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Neuroprotective Effect of High Intensity Interval Training Towards Neurodegenerative Disease: A Literature Review

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A B S T R A C T

Neurodegenerative disease is a disease that arise with symptoms of cognitive and movement deficit. Neurodegenerative disease has cause morbidity among patients due to limitation of living function. High-intensity interval training (HIIT) is a type of physical training that is characterized by alternating periods of intense exercise and recovery has emerged as a promising intervention in the context of neurodegenerative diseases, with growing evidence suggesting its potential to positively influence neurobiological mechanisms. HIIT has been shown to enhance brain-derived neurotrophic factor (BDNF) levels, promote neurogenesis, and improve synaptic plasticity, all of which are critical for maintaining cognitive function and neuronal health. Studies indicate that HIIT may mitigate neuroinflammation, reduce oxidative stress, and enhance mitochondrial function, thereby potentially slowing the progression of neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Furthermore, HIIT has been associated with improved cerebral blood flow and increased hippocampal volume, which are linked to better memory and executive function. While the exact mechanisms remain under investigation, the neuroprotective effects of HIIT highlight its potential as a non-pharmacological strategy to support brain health and combat the neurobiological decline associated with neurodegenerative disease.

Keywords: High intensity Interval Training, Neurobiology, Pathophysiology, Neurodegenerative

1. INTRODUCTION

Neurodegenerative diseases are a group of disorders characterized by the progressive degeneration and loss of structure or function of neurons in the central nervous system (CNS) or peripheral nervous system (PNS). This neuronal damage often leads to cognitive decline, motor dysfunction, and, in many cases, premature death. These diseases are typically chronic, progressive, and currently incurable, with symptoms worsening over time as more neurons are affected[1]. Several examples of neurodegenerative diseases are Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease, and Multiple Sclerosis[2]. Epidemiology of neurodegenerative diseases variates according to the type of disease. Alzheimer's is the most common form of dementia, accounting for 60-80% of all dementia cases. Parkinson's is the second most common neurodegenerative disorder after Alzheimer's. Approximately 1 million people in the U.S. and 10 million worldwide are living with Parkinson's. While other diseases are rarer to be found[3]. Neurodegenerative diseases have created a huge burden in patient aspect and also economic impact. Limitation in cognitive and motoric function leads to huge burden and leads to morbidity of other disease such as metabolic, cardiovascular, and psychiatric disorder. In economic aspect, neurodegenerative diseases causing a higher burden of healthcare expenditure. Study has shown that increase of 25-30% in household expenditure for family who live with neurodegenerative diseases patients. In hospital aspect, increase of hospital expenditure, bed occupancy, and remission rate also found to be increased due to complications and disease burden of neurodegenerative diseases[4,5]. High-Intensity Interval Training (HIIT) is a form of exercise that alternates between short bursts of intense physical activity and periods of lower-intensity recovery or rest. This training method is designed to maximize cardiovascular and metabolic benefits in a shorter amount of time compared to traditional moderate-intensity continuous exercise[6]. Typically, a HIIT session lasts between 10 to 30 minutes and includes exercises such as sprinting, cycling, or bodyweight movements performed at near-maximum effort for 20-60 seconds, followed by recovery periods of equal or longer duration[7]. HIIT has gained popularity due to its efficiency and effectiveness in improving aerobic and anaerobic fitness, increasing insulin sensitivity, and promoting fat loss. Additionally, HIIT has been shown to enhance mitochondrial function, reduce blood pressure, and improve overall cardiovascular health[8]. HIIT has shown promising potential in mitigating the progression and symptoms of neurodegenerative diseases. By promoting the release of brain-derived neurotrophic factor (BDNF), HIIT enhances neuroplasticity, synaptic function, and the survival of neurons, which are critical for maintaining cognitive and motor functions. HIIT also reduces neuroinflammation and oxidative stress, two key contributors to neuronal damage in conditions like Alzheimer's and Parkinson's disease. Additionally, HIIT improves cerebral blood flow and mitochondrial function, supporting energy metabolism in the brain. These neuroprotective effects suggest that HIIT could serve as a non-pharmacological intervention to slow disease progression, improve quality of life, and preserve cognitive and motor abilities in individuals with neurodegenerative disorders[9-12]. This review will analyze further mechanism in neurobiology about HIIT effect towards neurodegenerative diseases.

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2. METHOD

This journal is written in literature review method. This journal comprehensively understands about neurodegenerative diseases, HIIT, and effect of HIIT in neurodegenerative diseases. 58 journals are used as main data basis of this discussion. Journals that used are published with last 10 years and published in international journal index such as Google Scholar, NCBI, PMC, PubMed, and NIH. Keywords that used in finding resources used in this journal are neurodegenerative diseases, neurobiology, high intensity interval training, and pathophysiology.

3. DISCUSSION

3.1 Neurodegenerative Diseases: Definition and Pathophysiology

Neurodegenerative diseases are a group of disorders characterized by the progressive degeneration and loss of structure or function of neurons in the central or peripheral nervous system. These conditions often lead to cognitive decline, motor dysfunction, and behavioral changes, depending on the affected brain regions. Common examples include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The underlying mechanisms typically involve protein misfolding, oxidative stress, mitochondrial dysfunction, and neuroinflammation, though exact causes vary by disease. Most neurodegenerative disorders are incurable, with treatments focusing on symptom management and slowing progression. Age is the primary risk factor, but genetic mutations, environmental influences, and lifestyle factors may also contribute to their development[13-15].

There are several mechanisms lie that contribute to development of neurodegenerative diseases. As every subtype of neurodegenerative diseases has unique pathologic mechanism, it could be understood that each disease has similar features that is distinct in pathophysiology of neurodegenerative diseases. First hallmark of many neurodegenerative diseases is the accumulation of misfolded proteins that form toxic aggregates. In AD, extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (composed of hyperphosphorylated tau protein) disrupt synaptic function and trigger neuronal death. In PD, alpha-synuclein aggregates into Lewy bodies, impairing dopaminergic neurons in the substantia nigra. Similarly, in HD, mutant huntingtin protein forms cytoplasmic and nuclear inclusions, leading to striatal neuron degeneration. In ALS, misfolded superoxide dismutase 1 (SOD1) and TAR DNA-binding protein 43 (TDP-43) contribute to motor neuron toxicity. These protein aggregates interfere with normal cellular processes, including synaptic transmission, axonal transport, and proteostasis[16-19].

Second mechanism is mitochondrial dysfunction and oxidative stress. Neurons are highly metabolically active and rely on mitochondria for energy production. In neurodegenerative diseases, mitochondrial impairment leads to ATP depletion, increased reactive oxygen species (ROS), and oxidative damage. In PD, mitochondrial complex I dysfunction exacerbates dopaminergic neuron vulnerability. In AD, Aβ disrupts mitochondrial membranes, while in HD, mutant huntingtin directly impairs mitochondrial dynamics. Excessive ROS production damages lipids, proteins, and DNA, further accelerating neuronal degeneration[20-22].

Third mechanism is neuroinflammation. Chronic neuroinflammation plays a critical role in neurodegeneration. Microglia, the brain's resident immune cells, become overactivated in response to protein aggregates, releasing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and reactive oxygen species. While initially protective, sustained microglial activation leads to a toxic environment that exacerbates neuronal damage. Astrocytes also contribute by failing to support synaptic function and instead promoting inflammatory responses. In AD, microglial activation around Aβ plaques worsens tau pathology, while in PD, neuroinflammation in the substantia nigra accelerates dopaminergic neuron loss[23-25].

Fourth mechanism is impaired protein clearance pathway. The ubiquitin-proteasome system (UPS) and autophagy-lysosomal pathways are essential for clearing damaged proteins. In neurodegenerative diseases, these systems become dysfunctional, allowing toxic aggregates to accumulate. In PD, mutations in genes like *PARKIN* and *PINK1* disrupt mitophagy, leading to defective mitochondrial clearance. In AD, lysosomal dysfunction impairs Aβ and tau degradation. Similarly, in HD, impaired autophagy contributes to huntingtin aggregate persistence[26-28].

By each of mechanism explained above, neurodegenerative diseases progressed with synaptic dysfunction and neuronal death. Synaptic loss precedes neuronal death and is a key contributor to cognitive and motor deficits. Excitotoxicity due to excessive glutamate receptor activation leads to calcium overload and neuronal apoptosis, particularly in ALS and HD. Additionally, disrupted axonal transport, as seen in tauopathies like AD, impairs nutrient delivery and waste removal, further compromising neuron survival[29].

3.2 High Intensity Interval Training for Neurodegenerative Diseases

High-Intensity Interval Training (HIIT) is a form of cardiovascular exercise that alternates between short bursts of intense anaerobic activity and periods of lower-intensity recovery or rest. Typically lasting between 10 to 30 minutes, HIIT workouts maximize calorie burn, improve endurance, and enhance metabolic efficiency by pushing the body to near-maximum effort during the high-intensity phases[30]. This training method is highly efficient, as it elevates heart rate rapidly and induces excess post-exercise oxygen consumption (EPOC), leading to continued calorie expenditure after the workout. HIIT can be adapted to various exercises, including sprinting, cycling, bodyweight movements, and resistance training, making it a versatile and time-effective fitness strategy. There are several subtypes for HIIT. The most common type is traditional HIIT, which follows a fixed work-to-rest ratio, such as 30 seconds of all-out effort followed by 30 seconds of recovery. Another popular variation is Tabata, a strict 20-seconds-on, 10-seconds-off protocol repeated for four minutes, designed to maximize intensity and metabolic impact. EMOM (Every Minute on the Minute) HIIT involves performing a set number

of reps at the start of each minute, using the remaining time for rest before the next round begins. For endurance athletes, interval sprint training—such as alternating between 30-second sprints and one-minute jogs—improves both aerobic and anaerobic capacity. Meanwhile, circuit-based HIIT combines strength and cardio exercises in rapid succession with minimal rest, enhancing muscular endurance and fat loss. Some programs also incorporate pyramid HIIT, where work intervals gradually increase and then decrease in duration, adding variety and challenge. Each type offers unique benefits, allowing individuals to customize workouts based on preferences, fitness levels, and objectives[31-33].

HIIT may offer unique benefits for individuals with neurodegenerative diseases by enhancing brain function and slowing disease progression. HIIT's intense bursts of exercise followed by recovery periods stimulate the release of protein that supports neuron growth, synaptic plasticity, and cognitive function, which are key factors in combating neurodegeneration. For safety and effectiveness, modified HIIT protocols can be used, such as shorter high-intensity intervals (e.g., 20-30 seconds) paired with longer rest periods (e.g., 60 seconds), tailored to the individual's physical ability. Exercises like stationary cycling, seated marches, or resistance-based movements can be adapted to reduce fall risks while still elevating heart rate. Research suggests that HIIT may improve executive function, memory, and motor control by increasing blood flow to the brain and reducing inflammation. Further monitoring should be performed by fitness professionals to ensure proper intensity, minimizing injury risks, and to achieve highest benefit in improving neurodegenerative conditions[34-38].

3.3 Effect of High Intensity Interval Training in Neurobiology of Neurodegenerative Diseases

Application of HIIT in patients with neurodegenerative diseases in expectation to slow the disease progression and to maintain remain cognitive and motoric function, therefore establishing better quality of life. HIIT alternates short bursts of near-maximal exertion with recovery periods, inducing unique neurobiological adaptations that may counteract neurodegeneration. One of the most well-documented effects of HIIT is its ability to upregulate brain derived neurotrophic factor (BDNF), a key protein involved in neuronal survival, synaptic plasticity, and cognitive function. HIIT's intense bursts of activity trigger a rapid and sustained increase in circulating BDNF. The intermittent high-intensity bursts characteristic of HIIT create a unique metabolic challenge that appears particularly effective at upregulating BDNF expression compared to steady-state exercise. Exercise-induced BDNF upregulation occurs through calcium-dependent signaling cascades. During high-intensity exercise, muscle contractions release peripheral myokines (like irisin) that cross the blood-brain barrier and stimulate BDNF transcription.The BDNF-TrkB pathway activates downstream effectors (CREB, ERK, mTOR), promoting neuronal survival and dendritic arborization. This effect is especially crucial in Alzheimer's pathology, where BDNF not only enhances synaptic plasticity but also facilitates the clearance of toxic amyloid-beta aggregates through increased activity of neprilysin, a key amyloid-degrading enzyme. In Parkinson's, BDNF supports nigrostriatal dopamine neuron survival by enhancing mitochondrial function and reducing α-synuclein toxicity, which potentially slowing motor decline. The simultaneous HIIT-induced release of insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) creates a synergistic neurorestorative environment, promoting both neuronal survival and the angiogenesis necessary for maintaining cerebral blood flow in vulnerable brain regions[39-41].

In mitochondrial mechanism and oxidative stress, the alternating cycles of intense exertion and recovery during HIIT sessions create repeated metabolic challenges that stimulate mitochondrial biogenesis through activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signaling pathways. AMPK activation during high-intensity intervals increases PGC-1α expression 5-7 fold. SIRT1 deacetylase, induced by HIIT-mediated NAD+ elevation, further enhances PGC-1α activity. The effect of this pathway activation leads to Increases mitochondrial density by 20-30% in neuronal cells, upregulation of mitophagy receptors (PINK1/PARKIN), and stimulates superoxide dismutase and catalase production. his mitochondrial adaptation is particularly valuable in Parkinson's disease, where dopaminergic neurons in the substantia nigra are especially vulnerable to energy deficits. By enhancing the electron transport chain efficiency and boosting antioxidant defense mechanisms, HIIT helps neutralize the excessive reactive oxygen species that contribute to neuronal degeneration. The exercise-induced improvement in mitochondrial quality control mechanisms, including mitophagy, helps remove damaged mitochondria that might otherwise trigger apoptotic pathways. This mitochondrial rejuvenation effect may explain why HIIT has shown particular promise in Huntington's disease models, where mutant huntingtin protein directly impairs mitochondrial function[42-45].

The anti-inflammatory effects of HIIT add another layer of neuroprotection, addressing the chronic neuroinflammation that characterizes and exacerbates neurodegenerative conditions. The transient inflammatory response provoked by acute HIIT sessions appears to train the brain's immune system, leading to a long-term shift in microglial polarization from the pro-inflammatory M1 phenotype to the neuroprotective M2 phenotype. This immunological reprogramming reduces the chronic secretion of damaging cytokines like TNF-α and IL-6 while promoting the release of anti-inflammatory mediators such as IL-10. The exercise-modulated microglia become more efficient at clearing protein aggregates while less likely to initiate destructive neuroinflammatory cascades. Simultaneously, HIIT enhances the autophagy-lysosomal pathway, providing cells with improved machinery for disposing of misfolded proteins and damaged organelles, a process critically important across all major neurodegenerative disorders[46-48].

At the cerebrovascular level, HIIT induces robust adaptations that counteract the cerebral hypoperfusion and blood-brain barrier dysfunction common in neurodegeneration. The shear stress generated during high-intensity exercise bouts stimulates endothelial nitric oxide synthase activity, leading to improved vasodilation and cerebral blood flow regulation. This vascular remodelling extends to angiogenesis, with HIIT promoting the formation of new capillaries in brain regions particularly vulnerable to ischemic damage. The strengthened blood-brain barrier resulting from regular HIIT helps maintain the brain's delicate metabolic homeostasis by preventing the leakage of neurotoxic substances from the periphery while allowing efficient nutrient transport. These vascular effects may be especially relevant in vascular contributions to cognitive impairment and dementia[49-51].

The neurotransmitter-modulating effects of HIIT provide yet another therapeutic avenue, particularly for movement disorders like Parkinson's disease. The acute stress of high-intensity exercise triggers a substantial release of dopamine, noradrenaline, and serotonin, which may help compensate for

neurotransmitter deficits in neurodegenerative conditions. Over time, HIIT appears to upregulate dopamine receptor sensitivity and improve the efficiency of neurotransmitter reuptake mechanisms. In Huntington's disease models, HIIT has been shown to help restore balance in the basal ganglia circuitry by modulating GABAergic transmission, offering potential benefits for motor control. The cumulative effect of these neurobiological adaptations is the creation of a more resilient neural environment that can better withstand and compensate for the pathological processes driving neurodegeneration, potentially slowing disease progression and preserving cognitive and motor function for longer periods[52-54].

3.4 Study of High Intensity Interval Training and Neurodegenerative Diseases

There are several studies that have been conducted to determine the effect of HIIT towards patients with neurodegenerative diseases. Clinical studies have been done in patients with PD, while for AD is investigated through animal model trial. These studies outcome variates in cognitive function, motoric function, and also biomarkers hallmark. Study by Gomes et al., explores the effects of HIIT on both motor and non-motor symptoms in individuals with PD, as well as potential blood-based biomarkers linked to exercise response. Using a single-case experimental design with a crossover approach, the research highlights the variability in individual responses to HIIT, emphasizing that not all participants experienced the same benefits. Some individuals showed significant improvements in motor function (e.g., gait, balance) and non-motor symptoms (e.g., fatigue, mood), while others had minimal or no changes. Additionally, the study examined biomarkers such as brain-derived neurotrophic factor (BDNF) and inflammatory markers, finding that certain biological responses correlated with clinical improvements in some participants[55].

Other study among patients with PD was conducted by Malczynska-Sims et al., found that HIIT influences systemic inflammation in individuals PD, given that neuroinflammation plays a key role in disease progression. The researchers conducted a controlled trial where PD patients underwent a structured HIIT program, and inflammatory biomarkers—such as cytokines (e.g., TNF-α, IL-6, IL-1β) and C-reactive protein (CRP)—were measured before and after the intervention. The findings revealed that HIIT led to a significant reduction in pro-inflammatory markers, suggesting an anti-inflammatory effect of high-intensity exercise in PD. Additionally, participants showed improvements in motor symptoms (e.g., bradykinesia, balance) which correlated with the observed decrease in inflammation. The study proposes that HIIT may help mitigate PD-related neurodegeneration by modulating immune responses and reducing chronic inflammation. These results highlight the potential of exercise not only as a symptomatic therapy but also as a disease-modifying intervention in Parkinson's[56].

Another study investigated HIIT effect in mice that is modeled after AD. The researchers induced AD-like pathology by administering amyloid-beta (Aβ1-42) peptides, which are associated with neuronal damage and cognitive decline in AD. The rats were then subjected to an extremely short but intense HIIT protocol—just 8 minutes per day—over a set period. The findings revealed that this minimal yet high-intensity exercise significantly reduced neurodegeneration, improved cognitive function (assessed through behavioral tests), and decreased amyloid-beta plaque accumulation in the brain. Additionally, the study observed enhanced neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which supports neuronal survival and synaptic plasticity. These results suggest that even very brief bouts of high-intensity exercise may have a potent neuroprotective effect in AD, potentially by promoting brain health, reducing toxic protein buildup, and enhancing neurotrophic support. The study highlights the potential of time-efficient exercise interventions as a therapeutic strategy for Alzheimer's disease[57].

Lambertus, Geisler, and Morland investigates how different exercise intensities influence the neurogenesis in the adult brain, particularly in the hippocampus—a region critical for learning and memory. Using an animal model, the researchers compared the effects of HIIT with moderate-intensity continuous exercise (MICE) on markers of neurogenesis, BDNF levels and the proliferation of neural progenitor cells. The findings revealed that HIIT was significantly more effective than MICE in promoting neurogenesis, likely due to the greater physiological stress and metabolic demands imposed by high-intensity bursts, which enhance BDNF release and other growth factors. Additionally, HIIT led to improved cognitive performance in memory-related tasks, further supporting its superior impact on brain plasticity. These results suggest that short, intense bouts of exercise may be more efficient than longer, moderate workouts in stimulating brain repair and cognitive function, offering potential implications for optimizing exercise regimens to combat neurodegenerative diseases and age-related cognitive decline[58].

4.. CONCLUSION

The promising role of HIIT in mitigating neurodegeneration through multiple neurobiological mechanisms. Evidence suggests that HIIT enhances neurogenesis, upregulates neurotrophic factors (such as BDNF), reduces neuroinflammation, and decreases pathological protein accumulation (e.g., amyloid-beta in Alzheimer's or alpha-synuclein in Parkinson's). Additionally, HIIT improves cerebral blood flow, synaptic plasticity, and cognitive function, making it a potent non-pharmacological intervention for diseases like Alzheimer's and Parkinson's. While animal and preliminary human studies show robust neuroprotective effects, further clinical trials are needed to establish optimal HIIT protocols and long-term benefits. Nevertheless, the current findings underscore HIIT's potential as a time-efficient, accessible, and powerful strategy to combat neurodegenerative decline, emphasizing the importance of integrating exercise into preventive and therapeutic approaches.

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