIIT protocols result in a significantly greater surge of systemic BDNF compared to conventional aerobic exercise in the PD population?

2. What are the specific molecular pathways through which HIIT-induced BDNF affects motor control and cognitive executive functions?

3. To what extent do baseline disease severity and patient characteristics influence the neuroplastic response to high-intensity exercise?

Research Hypotheses.

1. HIIT induces a robust increase in BDNF levels, which serves as a primary driver of neuroprotection and synaptic reorganization in the parkinsonian brain.

2. The increase in BDNF expression following HIIT correlates positively with improvements in standardized motor scales (e.g., MDS-UPDRS) and cognitive performance.

3. HIIT acts as a disease-modifying therapy by enhancing mitochondrial quality control and reducing systemic neuroinflammation via the BDNF-TrkB signaling pathway.

2. Research Materials and Methods

The methodological framework of this narrative review is based on a structured and critical analysis of 28 selected scientific publications that examine the neurobiological and clinical impact of high-intensity interval training (HIIT) on Parkinson's disease (PD). To ensure a high level of academic rigor, a comprehensive literature search was conducted using the PubMed database, utilizing specific search terms including "High-Intensity Interval Training", "Parkinson's Disease", and "Brain-Derived Neurotrophic Factor". The selection of these works was designed to integrate multifaceted evidence, linking foundational clinical assessment standards with the latest advancements in molecular neuroscience to evaluate the role of BDNF as a central mediator of psychomotor health.

2.1. Characteristics of the Analyzed Material

The core evidence consists of 28 peer-reviewed scientific works. The chronological scope of the analyzed material spans from 2008 to 2026, allowing for a comprehensive view that connects established clinical benchmarks with cutting-edge research. Specifically, the material includes:

1. Foundational Clinimetric Standards: The landmark 2008 revision of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) by Goetz et al., which serves as the indispensable clinical framework for evaluating motor and non-motor outcomes across the analyzed studies [6].
2. Clinical and Randomized Controlled Trials (RCTs): A series of human studies (2016–2026) focusing on functional adaptations, motor control, and systemic neurotrophic responses to HIIT in patients with idiopathic PD [7, 8, 9, 10].
3. Experimental and Mechanistic Research: High-quality papers utilizing animal models and cellular analysis (2019–2026) to investigate mitochondrial dynamics, the muscle-

brain axis, and specific signaling pathways such as MAPK/ERK1/2 and PI3K/Akt [11, 12, 13, 14].

4. Modern Systematic Reviews: Comprehensive syntheses providing up-to-date insights into BDNF isoforms, lactate-induced neuroplasticity, and neuromuscular adaptations [3, 15, 5, 16]

2.2. Selection and Analytical Rigor

The 28 publications were analyzed based on their specific contribution to three thematic pillars:

1. Neurobiological Pathways: Works detailing the role of metabolic and myogenic triggers (e.g., lactate, irisin, PGC-1α) in the induction of BDNF and its subsequent effect on neuronal survival and mitochondrial quality control.
2. Clinical Psychomotor Metrics: Research providing quantitative data on motor performance (e.g., TUG, 6MWT) and cognitive outcomes (e.g., executive functions, memory) in relation to exercise intensity and duration.
3. Exercise Protocol Specificity: Studies comparing different exercise modalities to identify the optimal physiological stimulus required to reach the threshold for neuroplastic changes in the parkinsonian brain.

2.3. Data Synthesis Procedure

The analysis followed a narrative synthesis approach, where data from the 28 selected works were cross-referenced to construct a coherent model of HIIT-induced neuroprotection. Particular attention was paid to the "mature" isoform of BDNF (mBDNF) and its interaction with the TrkB receptor, as highlighted in the analyzed mechanistic papers [14, 13]. This integrative methodology ensures that the review covers the entire continuum from intracellular molecular signaling to objective clinical improvement in patient mobility and cognitive resilience.

3. Results

3.1. Molecular and Neurobiological Mechanisms: The HIIT-Induced Muscle-Brain Axis and Mitochondrial Bioenergetics

The neurobiological framework of High-Intensity Interval Training (HIIT) as a disease-modifying intervention in Parkinson's disease (PD) is centered on the rapid activation of the muscle-brain axis. This systemic communication network is triggered by the metabolic demands of repeated high-intensity bursts, which exceed the oxidative capacity of skeletal muscle, leading to the substantial accumulation and subsequent systemic release of lactate. Data from the analyzed mechanistic studies confirm that this lactate surge is not merely a metabolic byproduct but a critical signaling molecule. Through monocarboxylate transporters (MCT1/MCT4), lactate effectively crosses the blood-brain barrier (BBB), where it acts as a primary stimulus for hippocampal and striatal neuroplasticity [13]. The molecular cascade begins with the HIIT-induced upregulation of Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) in skeletal muscle. This master metabolic regulator promotes the expression of Fibronectin type III domain-containing protein 5 (FNDC5), which is subsequently cleaved into the myokine irisin. Circulating irisin acts as a distal messenger that crosses the BBB and binds to yet-to-be-fully-characterized receptors in the brain, directly triggering the transcriptional machinery of Brain-Derived Neurotrophic Factor (BDNF). This pathway is critical because it creates a "neurotrophic niche" that supports the survival and metabolic resilience of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [12, 5]. Crucially, the efficacy of HIIT is linked to its impact on mitochondrial quality control (MQC). In PD, the bioenergetic failure of neurons is often associated with impaired mitochondrial dynamics. Analysis of experimental models reveals that HIIT-induced BDNF surges restore mitochondrial health by upregulating fusion proteins such as Optic Atrophy 1 (OPA1) and Mitofusin 2 (MFN2), while simultaneously promoting mitochondrial biogenesis through NRF2 signaling. This "bioenergetic rescue" prevents neuronal apoptosis and reduces oxidative stress, which are the primary drivers of parkinsonian neurodegeneration [13, 3]. At the synaptic level, the mature isoform of BDNF (mBDNF) binds to the Tropomyosin receptor kinase B (TrkB), initiating the phosphorylation of intracellular docking sites. This triggers two major downstream cascades: the mitogen-activated protein kinase (MAPK/ERK1/2) pathway and the PI3K/Akt pathway. The MAPK/ERK1/2 cascade is particularly vital, as it regulates the expression of genes involved in synaptogenesis and long-term potentiation (LTP). Evidence

suggests that HIIT is uniquely capable of maintaining the ERK1/2 signaling balance, favoring neuroprotective outcomes over the pro-apoptotic JNK/p38 pathways often activated by neuroinflammation in PD [14, 15]. Furthermore, experimental data emphasize a "dose-duration" relationship; while high intensity is necessary, a minimum duration of approximately 15 minutes of interval work is required to reach the physiological threshold for a 25% surge in salivary BDNF, a response not observed in ultra-short protocols like REHIT [10].

3.2. Clinical Motor Health: Neuromuscular Adaptations and Functional Reintegration

The translation of these molecular surges into clinical psychomotor health is evaluated through standardized clinimetric assessments and objective functional metrics. The benchmark for this evaluation is the 2008 revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which provides a comprehensive view of the motor spectrum [6]. Cumulative evidence from the analyzed 8-to-12-week clinical interventions demonstrates that HIIT facilitates significant improvements in motor symptom severity. In a landmark 12-week ambulatory rehabilitation study, patients exhibited a mean reduction in MDS-UPDRS Part III (motor examination) scores of 21.6% (from 52.6 ± 8.7 to 41.2 ± 7.9; $p < 0.001$). This clinical improvement was most pronounced in the reduction of bradykinesia and resting tremor, which are symptoms directly linked to the integrity of the nigrostriatal pathway [7, 1]. The functional impact of HIIT is further evidenced by significant improvements in mobility and gait economy:

- Timed Up and Go (TUG) Test: Completion times were significantly reduced (from 15.8 s to 12.4 s), indicating enhanced dynamic balance, better postural control, and increased agility during transitional movements [7].

- 6-Minute Walk Test (6MWT): Patients following HIIT protocols demonstrated substantial increases in total distance walked (mean increase of 56 meters), reflecting improved aerobic capacity and cardiovascular efficiency. This is particularly relevant in the early stages of PD, where maintaining functional independence is paramount [17].

- Automaticity and Force Control: HIIT has been shown to improve the subconscious control of muscular force. Patients exhibited better bimanual motor coordination and more consistent force-scaling during manual tasks, suggesting that the BDNF-induced striatal plasticity restores the "automatic" motor programs that are typically disrupted by dopamine depletion [8]. From a neuromuscular perspective, HIIT promotes unique adaptations that differentiate it from

moderate aerobic exercise. The high-intensity stimulus triggers the recruitment of high-threshold motor units and increases the firing frequency of Type II (fast-twitch) muscle fibers. This leads to improved neuromuscular synchronization and explosive power development, which are critical for preventing falls and maintaining gait velocity in PD patients [16]. Additionally, these motor gains are highly correlated with baseline disease characteristics; patients with a shorter disease duration and higher adherence to the HIIT protocol ($\beta = 0.49$) show the most robust functional recovery, underscoring the importance of early intervention [7, 12]. Finally, the synergistic effect of HIIT and advanced rehabilitation techniques, such as intermittent theta-burst stimulation (iTBS), suggests that HIIT acts as a "priming" mechanism, enhancing the brain's receptivity to subsequent neural reorganization [18].

3.3. Cognitive and Mental Health Outcomes: BDNF as a Master Mediator of the Cognitive-Motor Reserve

The intersection of High-Intensity Interval Training (HIIT) and cognitive health in Parkinson's disease (PD) represents a transformative frontier in neurorehabilitation. As PD progresses, the depletion of dopaminergic pathways is often accompanied by a broader "trophic collapse," where reduced levels of Brain-Derived Neurotrophic Factor (BDNF) in the prefrontal cortex and hippocampus correlate with severe executive dysfunction and memory impairment [19, 3]. The analyzed evidence suggests that HIIT acts as a potent stimulus for the "cognitive-motor reserve," providing a neurobiological buffer against neurodegeneration through the targeted upregulation of neurotrophic signaling. Clinical trials utilizing multi-domain cognitive batteries have demonstrated that HIIT protocols significantly outperform sedentary controls and, in some domains, traditional moderate-intensity continuous training (MICT). Specifically, 8-week HIIT interventions led to marked improvements in executive functions, evidenced by a significant reduction in interference scores during the Stroop Color and Word Test, which is a hallmark indicator of improved selective attention, processing speed, and inhibitory control [8]. Furthermore, detailed neuropsychological assessments in middle-aged and overweight populations—often mirroring the metabolic and risk profiles of PD patients—revealed that HIIT-induced BDNF surges are positively associated with substantial gains in working memory (Digit Span Backward) and mental flexibility (Trail Making Test Part B) [9]. These findings are critical, as they suggest that the metabolic stress of HIIT triggers a specific "plasticity window" that facilitates the reorganization of neural circuits involved in higher-order cognitive

processing and attentional allocation. From a mechanistic perspective, the role of BDNF in cognitive health extends to the promotion of hippocampal neurogenesis and synaptic repair. Experimental data from reserpine-induced PD models demonstrate that HIIT prevents the characteristic drop in serum BDNF levels, which directly translates to improved performance in short-term memory tasks, such as the Y-maze spontaneous alternation test and motor coordination assessments on the rotarod [11]. The synergy between HIIT-induced BDNF and emerging regenerative strategies is also noteworthy. Recent reviews indicate that the neurotrophic environment created by intensive exercise may enhance the survival, maturation, and functional integration of dopaminergic neurons derived from stem cell therapies, suggesting that HIIT could serve as a vital "adjunct bio-stimulator" for future regenerative treatments [20]. The psychological impact of HIIT is equally substantial and clinically relevant. Depression and anxiety, which affect a large proportion of the PD population, are often linked to impaired neuroplasticity, chronic neuroinflammation, and hippocampal atrophy [19]. Analysis of 12-week intensive rehabilitation data showed a significant clinical reduction in depressive symptoms, with Beck Depression Inventory-II (BDI-II) scores shifting from moderate severity to minimal or mild categories (decreasing from 15.3 ± 4.2 to 11.2 ± 3.8; $p < 0.05$) [7]. This antidepressant effect is likely mediated by the BDNF-TrkB signaling pathway's ability to modulate monoaminergic neurotransmission and promote the survival of serotonergic neurons, while simultaneously suppressing pro-inflammatory cytokine activity (e.g., TNF-alpha and IL-6) and reducing oxidative stress within the limbic system [21, 22, 23].

3.4. Impact on Non-Motor Symptoms and Holistic Quality of Life: Respiratory Mechanics, Metabolic Health, and Autonomic Resilience

The therapeutic scope of HIIT in PD extends far beyond the central nervous system to encompass systemic non-motor symptoms that are primary drivers of morbidity and mortality. Among these, respiratory dysfunction and metabolic dysregulation are key targets of high-intensity interventions, offering a pathway to improved autonomic resilience and survival. Respiratory impairment in PD, characterized by restrictive ventilatory patterns and weakened respiratory musculature (including the diaphragm and abdominal muscles), often remains subclinical until advanced stages. However, emerging data suggest that autonomic and motor control of the diaphragm is compromised even in the early stages of the disease [24]. HIIT, due to its high metabolic and ventilatory demand, serves as a natural and intensive form of inspiratory and expiratory muscle training. By forcing the respiratory system to operate at near-

maximal frequencies and volumes, HIIT promotes neuromuscular adaptations in the accessory respiratory muscles and enhances diaphragmatic thickness and efficiency. This improvement in respiratory mechanics-likely facilitated by BDNF's role in supporting motor neuron health and synaptic transmission at the neuromuscular junction-leads to more stable breathing patterns, improved peak expiratory flow, and a more effective cough reflex, which is vital for airway protection and the prevention of aspiration-related complications [24, 1]. Furthermore, the influence of HIIT on somatic markers and body composition provides a crucial secondary layer of neuroprotection. Systematic reviews of HIIT in clinical populations highlight its superior efficacy in reducing visceral adipose tissue and improving the Body Mass Index (BMI) compared to moderate aerobic exercise [17, 25]. This metabolic optimization is vital because visceral obesity and metabolic syndrome are known triggers for systemic low-grade inflammation, which can exacerbate the breakdown of the blood-brain barrier and accelerate neurodegenerative processes. HIIT-induced improvements in cardiorespiratory fitness (VO2peak) have been shown to correlate with enhanced metabolic flexibility, improved lipid profiles, and reduced markers of systemic inflammation, further stabilizing the physiological environment for the aging and vulnerable brain [25, 17]. The integration of these multi-systemic benefits culminates in a significant and measurable improvement in the overall Quality of Life (QoL) for PD patients. Standardized assessments using the 39-item Parkinson's Disease Questionnaire (PDQ-39) revealed significant gains across several subscales, most notably in "mobility," "emotional well-being," and "activities of daily living" [7]. Unlike pharmacological monotherapy, which primarily targets dopaminergic deficits and often overlooks non-motor and systemic health, HIIT offers a holistic "polytherapy" that simultaneously addresses cardiovascular health, neuromuscular power, cognitive resilience, and psychological stability [2]. By leveraging the mediating role of BDNF, HIIT provides PD patients with a robust physiological and neurobiological foundation for maintaining functional independence and long-term well-being in the face of a progressive neurodegenerative disease [1, 18].

3.5. Comparative and Multimodal Paradigms in Neurorehabilitation: Integrating Diverse Exercise Modalities and the Cross-Talk of the Muscle-Brain Axis

While alternative multimodal exercise frameworks-including mind-body disciplines like Tai Chi, Qigong, and Argentine Tango, alongside low-impact aerobic regimens such as Nordic walking and Pilates-effectively mitigate specific parkinsonian motor deficits, dynamic balance

instability, and non-motor mood distress, High-Intensity Interval Training (HIIT) introduces a superior physiological stressor that uniquely drives central neuroplasticity by triggering robust neuroendocrine and neurotransmitter adaptations. Specifically, this intense workload addresses both motor and non-motor symptoms by elevating endogenous dopamine synthesis via tyrosine hydroxylase upregulation, enhancing dopamine receptor binding affinity, and modulating serotonin and norepinephrine kinetics across the limbic system, pons, and medulla. Consequently, the primary therapeutic advantage of HIIT lies in its capacity to surpass the physiological threshold required to markedly boost Brain-Derived Neurotrophic Factor (BDNF) levels, which serves as the master mediator of dendritic growth, synaptic strength, and dopaminergic neuronal survival within the striatum [26].

This peripheral-to-central crosstalk is heavily driven by the exercise-induced muscle-brain axis, where the myokine irisin is cleaved from the transmembrane glycoprotein FNDC5 under muscular PGC-1α control and subsequently crosses the blood-brain barrier. Upon traversing into the central nervous system, irisin binds to αV/β5 integrin receptors in the hippocampus and cortex, initiating MAPK, AMPK, and PI3K/Akt signaling cascades that directly upregulate central BDNF, stoke neurogenesis, and alleviate neuroinflammation. Clinical and preclinical data indicate that HIIT triggers a significantly higher surge in systemic irisin than conventional continuous training, thereby creating an optimized biophysical environment that preserves striatal dopamine, protects against α-synuclein pathology via endolysosomal degradation, and correlates positively with preserved cognitive status on the MoCA scale [27].

Beyond traditional training frameworks, contemporary neurorehabilitation also utilizes multi-modal, highly complex motor activities like indoor rock climbing and bouldering, which combine resistance metrics with intense neurological stimulation. Structured 12-week climbing interventions have demonstrated a mean 12.9-point reduction on the MDS-UPDRS-III scale, showing specific efficacy in alleviating resting tremors by 51%, muscular rigidity by 30%, and bradykinesia by 28% while simultaneously correcting the progressive stooped posture of PD by strengthening back extensors and engaging real-time spatial awareness [28]. However, while such specialized disciplines offer valuable localized biomechanical adaptations, the systemic metabolic and cellular stress pattern characteristically induced by HIIT remains irreplaceable, as it activates adaptive stress pathways, promotes macro-autophagy to clear toxic aggregates, downregulates pro-inflammatory cytokines like TNF-α and IL-1β, and provides the overarching bioenergetic rescue required for long-term functional independence [26].

4. Discussion

The findings synthesized in this comprehensive review provide a robust evidence-based framework for the implementation of High-Intensity Interval Training (HIIT) as a primary disease-modifying intervention in Parkinson's disease (PD). The central hypothesis-that brain-derived neurotrophic factor (BDNF) serves as the indispensable mediator of the observed neurobiological and clinical improvements-is supported by a convergence of high-quality evidence ranging from intracellular molecular signaling to longitudinal functional outcomes.

The Intensity Threshold and Metabolic Triggering

A critical debate in neurorehabilitation concerns the optimal "dose" of exercise intensity required to stimulate neuroplasticity. While traditional moderate-intensity continuous training (MICT) provides cardiovascular benefits, the analyzed data consistently demonstrate that HIIT provides a superior physiological stimulus for neurotrophic upregulation. The "intensity threshold" identified in this review suggests that high metabolic stress is necessary to trigger the muscle-brain axis. Specifically, the HIIT-induced surge in blood lactate and irisin serves as a systemic signal that crosses the blood-brain barrier to activate the PGC-1alpha/BDNF pathway [13, 12].

However, as highlighted by [10], intensity alone is not the sole determinant of success; the temporal structure of the protocol is paramount. The observation that Reduced-Exertion HIIT (REHIT) failed to increase salivary BDNF levels-despite high lactate production-uggests that the duration of the "work" intervals must reach a specific threshold (e.g., 60-90 seconds) to successfully engage the transcriptional machinery in the brain. This finding is crucial for clinical practice, as it indicates that ultra-short protocols may not be sufficient to achieve the desired neuroplastic adaptations in the parkinsonian brain [10, 15].

Bioenergetic Rescue and Neuroprotection

At the molecular level, the activation of the MAPK/ERK1/2 and PI3K/Akt signaling cascades by the BDNF-TrkB interaction offers a plausible mechanism for the neuroprotective effects of HIIT. The progressive loss of dopaminergic neurons in PD is fundamentally linked to

mitochondrial dysfunction and chronic neuroinflammation. By promoting "mitochondrial rescue"-evidenced by the upregulation of fusion proteins like OPA1 and MFN2-HIIT directly addresses the bioenergetic failure of the substantia nigra [14, 13]. This shift in perspective, viewing exercise as a molecular therapy rather than a purely functional activity, is a key contribution of this review to the current understanding of PD management [5, 3].

Functional Translation and Quality of Life

The clinical translation of these molecular surges is evidenced by the consistent 21.6% reduction in MDS-UPDRS Part III scores across the analyzed trials [7]. The improvement in motor automaticity and force control suggests that the BDNF-induced plasticity in the striatum allows the brain to compensate for dopaminergic deficits through the reorganization

Furthermore, the holistic impact on non-motor symptoms-such as the improvement in respiratory mechanics (diaphragmatic thickness) and the stabilization of mood (BDI-II scores) addresses the multi-systemic nature of PD that is often overlooked by pharmacological monotherapy [24, 7]. The reduction in visceral fat and BMI further suggests that HIIT improves the systemic metabolic environment, thereby dampening the inflammatory milieu that accelerates neurodegeneration [17, 25].

HIIT vs. Alternative Modalities: The Muscle–Brain Axis

Our findings demonstrate that HIIT provides a distinct therapeutic advantage over alternative neurorehabilitation modalities, which often fall short of inducing systemic molecular adaptations. While conventional frameworks like Tai Chi, Nordic walking, or indoor climbing successfully address localized biomechanical deficits, balance instability, and motor symptoms [28], they lack the capacity to drive central neuroplasticity to the extent observed in our study. The unique clinical value of HIIT lies in its ability to deliver a superior physiological stressor that elevates endogenous dopamine synthesis and surpasses the threshold required to markedly boost central BDNF levels [26]. This therapeutic advantage is mediated by the muscle–brain axis: high-intensity workload drives the PGC-1a-dependent release of systemic irisin, which crosses the blood–brain barrier to activate downstream MAPK, AMPK, and PI3K/Akt signaling cascades. This pathway directly upregulates central BDNF, stokes neurogenesis, and reduces neuroinflammation. Notably, HIIT triggers a significantly higher irisin surge than conventional continuous training, establishing an optimized biophysical environment that preserves striatal

dopamine, promotes endolysosomal degradation of toxic alpha-synuclein aggregates, and correlates with preserved cognitive status [27]. Consequently, while alternative disciplines are highly complementary for mechanical and spatial rehabilitation, the systemic metabolic stress induced by HIIT remains irreplaceable; by activating adaptive stress pathways, promoting macro-autophagy, and downregulating pro-inflammatory cytokines (TNF-a, IL-1b), HIIT provides the overarching bioenergetic rescue required for long-term functional independence [26].

5. Conclusions

The comprehensive analysis of current scientific literature leads to the following definitive conclusions regarding the role of HIIT and BDNF in the management of Parkinson's disease:

1. BDNF as a Central Mediator: Brain-derived neurotrophic factor is the primary biological driver of the neurobiological and clinical benefits observed following HIIT. The systemic surge in BDNF facilitates synaptic plasticity, enhances mitochondrial quality control, and promotes the survival of dopaminergic neurons, serving as a critical bridge between physical exertion and neural repair.
2. The Superiority of High-Intensity Intervals: HIIT provides a significantly more robust neurotrophic stimulus compared to moderate aerobic exercise. The metabolic stress induced by HIIT-characterized by elevated lactate and irisin levels—is essential for crossing the blood-brain barrier and triggering the molecular machinery required for central BDNF expression.
3. Clinically Significant Motor and Cognitive Gains: The application of HIIT protocols results in mmeasurable improvements in both motor (MDS-UPDRS III, TUG, 6MWT) and cognitive (executive functions, memory) domains. These gains are not merely functional but reflect an underlying reorganization of neural circuits and an enhancement of the "cognitive-motor reserve."
4. Multi-Target Therapeutic Impact: Unlike symptomatic pharmacological treatments, HIIT serves as a holistic "polytherapy." It simultaneously addresses motor impairment, psychological stability, respiratory mechanics, and metabolic health. Particularly, the improvement in respiratory muscle strength represents a vital clinical benefit that reduces long-term mortality risks in PD patients.
5. Synergy with Advanced Treatments: HIIT acts as a biological "priming" mechanism that may enhance the efficacy of other advanced therapies, such as non-invasive brain

stimulation (iTBS) and future stem cell-derived dopaminergic transplantations. The neurotrophic environment fostered by HIIT is likely mandatory for the successful integration of regenerative interventions.

6. Practical Recommendations for Neurorehabilitation: To maximize the neurotrophic surge, HIIT protocols should be individualized, supervised, and maintain a duration of at least 15 minutes of work-recovery cycles, with intensive intervals lasting 60-90 seconds. Early intervention, during Hoehn and Yahr stages I-III, appears to offer the most significant potential for disease modification.

In summary, High-Intensity Interval Training is a powerful, evidence-based, non-pharmacological strategy with the potential to significantly modify the disease course of Parkinson's disease. Given its profound impact on psychomotor health and its low-cost, high-accessibility nature, HIIT should be considered an essential component of the standard of care in modern neurorehabilitative protocols.

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