Review

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Review

Exercise-Induced Neuroplasticity: Adaptive Mechanisms and Preventive Potential in Neurodegenerative Disorders

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Abstract: Background/Objectives: Neurodegenerative diseases represent a growing global health challenge with limited therapeutic options. Physical exercise has emerged as a promising non-pharmacological intervention with potential neuroprotective effects. This narrative review examines the molecular, structural, and functional mechanisms through which exercise induces neuroplasticity and their implications for neurodegenerative disease prevention. **Methods**: This narrative review synthesized evidence from molecular, animal, and human studies on exercise-induced neuroplasticity and neurodegenerative disease prevention. We conducted a comprehensive literature search of peer-reviewed publications spanning molecular mediators, structural and functional adaptations, neuroimmune pathways, direct effects on pathological features, clinical and epidemiological evidence, and translational considerations. **Results**: Exercise induces neuroplasticity through multiple complementary pathways, including enhanced neurotrophic factor signaling, optimized neuroendocrine responses, epigenetic modifications, and improved metabolic signaling. These molecular changes support structural and functional adaptations, including hippocampal neurogenesis, enhanced synaptic plasticity, improved cerebrovascular function, and optimized network connectivity. Exercise directly impacts pathological features of neurodegenerative diseases by reducing protein aggregation, attenuating excitotoxicity and oxidative stress, and enhancing mitochondrial function. Clinical evidence consistently demonstrates associations between physical activity and reduced neurodegenerative risk, with intervention studies supporting causal benefits on cognitive function and brain structure. **Conclusions**: Exercise represents a multi-target intervention that addresses several pathological mechanisms simultaneously across various neurodegenerative conditions. Optimizing preventive efficacy requires consideration of exercise parameters, individual characteristics, and implementation strategies. Future research should focus on mechanistic gaps, biomarker development, and precision approaches that tailor interventions to individual risk profiles. Exercise's accessibility, minimal side effects, and multiple health benefits position it as a promising strategy to reduce the burden of neurodegenerative disease.

Keywords: neuroplasticity; exercise; neuroprotection; neurodegeneration; BDNF; inflammation; cognitive reserve; prevention; Alzheimer's disease; Parkinson's disease

1. Introduction

Neurodegenerative diseases represent a growing global health challenge, with conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis affecting millions worldwide [1]. These disorders are characterized by progressive neuronal loss and functional decline, with limited therapeutic options currently available. The personal, societal, and economic burden of

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these conditions is substantial and expected to increase dramatically as populations age [2]. This pressing reality has intensified the search for effective preventive strategies that could modify disease trajectories or delay onset.

Physical exercise has emerged as a promising non-pharmacological intervention with potential neuroprotective effects [3]. Epidemiological evidence consistently demonstrates that physically active individuals have reduced risk of cognitive decline and neurodegenerative disease development [4]. However, the biological mechanisms underlying these associations remain incompletely understood. The concept of neuroplasticity—the brain's capacity to adapt its structure and function in response to various stimuli—provides a framework for investigating how exercise might confer neuroprotection [5].

Neuroplasticity encompasses multiple processes occurring across molecular, cellular, and systems levels, including neurogenesis, synaptogenesis, angiogenesis, and changes in neural network connectivity [6]. Exercise has been shown to modulate these processes through various pathways involving neurotrophic factors, inflammatory mediators [7], metabolic signals, and epigenetic modifications [8]. Understanding these mechanisms is crucial for developing evidence-based exercise prescriptions and identifying potential therapeutic targets [9].

Despite significant advances in the field, several knowledge gaps persist regarding the optimal parameters of exercise (type, intensity, duration, and frequency) [5], the durability of exercise-induced adaptations [4], and variations in individual responsiveness. Additionally, the translation of mechanistic insights from animal models to human applications presents ongoing challenges. This narrative review aims to synthesize current evidence on the mechanisms through which exercise promotes neuroplasticity and their implications for neurodegenerative disease prevention.

We will examine the molecular mediators of exercise-induced neuroplasticity, structural and functional adaptations in the brain [10], neuroimmune and inflammatory pathways, direct effects on disease-specific pathological features, and clinical evidence supporting exercise as a preventive strategy. Furthermore, we will discuss translational implications for clinical practice and identify promising directions for future research. By integrating findings across these domains, this review seeks to advance our understanding of how exercise can be leveraged as a neuroprotective intervention against neurodegenerative disorders.

2. Molecular Mediators of Exercise-Induced Neuroplasticity

Exercise induces a complex cascade of molecular responses that drive neuroplasticity and potentially confer neuroprotection against neurodegenerative processes. These molecular mediators represent critical mechanisms through which physical activity may modify disease risk and progression. This section examines key signaling pathways activated by exercise that contribute to beneficial neuroplastic changes.

2.1. Neutrophic Factors

Brain-derived neurotrophic factor (BDNF) emerges as a central mediator in exercise-induced neuroplasticity [3,11]. Acute and chronic exercise consistently increase BDNF expression in the hippocampus and other brain regions in animal models [12]. In humans, peripheral BDNF levels rise following exercise sessions, with the magnitude of increase correlating with exercise intensity [13], [14]. BDNF binds primarily to tropomyosin receptor kinase B (TrkB), activating downstream signaling pathways including phosphatidylinositol 3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), and phospholipase C-γ (PLC-γ) [11]. These pathways promote neuronal survival, differentiation, and synaptic plasticity—processes particularly relevant to neurodegenerative disease prevention [15].

Other neurotrophic factors also respond to exercise stimuli. Insulin-like growth factor-1 (IGF-1) increases with exercise and can cross the blood-brain barrier to support neuronal growth and survival [16]. Notably, blocking IGF-1 signaling attenuates exercise-induced neurogenesis, suggesting its crucial role in mediating these effects [17]. Similarly, vascular endothelial growth factor (VEGF)

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increases with exercise and contributes to both angiogenesis and neurogenesis in the hippocampus [18]. The interactive effects between BDNF, IGF-1, and VEGF likely create a molecular environment conducive to neuroplasticity and neuroprotection [4,11].

2.2. Neuroendocrine Responses

Exercise activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in acute elevations of glucocorticoids that, when properly regulated, may enhance cognitive function and neuroplasticity [19]. Regular exercise appears to optimize HPA axis function, potentially counteracting the deleterious effects of chronic stress on brain health that have been implicated in neurodegenerative processes [20].

Exercise also stimulates the release of irisin, a myokine cleaved from fibronectin type III domain-containing protein 5 (FNDC5) in skeletal muscle [21]. Irisin can cross the blood-brain barrier and induce BDNF expression in the hippocampus, providing a direct muscle-brain communication pathway relevant to exercise-induced neuroplasticity [21,22]. Additionally, exercise-induced increases in circulating catecholamines may influence brain function through both direct and indirect mechanisms, including enhanced alertness and metabolic regulation [23].

2.3. Epigenetic Mechanisms

Emerging evidence indicates that exercise induces epigenetic modifications that regulate gene expression patterns favoring neuroplasticity [24]. DNA methylation changes in the BDNF gene promoter region occur with exercise, potentially underpinning sustained increases in BDNF expression [25]. Exercise also modulates histone modifications, particularly histone acetylation, which generally promotes a transcriptionally active chromatin state [26]. These epigenetic changes provide a mechanistic explanation for how transient exercise stimuli might lead to lasting effects on brain function and resilience against neurodegeneration [24,27].

2.4. Metabolic Signaling Pathways

Exercise activates several metabolic pathways with neuroplastic implications. AMP-activated protein kinase (AMPK), a cellular energy sensor activated during exercise, promotes mitochondrial biogenesis and metabolic efficiency in neurons [28]. Similarly, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) increases with exercise and regulates mitochondrial function while also influencing BDNF expression [29]. Exercise-induced activation of sirtuins, particularly SIRT1, may enhance neuroprotection through deacetylation of targets like PGC-1α and Forkhead box O (FOXO) transcription factors [30].

The mammalian target of rapamycin (mTOR) pathway, which regulates protein synthesis and cellular growth, is also modulated by exercise in ways that may support synaptic plasticity and neurogenesis [31]. Intriguingly, metabolic adaptations to exercise appear to shift brain metabolism toward enhanced efficiency and resilience, potentially countering the bioenergetic deficits observed in many neurodegenerative conditions [32,33].

Understanding these molecular mediators provides a foundation for developing targeted interventions that could simulate or enhance exercise benefits, particularly for individuals with limited exercise capacity. Furthermore, these mechanisms highlight potential biomarkers for monitoring exercise efficacy in clinical populations and suggest parameters that might optimize exercise prescription for neuroprotection.

3. Structural and Functional Adaptations

Exercise induces remarkable structural and functional adaptations in the brain that may underlie its neuroprotective effects against neurodegenerative processes. These adaptations occur across multiple time scales and brain regions, collectively enhancing neural resilience. This section examines

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the key exercise-induced structural and functional changes with particular relevance to neurodegenerative disease prevention.

3.1. Hippocampal Neurogenesis

One of the most well-documented effects of exercise on brain structure is enhanced adult hippocampal neurogenesis—the generation of new neurons in the dentate gyrus region of the hippocampus [34]. Rodent studies consistently demonstrate that voluntary wheel running increases neural progenitor cell proliferation, survival, and differentiation into mature neurons [34,35]. These new neurons integrate into existing circuits and contribute to hippocampal function, particularly pattern separation and memory formation [36].

The neurogenic effects of exercise appear dose-dependent, with moderate-intensity exercise typically producing optimal results [37]. Multiple mechanisms likely contribute to exercise-induced neurogenesis, including increased cerebral blood flow, enhanced neurotrophic factor signaling (particularly BDNF and IGF-1), and reduced inflammation [38,39]. While direct evidence of exercise-induced neurogenesis in humans remains challenging to obtain, indirect neuroimaging and peripheral biomarker studies support the translational relevance of these findings [40,41].

In the context of neurodegenerative diseases, enhanced hippocampal neurogenesis may provide a compensatory mechanism against neuronal loss and contribute to cognitive reserve—the brain's resilience against pathological insults [42]. Indeed, animal models of Alzheimer's and Parkinson's disease show that exercise can partially rescue impaired neurogenesis associated with these conditions [43].

3.2. Synaptic Plasticity and Dendritic Remodeling

Exercise enhances synaptic plasticity—the ability of synapses to strengthen or weaken over time—across multiple brain regions [44]. Both long-term potentiation (LTP) and long-term depression (LTD), cellular correlates of learning and memory, are modulated by exercise [45]. Running increases the expression of synaptic proteins involved in neurotransmission and structural plasticity, including synaptophysin, synapsin I, and postsynaptic density protein 95 (PSD-95) [46,47].

At the structural level, exercise promotes dendritic remodeling, increasing dendritic length, complexity, and spine density in hippocampal and cortical neurons [48]. These morphological changes expand the connectivity potential of neurons and may provide structural substrates for enhanced cognitive function [49]. Notably, these adaptations occur not only during development but also throughout adulthood and even in aging, suggesting a lifelong capacity for exercise-induced structural remodeling [50].

Exercise-induced synaptic plasticity may directly counteract the synapse loss characteristic of many neurodegenerative conditions. In Alzheimer's disease models, exercise preserves synaptic integrity despite amyloid pathology, potentially through BDNF-mediated mechanisms [51,52]. Similarly, in Parkinson's disease models, exercise mitigates synaptic dysfunction in corticostriatal circuits through enhanced dopaminergic signaling and spine formation [53].

3.3. Cerebrovascular Adaptations

Exercise induces significant adaptations in the cerebrovascular system, with important implications for brain health and neurodegenerative disease prevention. Angiogenesis—the formation of new blood vessels—occurs in response to regular exercise, particularly in the hippocampus and motor cortex [54]. This increased vascular density improves oxygen and nutrient delivery while enhancing the clearance of metabolic waste products [55].

Beyond structural changes, exercise enhances cerebrovascular function through improved endothelial nitric oxide production, increased cerebral blood flow, and enhanced cerebrovascular reactivity [56], [57]. These adaptations may protect against the vascular contributions to cognitive impairment and neurodegeneration [58]. Indeed, cerebrovascular dysfunction often precedes and

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contributes to neurodegenerative pathology, making exercise-induced vascular adaptations particularly relevant for disease prevention [59].

Regular physical activity also promotes blood-brain barrier (BBB) integrity, potentially reducing the infiltration of neurotoxic substances and inflammatory mediators [60]. The cerebrovascular benefits of exercise appear particularly important in aging, when vascular dysfunction becomes more prevalent and contributes to neurodegeneration [61,62].

3.4. Network Connectivity Changes

Modern neuroimaging techniques have revealed that exercise influences large-scale brain network organization and connectivity [63]. Regular physical activity enhances functional connectivity within and between networks involved in cognitive control, memory, and sensorimotor function [64], [65]. These connectivity changes may reflect more efficient information processing and compensatory mechanisms that support cognitive performance despite age-related decline or pathology [66].

Exercise particularly impacts the default mode network (DMN), which shows disrupted connectivity in neurodegenerative conditions [67]. Interventional studies demonstrate that aerobic exercise can partially normalize DMN connectivity in older adults, potentially counteracting pathological network changes [68,69]. Additionally, exercise influences connectivity in the hippocampal-cortical memory system, potentially supporting memory function through enhanced network integration [70].

White matter integrity, essential for efficient communication between brain regions, also responds to exercise [71]. Regular physical activity is associated with greater white matter volume and improved microstructural properties in fiber tracts connecting frontal, temporal, and parietal regions [72], [73]. These white matter adaptations may provide structural substrates for enhanced network function and cognitive reserve against neurodegenerative processes [74].

The structural and functional adaptations described above offer multiple potential mechanisms through which exercise may prevent or mitigate neurodegenerative diseases. By enhancing neurogenesis, synaptic plasticity, cerebrovascular function, and network connectivity, exercise appears to build “brain reserves” that could delay symptom onset or slow progression even in the presence of pathology. Understanding these adaptations provides a neurobiological foundation for exercise as a preventive strategy against neurodegeneration and highlights potential targets for therapeutic development.

4. Neuroimmune and Inflammatory Pathways

Anti-inflammatory effects. Neuroinflammation plays a crucial role in the pathogenesis of neurodegenerative diseases, making the anti-inflammatory effects of exercise particularly relevant for disease prevention. Exercise modulates complex neuroimmune interactions that can create a more favorable environment for neuronal survival and function. This section examines how exercise influences inflammatory processes in the brain and their implications for neurodegenerative disease prevention.

4.1. Anti-inflammatory Effects

Regular physical activity consistently demonstrates anti-inflammatory effects both peripherally and centrally [75,76]. While acute exercise transiently increases circulating pro-inflammatory cytokines, chronic exercise training leads to lower baseline levels of inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [77,78]. This systemic anti-inflammatory effect may indirectly benefit the brain by reducing peripheral inflammation that can communicate with and influence central inflammatory processes [79].

In the central nervous system, exercise reduces the expression of pro-inflammatory cytokines and increases anti-inflammatory mediators in multiple brain regions, particularly the hippocampus

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[7,80]. This shift toward an anti-inflammatory environment may protect against the chronic low-grade neuroinflammation associated with aging and neurodegenerative conditions [81]. Exercise-induced release of muscle-derived anti-inflammatory factors, including IL-10 and IL-1 receptor antagonist (IL-1ra), may contribute to these central effects by crossing the blood-brain barrier or signaling through vagal afferents [82,83].

The anti-inflammatory effects of exercise appear particularly beneficial in the context of metabolic disorders that increase neuroinflammation and neurodegenerative risk. In animal models of obesity and diabetes, exercise attenuates hippocampal inflammation and associated cognitive deficits [84,85]. Similarly, in humans with metabolic syndrome, regular physical activity reduces systemic inflammation and may mitigate related cognitive impairment [86,87].

4.2. Microglial Phenotype Regulation

Microglia, the resident immune cells of the brain, exist on a spectrum from pro-inflammatory (M1-like) to anti-inflammatory, neuroprotective (M2-like) phenotypes [88]. Exercise appears to shift microglial activation toward the neuroprotective M2-like state characterized by enhanced phagocytic activity, increased production of anti-inflammatory cytokines, and release of neurotrophic factors [89,90].

In aged animals, exercise reverses the age-associated shift toward pro-inflammatory microglial priming, potentially through mechanisms involving CX3CL1 (fractalkine) signaling [91,92]. Similarly, in models of Alzheimer's disease, physical activity reduces microglial activation associated with amyloid pathology while enhancing clearance of amyloid-beta through promotion of phagocytic activity [93,94]. This dual effect on microglia—reducing harmful inflammatory activation while enhancing beneficial clearance functions—may be particularly relevant for preventing protein aggregation-related neurodegenerative diseases [95].

Interestingly, microglial regulation by exercise may involve communication with peripheral immune cells, including regulatory T cells, which increase with regular physical activity [96]. These cells can infiltrate the brain under certain conditions and produce anti-inflammatory cytokines that influence microglial phenotype [97]. The interplay between peripheral and central immune responses in exercise-mediated neuroprotection represents an active area of investigation with therapeutic implications [98].

4.3. Cytokine Profiles

Exercise shifts the balance of cytokines in the brain toward an anti-inflammatory profile that supports neuroplasticity and resilience [99]. While acute exercise transiently increases IL-6, this is followed by increases in anti-inflammatory cytokines, including IL-10 and IL-1ra [27]. With regular training, baseline levels of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) decrease while anti-inflammatory mediators increase or maintain higher responsiveness [100,101].

The cytokine profile changes induced by exercise may directly influence neurogenesis, synaptic plasticity, and cognitive function [102]. For example, IL-10 promotes neuronal survival and neurogenesis, while IL-1ra blocks the negative effects of IL-1β on synaptic plasticity and memory [103]. Exercise-induced reductions in TNF-α may be particularly beneficial, as this cytokine is elevated in multiple neurodegenerative conditions and can induce neuronal apoptosis when chronically elevated [104].

The temporal dynamics of cytokine responses to exercise may be critical for understanding its benefits. The transient increases in certain inflammatory mediators during acute exercise may trigger adaptive responses, including antioxidant enzyme upregulation and stress protein expression, that enhance cellular resilience [105], [106]. This "hormetic" response—a beneficial adaptation to mild, intermittent stress—may underlie some of exercise's neuroprotective effects [107].

4.4. Blood-Brain Barrier Integrity

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The blood-brain barrier (BBB) plays a crucial role in maintaining brain homeostasis and protecting neural tissue from peripheral toxins and inflammatory mediators [37]. BBB dysfunction occurs in aging and neurodegenerative diseases, potentially contributing to disease progression through increased permeability to harmful substances and immune cells [108,109].

Exercise appears to enhance BBB integrity through multiple mechanisms [110]. Regular physical activity upregulates tight junction proteins, including occludin and claudin-5, which maintain BBB structural integrity [111]. Exercise also enhances the expression of glucose transporter 1 (GLUT-1) in brain endothelial cells, potentially improving cerebral glucose metabolism while maintaining barrier function [112].

In animal models of neurodegenerative diseases, exercise attenuates BBB disruption and associated cognitive deficits [60,113]. For example, in models of Alzheimer's disease, physical activity reduces BBB leakage associated with amyloid pathology and rescues cognitive function [114]. Similarly, in models of Parkinson's disease, exercise prevents BBB breakdown in the substantia nigra and mitigates dopaminergic neuron loss [115].

The protective effects of exercise on BBB integrity may involve reduced oxidative stress and inflammation in cerebrovascular endothelial cells [116]. Additionally, exercise-induced increases in angiogenic factors like VEGF promote not only angiogenesis but also the recruitment of pericytes that support BBB function [117,118]. Through these mechanisms, regular physical activity may help maintain a selective, functional barrier that protects against neurodegenerative processes while allowing beneficial nutrient transport.

Understanding the neuroimmune adaptations to exercise provides insights into potential preventive mechanisms against neurodegeneration. By reducing neuroinflammation, promoting neuroprotective microglial phenotypes, optimizing cytokine profiles, and maintaining BBB integrity, exercise creates an environment conducive to neuronal health and resilience. These adaptations may be particularly important in the context of aging, when neuroinflammatory processes become more prominent and contribute to neurodegenerative vulnerability.

5. Exercise Effects on Pathological Features of Neurodegenerative Diseases

Beyond its general effects on neuroplasticity and neuroimmune function, physical exercise directly impacts specific pathological features of neurodegenerative diseases. These targeted effects may contribute substantially to exercise's preventive potential. This section examines how exercise influences key pathological processes across major neurodegenerative conditions.

5.1. Amyloid-β and Tau Pathology

The accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles represents hallmark pathologies in Alzheimer's disease (AD). Evidence from animal models consistently demonstrates that exercise reduces Aβ burden [52,119]. In transgenic AD mice, voluntary running decreases Aβ plaque load in the hippocampus and cortex while reducing soluble Aβ levels [94,120]. These effects occur through multiple mechanisms, including enhanced Aβ clearance, reduced Aβ production, and improved proteostasis [121].

Exercise appears to enhance Aβ clearance through several pathways. Physical activity upregulates Aβ-degrading enzymes, including neprilysin and insulin-degrading enzyme (IDE) [122,123]. Exercise also improves glymphatic clearance—the brain's waste removal system—potentially through increased cerebral blood flow and reduced neuroinflammation [124,125]. Additionally, exercise enhances microglial phagocytosis of Aβ while reducing pro-inflammatory microglial activation that can exacerbate amyloid pathology [126].

Regarding tau pathology, regular exercise reduces tau hyperphosphorylation in several transgenic mouse models [127,128]. This effect appears mediated through modulation of kinases and phosphatases that regulate tau phosphorylation status, including glycogen synthase kinase-3β (GSK-3β) and protein phosphatase 2A (PP2A) [85,129]. Exercise also enhances autophagy—a cellular degradation system—potentially promoting clearance of pathological tau species [130,131].

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In humans, observational studies indicate that physically active individuals have lower amyloid and tau burden as measured by PET imaging and cerebrospinal fluid biomarkers [132,133]. Interventional studies show that exercise can improve cognition in patients with mild cognitive impairment and early AD, though evidence for direct effects on pathology in humans remains limited [86,134]. Nevertheless, the consistent effects observed in animal models suggest that exercise may directly impact AD pathophysiology, potentially slowing pathological progression when implemented early.

5.2. α-Synuclein Aggregation

Alpha-synuclein (α-syn) aggregation represents the primary pathological hallmark of Parkinson's disease (PD) and other synucleinopathies. Mounting evidence suggests that exercise influences α-syn metabolism and aggregation, potentially mitigating this pathological process [135]. In rodent models of PD, forced exercise reduces α-syn aggregation in the substantia nigra and striatum while attenuating associated neuroinflammation [115,136].

The mechanisms underlying these effects likely involve enhanced proteostasis—the cellular machinery that maintains protein homeostasis. Exercise upregulates molecular chaperones, particularly heat shock proteins (HSPs), that assist in protein folding and prevent aggregation [137]. Additionally, exercise enhances autophagy-lysosomal function, a primary pathway for α-syn clearance [138]. The ubiquitin-proteasome system, another degradation pathway relevant to α-syn clearance, also shows enhanced function with regular physical activity [139].

Beyond effects on α-syn directly, exercise protects dopaminergic neurons through multiple complementary mechanisms. Physical activity increases levels of neurotrophic factors in the basal ganglia, particularly glial cell line-derived neurotrophic factor (GDNF) and BDNF, which support dopaminergic neuron survival [140,141]. Exercise also reduces oxidative stress in these neurons, potentially through upregulation of antioxidant enzymes and improved mitochondrial function [81,142].

In PD patients, regular exercise improves motor symptoms, potentially by enhancing dopaminergic signaling and promoting compensatory mechanisms [143,144]. While direct evidence for exercise effects on α-syn pathology in humans remains limited, the convergent evidence from animal models and clinical benefits observed in patients supports exercise as a promising intervention for modifying disease progression [145,146].

5.3. Excitotoxity and Oxidative Stress

Excitotoxicity—neuronal damage resu[149lting from excessive glutamate receptor activation—and oxidative stress represent common pathological mechanisms across multiple neurodegenerative conditions [147]. Exercise appears to mitigate both processes through complementary adaptations that enhance neuronal resilience [3,148].

Regarding excitotoxicity, exercise modulates glutamatergic signaling through multiple mechanisms. Regular physical activity normalizes glutamate receptor expression and function, particularly N-methyl-D-aspartate (NMDA) receptors implicated in excitotoxic cascades [149]. Exercise also enhances the expression of glutamate transporters in astrocytes, promoting efficient glutamate clearance from synaptic spaces [150,151]. Additionally, exercise increases GABAergic inhibitory tone in several brain regions, potentially counterbalancing excessive excitatory signaling [44].

Exercise powerfully influences redox homeostasis in the brain, generally enhancing antioxidant capacity and reducing oxidative damage [152,153]. While acute exercise transiently increases reactive oxygen species (ROS) production, chronic training upregulates antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase [154,155]. This adaptive response, consistent with hormetic principles, enhances cellular capacity to manage oxidative challenges [156].

Importantly, exercise reduces oxidative damage to cellular components implicated in neurodegeneration. Regular physical activity decreases lipid peroxidation, protein carbonylation,

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and DNA oxidation in brain regions vulnerable to neurodegeneration [51,157]. These effects appear particularly pronounced in aging, when oxidative stress increases and contributes to neurodegenerative vulnerability [158,159].

The neuroprotective effects of exercise against excitotoxicity and oxidative stress extend across multiple neurodegenerative conditions. In Huntington's disease models, exercise reduces striatal excitotoxicity and associated neuronal loss [160,161]. In amyotrophic lateral sclerosis (ALS) models, exercise attenuates oxidative damage in motor neurons and delays symptom onset, though effects appear intensity-dependent [162,163]. These cross-cutting effects highlight exercise's potential to address common pathological mechanisms rather than disease-specific pathologies alone.

5.4. Mitochondrial Function and Bioenergetics

Mitochondrial dysfunction represents a central feature of neurodegenerative pathogenesis, contributing to bioenergetic deficits, oxidative stress, and ultimately neuronal death [164]. Exercise robustly improves mitochondrial function and cellular bioenergetics through adaptations that enhance energy production efficiency and resilience [29,165].

Regular physical activity increases mitochondrial biogenesis—the generation of new mitochondria—in multiple brain regions [166,167]. This effect occurs primarily through activation of PGC-1α, a transcriptional coactivator that regulates genes involved in mitochondrial replication and function [168,169]. Exercise also enhances the expression of mitochondrial enzymes in the electron transport chain, potentially improving ATP production capacity [170,171].

Beyond biogenesis, exercise improves mitochondrial quality control mechanisms that maintain a healthy mitochondrial pool. Physical activity enhances mitophagy—the selective autophagy of damaged mitochondria—preventing the accumulation of dysfunctional organelles that can generate excessive ROS and trigger cell death [172,173]. Exercise also promotes mitochondrial dynamics, facilitating the fusion and fission processes that maintain functional mitochondrial networks [174,175].

In the context of neurodegenerative diseases, exercise-induced mitochondrial adaptations may directly counter disease-specific bioenergetic deficits. In AD models, exercise improves hippocampal mitochondrial function despite amyloid pathology, potentially through enhanced calcium handling capacity and reduced oxidative damage [130,176]. In PD models, physical activity protects nigral dopaminergic neurons against mitochondrial toxins while enhancing complex I activity—a respiratory chain component often deficient in PD [177,178].

Interestingly, exercise enhances metabolic flexibility in neural tissues, potentially allowing neurons to utilize alternative fuel sources when glucose metabolism is compromised [179,180]. This adaptation may be particularly relevant in neurodegenerative conditions where cerebral glucose hypometabolism precedes clinical symptoms [181,182]. By enhancing ketone body utilization and lactate transport, exercise may provide metabolic substrates that bypass impaired glucose metabolism [12,183].

The direct effects of exercise on pathological features of neurodegenerative diseases highlight its potential as a targeted preventive strategy. By addressing specific disease mechanisms—whether amyloid and tau pathology in AD, α-synuclein aggregation in PD, or common processes like excitotoxicity and mitochondrial dysfunction—exercise represents a multifaceted intervention that may modify disease trajectories. These mechanistic insights provide a rationale for implementing exercise early in disease courses or preventively in at-risk populations, potentially delaying pathological progression and symptom onset.

6. Clinical and Epidemiological Evidence

The mechanistic insights described in previous sections are complemented by substantial clinical and epidemiological evidence supporting exercise as a preventive strategy against neurodegenerative diseases. These studies establish associations between physical activity and disease risk while providing insights into dose-response relationships and exercise modality

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considerations. This section examines the human evidence for exercise effects on neurodegenerative outcomes.

6.1. Exercise and Cognitive Outcomes

Observational studies consistently demonstrate that physically active individuals maintain better cognitive function across the lifespan compared to sedentary counterparts [184,185]. A meta-analysis of 15 prospective studies including over 33,000 participants without dementia at baseline found that physical activity was associated with a 38% reduced risk of cognitive decline [186]. Similarly, another meta-analysis of 16 prospective studies with over 160,000 participants demonstrated that higher levels of physical activity were associated with approximately 40% reduced risk of Alzheimer's disease [187].

The cognitive domains most consistently benefiting from exercise include executive function, processing speed, and memory—functions commonly impaired in neurodegenerative conditions [188,189]. Interestingly, these cognitive benefits appear across the spectrum from healthy aging to mild cognitive impairment (MCI) and early-stage dementia, suggesting exercise may be beneficial even after cognitive changes have begun [190,191].

Randomized controlled trials (RCTs) provide stronger evidence for causal relationships between exercise and cognitive outcomes. A meta-analysis of 39 RCTs with 2,049 participants demonstrated that aerobic exercise interventions significantly improved attention, executive function, and memory in healthy older adults [192]. In individuals with MCI, a 6-month aerobic exercise intervention improved executive function and increased hippocampal volume compared to stretching controls [193]. Even in patients with early Alzheimer's disease, a meta-analysis of 18 RCTs found moderate positive effects of exercise on global cognition [194].

Neuroimaging studies provide additional evidence for exercise effects on brain structure and function relevant to neurodegeneration. Higher fitness levels and regular physical activity are associated with greater gray matter volume in regions vulnerable to age-related atrophy, particularly the hippocampus and prefrontal cortex [195,196]. Longitudinal intervention studies demonstrate that aerobic exercise increases hippocampal volume in healthy older adults, potentially counteracting age-related volume loss [41,197]. Similarly, exercise enhances white matter integrity and functional connectivity in networks affected by neurodegenerative processes [198,199].

6.2. Preventive Potential Across Neurodegenerative Conditions

While Alzheimer's disease has received the most research attention, evidence suggests exercise may provide preventive benefits across multiple neurodegenerative conditions. For Parkinson's disease (PD), prospective cohort studies demonstrate that moderate to vigorous physical activity is associated with 34-43% reduced risk of developing the condition [200,201]. A meta-analysis of 8 prospective studies found that higher physical activity levels were associated with a significant reduction in PD risk (RR: 0.66, 95% CI: 0.57-0.78) [202]. These protective associations appear stronger for moderate to vigorous activity and may be more pronounced in men than women [203].

For patients already diagnosed with PD, exercise interventions improve motor symptoms, gait, balance, and quality of life [204,205]. A meta-analysis of 18 RCTs demonstrated that various exercise modalities improved UPDRS motor scores, with particularly strong effects for resistance training and tai chi [206]. Beyond motor symptoms, emerging evidence suggests exercise may improve non-motor symptoms including cognition and depression in PD patients [207,208].

Regarding amyotrophic lateral sclerosis (ALS), the relationship with exercise appears more complex. Some studies suggest that intense physical activity or specific occupational activities may increase ALS risk, potentially through oxidative stress mechanisms [209,210]. However, moderate physical activity has not been consistently associated with increased risk, and some evidence suggests it may be protective when implemented appropriately [211,212]. The seemingly paradoxical relationship may reflect an interaction between exercise intensity, genetic susceptibility, and underlying pathophysiology [213].

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For Huntington's disease (HD), a genetic condition with complete penetrance, exercise cannot prevent disease occurrence but may delay symptom onset or slow progression. Animal studies demonstrate that exercise delays motor symptom onset, improves motor function, and reduces striatal neurodegeneration in HD models [161,214]. Limited clinical studies in pre-symptomatic and early-stage HD patients suggest exercise may improve motor function, cognitive performance, and quality of life [215,216]. These findings highlight the potential for exercise to modify disease trajectories even in conditions with strong genetic determinants.

6.3. Dose-Response Relationships

Understanding dose-response relationships is crucial for optimizing exercise prescriptions for neurodegenerative disease prevention. Current evidence suggests a non-linear relationship between exercise volume and cognitive benefits, with moderate amounts typically providing optimal effects [217,218]. A meta-analysis of prospective studies found that the largest risk reduction for cognitive decline occurred with moderate physical activity levels, with minimal additional benefit from higher volumes [219].

Regarding intensity, moderate-to-vigorous aerobic exercise (approximately 60-75% of maximum heart rate) appears most consistently associated with cognitive benefits and reduced neurodegenerative risk [220,221]. However, even light-intensity physical activity, such as walking, shows protective associations when performed regularly [222,223]. This suggests that incorporating regular movement throughout the day, rather than focusing solely on structured exercise sessions, may provide meaningful benefits.

Exercise frequency also influences outcomes, with most studies reporting optimal cognitive benefits with 3-5 sessions per week [224]. Interestingly, some evidence suggests that even one or two weekly sessions of vigorous activity may provide substantial protective benefits, supporting the concept that some exercise is significantly better than none [225,226].

Duration requirements appear to vary by intensity, with longer durations needed for lower-intensity activities to achieve comparable benefits. Most successful interventions for cognitive outcomes involve 30-60 minute sessions, though accumulated shorter bouts may provide similar benefits when total volume is matched [227]. Importantly, longitudinal studies suggest that sustained participation over months to years is necessary for optimal neuroprotection, highlighting the importance of establishing sustainable exercise habits [228,229].

6.4. Exercise Modality Considerations

Different exercise modalities may offer complementary benefits for neurodegenerative disease prevention. Aerobic exercise most consistently demonstrates positive effects on cognitive function, hippocampal volume, and cerebral blood flow [230,231]. A meta-analysis of 29 RCTs found that aerobic exercise produced the largest effects on executive function compared to other modalities [232].

Resistance training shows emerging evidence for cognitive benefits, particularly for executive function and memory [233,234]. Mechanisms may involve increased production of myokines, reduced inflammation, and enhanced insulin sensitivity [46,235]. Interestingly, combined aerobic and resistance training may provide greater cognitive benefits than either modality alone, suggesting synergistic effects [236,237].

Mind-body exercises, including tai chi, yoga, and dance, demonstrate promising effects on cognitive function and motor symptoms in older adults and neurodegenerative populations [238,239]. These modalities combine physical activity with cognitive, social, and mindfulness components that may enhance neuroplasticity through multiple pathways [240,241]. A meta-analysis of 32 RCTs found that tai chi improved cognitive performance in older adults with and without cognitive impairment [242].

Cognitively challenging exercise forms, such as dance, tennis, or martial arts, may provide enhanced benefits through simultaneous physical and cognitive engagement [243,244]. These

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activities require coordination, adaptation, and executive function during movement, potentially stimulating neuroplasticity through multiple mechanisms [245,246]. This supports the concept of "dual-task" training as a particularly effective approach for neurodegenerative disease prevention [247].

The clinical and epidemiological evidence reviewed here supports exercise as a promising preventive strategy against neurodegenerative diseases. The consistent associations between physical activity and reduced disease risk, combined with demonstrated benefits on cognitive function and brain structure, provide a compelling rationale for implementing exercise interventions. Understanding dose-response relationships and modality considerations allows for optimizing exercise prescriptions for at-risk populations, potentially enhancing preventive efficacy.

7. Translational Implications

Translating the extensive mechanistic and clinical evidence on exercise-induced neuroplasticity into effective preventive strategies requires careful consideration of implementation challenges and personalization approaches. This section examines the translational implications of exercise research for neurodegenerative disease prevention, focusing on practical considerations for clinical application.

7.1. Exercise Prescription Considerations

Developing evidence-based exercise prescriptions for neurodegenerative disease prevention requires balancing efficacy with adherence and safety considerations [248,249]. The traditional FITT-VP framework (Frequency, Intensity, Time, Type, Volume, and Progression) provides a useful structure for prescription development [250]. Based on current evidence, a general prescription for cognitive health and neurodegenerative disease prevention might include:

- Frequency: 3-5 days per week of aerobic activities, with additional 2-3 days of resistance training [218,251]
- Intensity: Moderate intensity (approximately 60-75% of maximum heart rate) for most sessions, with some vigorous intervals (>75% maximum heart rate) if tolerated [252,253]
- Time: 30-60 minutes per session, which may be accumulated in shorter bouts (10+ minutes) for those with limited capacity [254]
- Type: Multimodal approach combining aerobic, resistance, and motor skill components, with emphasis on cognitively engaging activities [192,255]
- Volume: Approximately 150 minutes of moderate-to-vigorous activity weekly, with additional light activity throughout the day [256]
- Progression: Gradual increases in duration before intensity, with periodic variation to maintain engagement and challenge [257,258]

However, these general guidelines require modification based on individual factors including age, baseline fitness, comorbidities, and preferences [259]. For older adults with mobility limitations or chronic conditions, low-impact modalities such as recumbent cycling, water-based exercises, or chair-based routines may provide accessible alternatives while still conferring cognitive benefits [220,260].

Clinical monitoring becomes particularly important for high-risk individuals, including those with cardiovascular disease, orthopedic limitations, or neurological symptoms [261]. Pre-exercise screening using validated tools such as the Physical Activity Readiness Questionnaire (PAR-Q+) can identify individuals requiring medical clearance before increasing activity levels [262]. For those with established neurodegenerative conditions, supervision by trained exercise physiologists or physical therapists may optimize safety and efficacy [145,263].

7.2. Personalization Approaches for At-Risk Populations

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Different neurodegenerative conditions and risk profiles may benefit from tailored exercise approaches that target specific pathological mechanisms [264,265]. For individuals at risk of Alzheimer's disease, particularly those with genetic predisposition (e.g., APOE ε4 carriers) or family history, aerobic exercise emphasizing hippocampal engagement appears most beneficial [266]. Some evidence suggests that APOE ε4 carriers may show enhanced cognitive responses to exercise interventions, potentially reflecting compensatory mechanisms or greater room for improvement [267].

For those with Parkinson's disease risk factors or prodromal symptoms, exercises focusing on dual-task performance, balance, amplitude training, and rhythmic activities may provide targeted benefits [268]. Programs like Dance for Parkinson's and LSVT BIG have demonstrated efficacy for symptom management and may have preventive potential when implemented early [269]. The incorporation of external cueing and attentional strategies appears particularly valuable for this population [270].

Age-specific considerations are also important, as different life stages may benefit from distinct exercise approaches [271]. In midlife (40-60 years), when neurodegenerative pathology often begins accumulating without symptoms, vigorous aerobic training and resistance exercise focusing on metabolic health may provide optimal preventive effects [272]. In contrast, older adults (65+ years) may benefit more from multimodal programs emphasizing fall prevention, social engagement, and gradual progression [273].

Personalization may extend to timing considerations, with evidence suggesting that exercise timing relative to circadian rhythms influences outcomes [274]. Morning exercise has been associated with better adherence and cognitive benefits in some populations, potentially through interactions with cortisol cycles and sleep quality [275]. However, individual chronotype variations suggest that optimal timing may differ between "morning larks" and "night owls," highlighting another dimension for personalization [276].

Technological approaches to personalization are rapidly evolving, with wearable devices, smartphone applications, and remote monitoring systems enabling dynamic adjustment of exercise prescriptions [277]. These technologies can track adherence, physiological responses, and performance metrics to optimize exercise dose while providing motivational feedback [278]. For example, heart rate variability monitoring during exercise may help identify optimal intensity zones for neuroprotective effects while minimizing stress responses [279].

7.3. Integration with other Lifestyle Interventions

Exercise appears to function synergistically with other lifestyle factors to enhance neuroprotection, suggesting that integrated approaches may provide optimal benefits [280]. The FINGER trial demonstrated that a multidomain intervention combining exercise, cognitive training, dietary modification, and vascular risk management improved cognitive function in at-risk older adults more effectively than single-domain approaches [281]. Similar multidomain trials including MAPT and PreDIVA have provided supportive, though somewhat mixed, evidence for this integrated approach [282].

Nutritional factors appear particularly complementary to exercise effects on brain health [283]. Mediterranean-style diets rich in polyphenols, omega-3 fatty acids, and antioxidants may enhance exercise-induced neuroplasticity through shared mechanisms involving BDNF signaling, reduced inflammation, and improved vascular function [284,285]. Some evidence suggests that protein consumption in close proximity to resistance exercise may enhance muscle protein synthesis and release of myokines with neuroprotective effects [286,287].

Cognitive engagement during or proximal to exercise may also amplify neuroplastic responses [288]. "Exergaming" approaches combining physical activity with cognitive challenges have shown promising results for cognitive enhancement in older adults [289,290]. Similarly, performing cognitive tasks immediately following exercise may leverage the transiently enhanced plasticity induced by acute exercise, potentially strengthening learning and memory consolidation [291,292].

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Sleep quality represents another important complementary factor, as exercise can improve sleep architecture while adequate sleep enhances exercise recovery and cognitive performance [293]. Addressing sleep disturbances may therefore improve exercise adherence and efficacy for neurodegenerative prevention [294]. Conversely, excessive evening exercise may disrupt sleep in sensitive individuals, highlighting the need for personalized timing recommendations [295].

Stress management techniques, including mindfulness meditation and breathing exercises, may complement physical activity by reducing cortisol levels and neuroinflammation [296]. The combination of moderate exercise with stress reduction practices potentially provides dual benefits: exercise-induced resilience to stress and reduced chronic stress that might otherwise impair neuroplasticity [297].

7.4. Challenges in Implementation

Despite substantial evidence supporting exercise for neurodegenerative disease prevention, significant implementation challenges remain [298]. Perhaps most fundamental is the challenge of behavior change—initiating and maintaining physical activity habits in predominantly sedentary populations [299]. Behavioral economic approaches, including commitment devices, social incentives, and immediate rewards, show promise for increasing exercise adherence [300]. Additionally, motivational interviewing techniques and stages-of-change models provide frameworks for tailoring behavioral strategies to individual readiness levels [301].

Access disparities present another implementation challenge, as socioeconomic factors influence both exercise opportunities and neurodegenerative disease risk [302]. Community-based programs in accessible locations, subsidized memberships for fitness facilities, and home-based exercise options with minimal equipment requirements may help address these disparities [303]. Technological solutions including smartphone apps and online communities may expand access, though digital literacy barriers must be considered for older populations [304].

Healthcare system integration represents a crucial implementation pathway that remains underdeveloped [305]. Exercise prescriptions remain underutilized in clinical settings due to time constraints, limited provider training, and reimbursement challenges [306]. Programs like Exercise is Medicine aim to address these barriers by standardizing assessment and prescription protocols while developing referral networks to qualified exercise professionals [307]. Expanding these initiatives may facilitate wider implementation of exercise as preventive medicine for neurodegenerative conditions [308].

Public health messaging around exercise for brain health requires refinement to effectively motivate behavior change [309]. Messages emphasizing immediate benefits (improved mood, energy, sleep) alongside long-term neuroprotection may increase relevance across age groups [310]. Additionally, framing exercise as a positive addition rather than an obligatory burden may reduce resistance, particularly among those with negative past experiences with physical activity [311].

The translation of exercise research into effective preventive strategies for neurodegenerative diseases requires addressing these implementation challenges while refining personalization approaches. By developing targeted exercise prescriptions, integrating complementary lifestyle factors, and addressing barriers to adoption, clinicians and public health professionals can leverage the neuroplastic potential of physical activity to reduce the growing burden of neurodegenerative diseases.

8. Future Research Directions

Despite significant advances in our understanding of exercise-induced neuroplasticity and its potential for neurodegenerative disease prevention, important research gaps remain. Addressing these gaps could enhance the development of evidence-based prevention strategies and optimize their implementation. This section examines promising future research directions across mechanistic, methodological, and translational domains.

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8.1. Mechanistic Gaps

Several mechanistic questions require further investigation to fully understand exercise-induced neuroprotection [312]. The relative contributions of different pathways—neurotrophic, anti-inflammatory, vascular, and metabolic—to exercise-mediated benefits remain incompletely characterized [313]. Future research should employ experimental designs that selectively block or enhance specific pathways to determine their necessity and sufficiency for neuroprotective effects [314]. For example, using conditional knockouts of BDNF or its receptor TrkB in specific brain regions could help establish the causal role of this pathway in exercise-induced cognitive benefits [315].

The systemic versus local origins of exercise-induced neuroplasticity represent another important mechanistic question [316]. While peripheral factors like myokines, hepatokines, and immune mediators clearly influence brain function, their relative importance compared to direct neural activation remains unclear [317]. Research designs comparing systemic administration of exercise-induced factors with localized brain interventions could help disentangle these mechanisms [318]. The recently identified "exercisekines" and extracellular vesicles released during physical activity represent promising targets for such investigations [319].

The temporal dynamics of exercise-induced adaptations require further characterization, particularly regarding the persistence of effects after exercise cessation [320]. Longitudinal studies with multiple time points are needed to determine how quickly different adaptations develop, their maintenance duration, and potential rebound effects [321]. This information is crucial for optimizing exercise prescription parameters, including frequency and periodization [322].

Individual variability in responsiveness to exercise represents a critical research frontier [323]. Some individuals show robust cognitive and neuroplastic responses to physical activity, while others demonstrate minimal changes despite similar training regimens [324]. Understanding the genetic, epigenetic, physiological, and psychological factors underlying this variability could inform personalized approaches [325]. Multi-omics technologies, including genomics, proteomics, and metabolomics, offer powerful tools for characterizing response heterogeneity [326].

8.2. Methological Considerations

Advancing exercise-neuroplasticity research requires methodological refinements to enhance reliability, validity, and translational potential [327]. Standardization of exercise protocols represents a fundamental need, as variability in intensity quantification, progression parameters, and supervision methods complicates cross-study comparisons [328]. Consensus guidelines for describing exercise interventions with precision would facilitate more meaningful meta-analyses and replication efforts [329].

Novel neuroimaging approaches offer promising opportunities for non-invasive assessment of exercise effects on brain structure and function [330]. Advanced techniques including arterial spin labeling, functional connectivity analyses, diffusion kurtosis imaging, and PET imaging of neuroinflammation could provide more sensitive and specific measures of exercise-induced changes [331]. Multimodal imaging combining structural, functional, and molecular measures may be particularly informative for characterizing comprehensive brain adaptations [332].

Improved biomarker development represents another methodological priority [333]. Blood-based markers reflecting neuroplasticity, neuroinflammation, and neurodegeneration could provide accessible monitoring tools for exercise efficacy [334]. Promising candidates include exosomal microRNAs, protein panels measuring neurotrophic factors and cytokines, and metabolites reflecting brain energy metabolism [335]. Validation of these markers against direct brain measures and clinical outcomes remains essential [336].

Animal models that better recapitulate human neurodegenerative conditions could enhance mechanistic insights with greater translational relevance [337]. Emerging genetic models incorporating multiple pathological features and age-related changes may provide more clinically relevant platforms for testing exercise interventions [338]. Additionally, models allowing voluntary

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versus forced exercise comparisons could help disentangle stress-related confounds from direct physical activity benefits [339].

8.3. Novel Biomarkers of Exercise-Induced Neuroplasticity

Developing reliable, sensitive biomarkers of exercise-induced neuroplasticity represents a crucial research priority with significant clinical implications [340]. These biomarkers could serve multiple purposes: identifying individuals likely to benefit from specific exercise regimens, monitoring intervention efficacy, and providing early indicators of neuroprotection before clinical symptoms emerge [341].

Blood-based biomarkers offer practical advantages for longitudinal monitoring [342]. Recent advances in blood sampling techniques have enabled detection of brain-derived extracellular vesicles carrying proteins, lipids, and microRNAs that reflect central nervous system states [343]. Exercise-responsive microRNAs, particularly those involved in BDNF regulation, synaptic plasticity, and mitochondrial biogenesis, represent promising candidates for monitoring neuroplastic responses [344]. Similarly, proteomic panels measuring multiple neurotrophic factors, inflammatory markers, and metabolic regulators may provide more comprehensive assessment than single-protein approaches [345].

Neurophysiological measures including electroencephalography (EEG) and transcranial magnetic stimulation (TMS) offer direct assessment of functional neuroplasticity with high temporal resolution [346]. Event-related potentials during cognitive tasks show sensitivity to exercise interventions and correlate with performance improvements [347]. Similarly, TMS protocols measuring cortical excitability, intracortical inhibition, and late cortical disinhibition detect neuroplastic changes following both acute and chronic exercise [348]. These techniques could provide more proximal measures of brain adaptation than behavioral outcomes alone [349].

Digital biomarkers derived from wearable technology and smartphone-based assessment are emerging as scalable, ecologically valid measurement approaches [350]. Continuous monitoring of gait parameters, sleep quality, heart rate variability, and daily activity patterns may capture subtle changes preceding clinical improvement [351]. Similarly, frequent brief cognitive assessments via smartphone applications can detect trajectory changes with greater sensitivity than infrequent laboratory testing [352]. The combination of passive monitoring with active assessment offers particularly rich characterization of exercise effects across contexts.

The integration of multiple biomarker modalities through advanced analytical approaches represents a promising direction for capturing exercise-induced neuroplasticity comprehensively [353]. Machine learning methods can identify patterns across biomarker types that predict individual responses more accurately than single measures [354]. Longitudinal modeling approaches incorporating repeated biomarker assessments may detect subtle changes and individual trajectories missed by traditional group-level analyses [355].

8.4. Precision Approaches to Prevention

Advancing toward precision prevention approaches represents a critical frontier in exercise research for neurodegenerative disease [356]. Initial efforts should focus on identifying responder phenotypes—characteristic profiles of individuals who show robust neuroplastic and cognitive responses to specific exercise modalities [357]. Large dataset analyses incorporating genetic, physiological, neuroimaging, and behavioral measures could reveal patterns predicting differential responsiveness [358]. These analyses would ideally include diverse populations across ages, comorbidity profiles, and genetic risk factors to capture heterogeneity comprehensively [359].

Adaptive intervention designs offer promising frameworks for developing personalized exercise prescriptions [360]. Sequential Multiple Assignment Randomized Trial (SMART) designs allow systematic optimization of intervention sequences based on individual responses [361]. Similarly, Multiphase Optimization Strategy (MOST) approaches can efficiently test multiple intervention components to identify optimal combinations for specific populations [362]. These

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experimental paradigms could determine which exercise parameters (modality, intensity, timing) should be adjusted based on which individual characteristics [363].

Digital health technologies enable dynamic prescription approaches that continuously adjust based on real-time monitoring [364]. Closed-loop systems incorporating wearable sensors, smartphone-based cognitive assessment, and algorithm-driven prescription adjustments could optimize exercise parameters on an ongoing basis [365]. These approaches might be particularly valuable for maintaining effectiveness during changing health states, motivation levels, or environmental circumstances [366].

Integration of exercise with other interventions through precision approaches represents another promising direction [367]. Nutritional supplements, cognitive training, sleep optimization, and stress management might show synergistic effects with exercise in specific populations [368]. Factorial experimental designs can efficiently test these combinations while identifying interaction effects that inform optimal multimodal regimens [369]. For example, omega-3 supplementation might enhance exercise benefits specifically in APOE ε4 carriers, while cognitive-motor dual-tasks might provide optimal benefits for those with particular cognitive profiles [370].

The future research directions outlined here highlight the multidisciplinary nature of exercise-neuroplasticity research and its potential for advancing neurodegenerative disease prevention. By addressing mechanistic gaps, refining methodological approaches, developing sensitive biomarkers, and pursuing precision prevention strategies, researchers can enhance our understanding of exercise-induced neuroplasticity while optimizing its translation into effective preventive interventions. These advances may ultimately contribute to reducing the growing burden of neurodegenerative diseases through evidence-based, personalized exercise approaches.

9. Conclusions

Exercise-induced neuroplasticity represents a promising avenue for neurodegenerative disease prevention, supported by converging evidence from molecular, animal, and human studies. This narrative review has synthesized current knowledge across multiple domains, revealing the complex and multifaceted mechanisms through which physical activity may confer neuroprotection and enhance resilience against neurodegenerative processes.

The molecular mediators of exercise-induced neuroplasticity—including neurotrophic factors, neuroendocrine responses, epigenetic modifications, and metabolic signaling pathways—create a molecular environment conducive to neuronal health and function. These pathways support structural and functional adaptations, including enhanced hippocampal neurogenesis, synaptic plasticity, cerebrovascular function, and network connectivity. Meanwhile, exercise's effects on neuroimmune and inflammatory pathways help maintain a balanced inflammatory milieu that supports neuroplasticity and opposes chronic neuroinflammation associated with neurodegenerative conditions.

Particularly compelling is exercise's direct impact on pathological features of neurodegenerative diseases. By reducing amyloid and tau pathology, mitigating α-synuclein aggregation, attenuating excitotoxicity and oxidative stress, and enhancing mitochondrial function, physical activity appears to address multiple disease mechanisms simultaneously. This multi-target approach contrasts with most pharmacological strategies focused on single pathways and may explain exercise's broad efficacy across conditions.

Clinical and epidemiological evidence consistently demonstrates associations between physical activity and reduced neurodegenerative disease risk, with randomized controlled trials supporting causal benefits on cognitive function and brain structure. The apparent dose-response relationships and modality considerations highlighted in this review provide a foundation for evidence-based exercise prescriptions tailored to neurodegenerative prevention.

Translating this knowledge into effective prevention strategies requires attention to personalization approaches, integration with complementary lifestyle factors, and implementation strategies that address adherence barriers. Future research should focus on filling mechanistic gaps,

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developing sensitive biomarkers of exercise-induced neuroplasticity, and advancing precision approaches that optimize interventions for individual characteristics and risk profiles.

Exercise represents a cost-effective, accessible intervention with minimal side effects and multiple health benefits beyond brain function. Its potential to modify neurodegenerative disease trajectories warrants increased attention in clinical practice, public health initiatives, and research prioritization. By advancing our understanding of exercise-induced neuroplasticity and optimizing its implementation, we may develop more effective strategies to reduce the growing burden of neurodegenerative diseases in our aging population.

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Abbreviations

The following abbreviations are used in this manuscript:[157]

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
TLA	Three letter acronym
LD	Linear dichroism

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