REVIEW

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Neural Plasticity in Neurodegeneration: Exploring Adaptive and Maladaptive Mechanisms for Therapeutic Advances

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Abstract

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, represent a significant challenge for modern medicine, marked by progressive neuronal dysfunction and loss. Emerging evidence highlights the critical role of neuroplasticity, the brain's ability to reorganize and adapt in response to damage, in mitigating cognitive and functional decline in these diseases. This review examines the molecular mechanisms underlying synaptic plasticity, with a focus on the interaction between neuroinflammation and plasticity in neurodegenerative conditions. We explore various therapeutic strategies, including pharmacological interventions, non-pharmacological approaches like physical exercise and cognitive training, and advanced technologies such as brain-computer interfaces (BCIs) and neuroimaging techniques. High-efficiency omics technologies, including genomics, proteomics, and metabolomics, have provided valuable insights into the genetic, molecular, and biochemical factors that influence synaptic function and plasticity. Additionally, immune modulation, through pharmacological and cellular therapies, offers a promising avenue for enhancing neuroplasticity. This review also emphasizes the integration of multimodal strategies, combining pharmacological treatments with advanced neurorehabilitation techniques. By understanding the intricate molecular networks that govern plasticity, researchers can develop more targeted and personalized therapies, aiming to preserve brain function and slow disease progression in individuals with neurodegenerative diseases.

Keywords: Neuroplasticity, neurodegenerative diseases, synaptic plasticity, therapeutic strategies, brain-computer interfaces (BCIs)

Introduction

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS) represent a significant challenge in modern medicine due to their progressive nature and lack of effective treatments (1). These disorders are primarily characterized by the gradual loss of neuronal function, leading to severe cognitive, motor, and sensory impairments (2). At the molecular level, protein aggregation, mitochondrial dysfunction, and chronic neuroinflammation are among the key pathological mechanisms driving neuronal degeneration. These processes contribute to synaptic loss, oxidative

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stress, and neuronal apoptosis, ultimately resulting in irreversible neural damage (3).

While these mechanisms are central to disease progression, growing evidence highlights the crucial role of brain plasticity in modulating neurodegenerative outcomes. Neuroplasticity, defined as the nervous system's ability to adapt and reorganize in response to internal and external stimuli, plays a fundamental role in maintaining neural function and compensating for damage (4). This phenomenon involves intricate molecular and structural changes, including alterations in gene expression, neurotransmitter dynamics, neurotrophic factor regulation, and synaptic remodeling (5). However, the dysregulation of plasticity mechanisms may also exacerbate disease progression by attempting to compensate for neuronal loss in an inefficient or maladaptive manner (4).

Recent studies have highlighted the dual role of neuroplasticity in neurodegenerative diseases (6). While impaired or maladaptive plasticity may accelerate disease pathology, targeted interventions aimed at enhancing functional reorganization could provide promising therapeutic benefits (7). Harnessing the brain's intrinsic plasticity mechanisms may offer novel strategies for neuronal repair, functional compensation, and delaying neurodegenerative decline (8).

This study aims to explore the pathophysiological basis of neuroplasticity in neurodegenerative diseases, emphasizing its potential as a therapeutic target. By understanding how plasticity contributes to both disease progression and recovery, novel approaches for neuroprotective treatments may be developed. The dual nature of neuroplasticity, both adaptive and maladaptive, is conceptually illustrated in Figure 1.

Material and Method

The role of neural plasticity in the management of neurodegenerative diseases has gained increasing attention in recent years. Previous reviews have explored selected aspects of this field, such as synaptic remodeling in Alzheimer's disease, neurotrophic factor regulation in Parkinson's disease, or the impact of neuroinflammation on neural circuitry. However, most of these studies focus on single diseases, isolated molecular pathways, or individual therapeutic strategies, without providing an integrated framework that connects molecular mechanisms, cellular adaptations, and clinical implications across multiple neurodegenerative disorders.

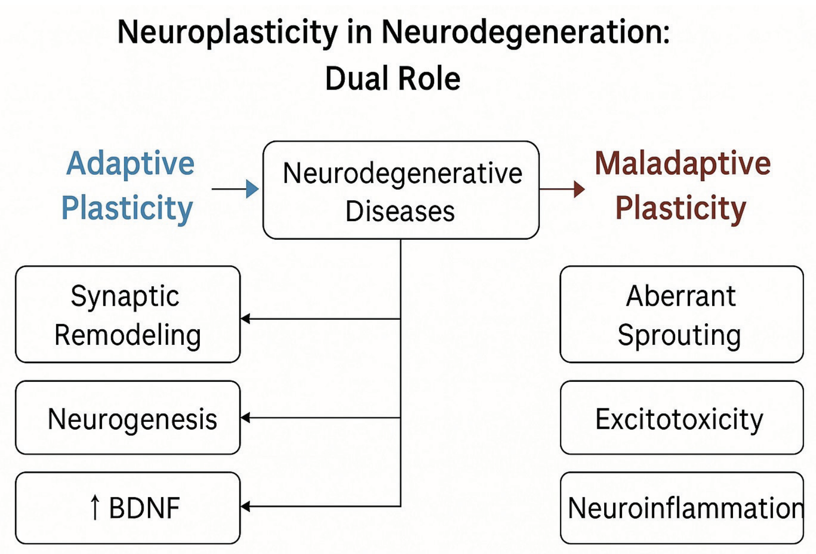

Figure 1

The Dual Role of Neuroplasticity in Neurodegenerative Diseases.

*This conceptual diagram illustrates the bidirectional nature of neuroplasticity in neurodegenerative diseases. While adaptive plasticity promotes functional compensation through synaptic remodeling, neurogenesis, and neurotrophic factor support, maladaptive plasticity contributes to disease progression via aberrant circuit rewiring, excitotoxicity, and chronic neuroinflammation. Understanding this duality is crucial for developing targeted therapies that enhance beneficial plasticity while suppressing pathological remodeling. Figure created by the author.

This review addresses this gap by synthesizing current evidence on both adaptive and maladaptive roles of neuroplasticity across major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). In doing so, it highlights:

- The molecular and cellular mechanisms underlying neuroplasticity, such as synaptic reorganization, neurotransmitter dynamics, and neurotrophic factor signaling.

- The functional implications of these mechanisms for disease progression, compensatory remodeling, and cognitive/motor outcomes.

- The therapeutic strategies aimed at enhancing beneficial plasticity or mitigating maladaptive changes, integrating preclinical and clinical perspectives.

A structured literature review was conducted to identify relevant studies published between 2018 and 2024. Databases including PubMed, Google Scholar, and Elsevier were searched using combinations of the following keywords: neuroplasticity, synaptic remodeling, neurodegenerative diseases, Alzheimer's, Parkinson's, ALS, neural adaptation, therapeutic neuroplasticity.

The inclusion criteria were as follows:

- Studies specifically examining the adaptive and maladaptive roles of neuroplasticity in neurodegeneration.

- Research addressing molecular and cellular mechanisms, including synaptic reorganization, neurotransmitter regulation, and neurotrophic factor signaling.

- Investigations of therapeutic interventions designed to enhance neuroplasticity for neuroprotection or functional recovery.

- Peer-reviewed articles in high-impact journals in the fields of neuroscience, neurology, and neurodegeneration.

Studies focusing exclusively on non-neurodegenerative conditions, or those lacking mechanistic insights into neuroplasticity, were excluded. This approach ensures that the review provides a comprehensive and integrated perspective, bridging molecular mechanisms and therapeutic applications to guide future research directions.

1. Mechanisms That Modulate Brain Plasticity

1.1. Synaptic Plasticity in Neurodegeneration: Molecular Mechanisms and Therapeutic Implications

Synaptic plasticity, a fundamental process underlying neuronal adaptation and functional reorganization, plays a crucial role in maintaining cognitive and motor functions (7). This mechanism involves dynamic changes in synaptic strength, neurotransmitter release regulation, receptor trafficking, and dendritic spine remodeling in response to neuronal activity (5). The ability of synapses to adapt is essential for learning, memory consolidation, and motor coordination, making synaptic plasticity a critical target in neurodegenerative disease research.

In neurodegenerative diseases, synaptic plasticity is progressively impaired, leading to synaptic dysfunction, network disintegration, and cognitive or motor deficits. In Alzheimer's disease (AD), the accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau proteins interferes with synaptic signaling, disrupting long-term potentiation (LTP) and long-term depression (LTD), the primary mechanisms of synaptic reinforcement and weakening (5). These disruptions result in deficits in learning, memory formation, and synaptic resilience. Similarly, in Parkinson's disease (PD), the degeneration of dopaminergic neurons in the substantia nigra leads to dysfunctional cortico-striatal synaptic plasticity, impairing adaptive mechanisms necessary for motor control (9).

Recent therapeutic approaches aim to modulate synaptic plasticity to counteract the harmful effects of neurodegenerative diseases. Pharmacological interventions targeting glutamatergic and dopaminergic neurotransmission have demonstrated promising results in preclinical and clinical studies (10, 11). For instance:

- NMDA receptor modulators (e.g., memantine) help preserve synaptic integrity by preventing excitotoxicity in AD.

- Dopamine agonists and L-DOPA therapy aim to restore dopaminergic signaling and enhance synaptic function in PD.

- BDNF-based therapies and neurotrophic factor modulation promote synaptic resilience and neuroprotection in multiple neurodegenerative conditions.

In addition to pharmacological approaches, non-invasive neuromodulation techniques such as transcranial magnetic stimulation (TMS) and

Table 1 Synaptic Plasticity Mechanisms in Neurodegenerative Diseases

Synaptic Mechanism	Effect in Neurodegenerative Diseases	Therapeutic Implications
Neurotransmitter Release Regulation	Impaired neurotransmitter release in AD and **PD**	Targeting neurotransmitter systems for synaptic recovery
Changes in Dendritic Protrusions	Synaptic reorganization is disrupted in Alzheimer's	Pharmacological agents to restore dendritic structures
Long-term Potentiation/Depression (LTP/LTD)	Deficits in LTP and LTD lead to cognitive decline	Synaptic plasticity modulation through non-pharmacological techniques

transcranial direct current stimulation (tDCS) have shown potential in enhancing synaptic plasticity and compensatory mechanisms in both AD and PD patients (12). Furthermore, emerging strategies like gene therapy, optogenetics, and neuroprosthetics are being investigated for their ability to restore synaptic function and network integrity in advanced neurodegeneration. Table 1 summarizes the key molecular mechanisms of synaptic plasticity, their disruption in neurodegenerative diseases, and targeted therapeutic strategies aimed at restoring synaptic function.

1.2. Neurotrophic Factors: Role in Brain Plasticity and Neurodegenerative Disorders

Neurotrophic factors play a crucial role in regulating brain plasticity by promoting neuronal survival, differentiation, and synaptic remodeling (13). These trophic molecules, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF), contribute to neuronal network stability and adaptive responses to injury (14). By enhancing synaptic connectivity and regulating neurotransmitter dynamics, neurotrophic factors support learning, memory processes, and motor function, making them critical for both healthy brain function and resilience against neurodegeneration.

Disruptions in neurotrophic factor signaling have been identified as key contributors to the progression of neurodegenerative diseases, leading to synaptic dysfunction, neuronal loss, and cognitive decline (15). In AD, reduced BDNF expression and impaired TrkB receptor activation contribute to hippocampal atrophy, synaptic weakening, and deficits in memory consolidation (16,17). Similarly, in PD, decreased levels of GDNF and NGF correlate with dopaminergic neuron degeneration, exacerbating motor impairments and limiting compensatory plasticity mechanisms (18). The core mechanisms involving neurotrophic signaling, synaptic remodeling, and neurogenesis are schematically presented in Figure 2.

Given the essential role of neurotrophic factors in neuronal maintenance, several therapeutic strategies have been explored to enhance their function and restore neuroplasticity. The administration of exogenous BDNF and GDNF has demonstrated neuroprotective effects in preclinical studies, although their clinical application remains limited due to poor blood-brain barrier permeability and short biological half-life (19). To overcome these challenges, gene therapy approaches utilizing viral vector-mediated BDNF and GDNF delivery have shown potential for long-term neuroprotection and functional recovery. Additionally, small-molecule mimetics targeting neurotrophic factor receptors, such as TrkB and RET agonists, offer an alternative strategy by activating endogenous neurotrophic pathways without the pharmacokinetic limitations of direct protein administration.

Beyond direct neurotrophic modulation, recent studies have highlighted the role of neuroinflammation in regulating neurotrophic signaling. Pro-inflammatory cytokines such as TNF-α and IL-1β have been shown to suppress BDNF and NGF expression, accelerating neuronal degeneration and limiting the brain's ability to adapt to progressive damage (18). As a result, therapies aimed at reducing inflammation, including NSAIDs, monoclonal antibodies targeting cytokine pathways, and lifestyle interventions (e.g., exercise and dietary modifications), may indirectly enhance neurotrophic factor signaling and neuroplasticity.

As summarized in Table 2, neurotrophic factors play a pivotal role in both the pathophysiology of neurodegenerative diseases and the development

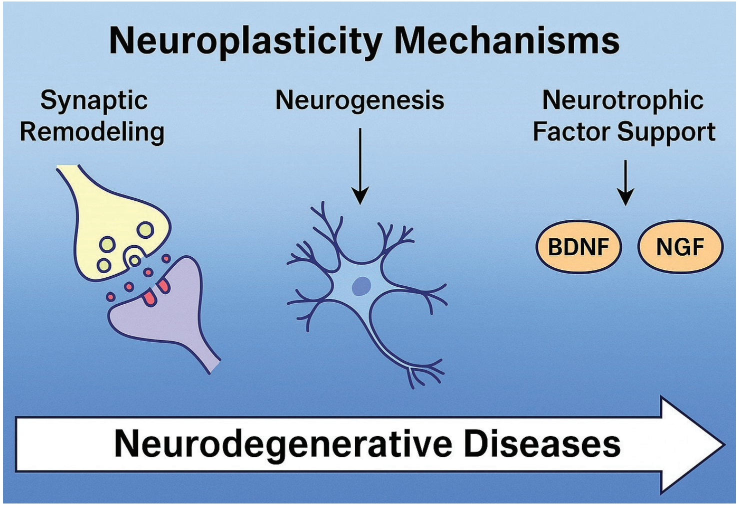

Figure 2
Core Mechanisms of Neuroplasticity in Neurodegenerative Disorders.
*This schematic illustration highlights the primary mechanisms involved in neuroplasticity within neurodegenerative diseases, including synaptic remodeling, neurogenesis, and neurotrophic factor signaling. These interconnected pathways collectively contribute to the brain's ability to compensate for neuronal loss and maintain functional capacity. The diagram underscores how these processes converge in the context of Alzheimer’s, Parkinson’s, and Huntington’s disease. Figure created by the author.

Table 2 Neurotrophic Factors and Their Effects on Neurodegenerative Diseases

Neurotrophic Factor	Role in Brain Plasticity	Effect in Neurodegenerative Diseases	Therapeutic Potential
BDNF (Brain-Derived Neurotrophic Factor)	Supports neuronal survival, differentiation, and synaptic plasticity.	Impaired BDNF signaling is associated with cognitive decline in AD.	BDNF supplementation or gene therapy to enhance plasticity.
NGF (Nerve Growth Factor)	Supports cholinergic neuron survival and synapse formation.	Reduced NGF levels are linked to cognitive impairment in AD and PD.	NGF supplementation or modulation to protect neurons.
GDNF (Glial-Derived Neurotrophic Factor)	Promotes dopaminergic neuron survival and neural regeneration.	GDNF is being investigated for its potential in treating PD.	GDNF infusion or gene therapy to restore dopaminergic function.
CNTF (Ciliary Neurotrophic Factor)	Supports the brain’s adaptive capacity, enhances neurotrophic factor release.	In ALS, CNTF may help in preserving motor neurons.	CNTF-based therapies for ALS and motor neuron diseases.

of emerging treatment strategies targeting brain plasticity. Future research should focus on optimizing therapeutic delivery methods, improving receptor specificity, and integrating neurotrophic modulation with other neuroprotective strategies to enhance clinical outcomes.

1.3. Glial Cell Contributions to Neural Plasticity in Health and Neurodegeneration

Although neurons are traditionally considered the primary drivers of brain plasticity, growing evidence suggests that glial cells, particularly microglia and astrocytes, play an essential role in modulating neural adaptation, synaptic remodeling, and neuroinflammation (20). These cells actively interact with neuronal circuits, influencing both physiological and pathological plasticity processes.

Microglia, the resident immune cells of the brain, are highly dynamic and continuously survey the neural environment. Under physiological conditions, microglia regulate synaptic function by pruning excessive synapses, clearing debris, and secreting neurotrophic factors that support synaptic plasticity (21,22). However, in neurodegenerative diseases, chronic microglial activation creates a sustained neuroinflammatory state, characterized by the excessive release of pro-inflammatory cytokines (TNF-α, IL-1β), chemokines, and reactive oxygen species (ROS). This persistent activation disrupts neurotransmitter signaling, impairs synaptic integrity, and promotes neuronal apoptosis, ultimately compromising neuroplasticity (23,24, 25).

Astrocytes, the most abundant glial cells in the central nervous system, also play a critical role in supporting neuronal plasticity. They maintain synaptic homeostasis by regulating neurotransmitter uptake (e.g., glutamate clearance), modulating ion concentrations, and influencing synaptic transmission (22,8). Under pathological conditions, astrocytes undergo reactive transformation, shifting into a pro-inflammatory state that exacerbates neuroinflammation and disrupts neuronal function. Astrocytic overproduction of inflammatory mediators further amplifies synaptic dysfunction and contributes to neurodegenerative progression (16).

2. Aging and Plasticity

2.1. Aging and Brain Plasticity: How Age-Related Changes Influence Neurodegenerative Disease Progression

Brain plasticity declines progressively with aging, affecting synaptic remodeling, neurogenesis, and neuronal resilience to injury. This reduction in plasticity contributes significantly to the onset and progression of neurodegenerative diseases, as the brain loses its capacity to compensate for neuronal loss and dysfunction. One of the hallmark changes of aging is the emergence of low-grade chronic neuroinflammation, partially mediated by microglial priming and the sustained release of pro-inflammatory cytokines such as IL-1 and IL-6. This inflammatory state disrupts neuronal homeostasis, weakens synaptic integrity, and accelerates cognitive decline (26).

Aging microglia exhibit a pro-inflammatory phenotype, characterized by excessive cytokine production, impaired debris clearance, and increased oxidative stress. As a result, rather than maintaining a protective neuroimmune balance, aged microglia promote chronic neuroinflammation that exacerbates synaptic dysfunction and neuronal loss. The sustained release of inflammatory mediators has been directly linked to the progression of Alzheimer’s and PD, where chronic inflammation further weakens compensatory neuroplasticity mechanisms (27).

Beyond neuroinflammation, age-related reductions in neuroplasticity also involve a diminished ability to regulate synaptic strength, neurotrophic factor signaling, and neural network remodeling. The downregulation of neurotrophic factors such as BDNF and NGF significantly impairs neuronal survival, synaptic maintenance, and adaptive plasticity responses (2,28). Additionally, decreased neurogenesis in the hippocampus contributes to cognitive deficits and reduced neural circuit flexibility, further limiting the brain's ability to recover from damage or disease progression.

As summarized in Table 3, key age-related changes-including chronic microglial activation, neuroinflammation, impaired neurotrophic signal-ing, and synaptic deterioration-contribute to the acceleration of neurodegenerative disease processes. This decline in adaptive plasticity reduces the brain’s ability to counteract progressive neuronal loss, underscoring the importance of age-related mechanisms in the development of neurodegenerative conditions (29).

2.2. Epigenetic Regulation of Brain Plasticity in Aging and Neurodegeneration

Aging is associated with significant alterations in epigenetic regulation, which influence gene expression patterns critical for brain plasticity (30). Alongside age-related neuroinflammation and the decline in neurotrophic factor signaling, epigenetic modifications play a key role in shaping neuronal structure, function, and adaptability. These changes include DNA methylation alterations, histone modifications, and non-coding RNA dysregulation, all of which contribute to the progressive loss of synaptic plasticity and neuronal resilience (31).

One of the most well-studied epigenetic changes in aging is DNA methylation-driven silencing of genes involved in synaptic function. In particular, BDNF gene promoter hypermethylation has been linked to reduced synaptic plasticity, cognitive decline, and the acceleration of neurodegenerative disease progression (32). Similarly, histone deacetylation suppresses the expression of genes required for neuronal repair and

Table 3 Aging and Its Effects on Brain Plasticity

Age-Related Change	Impact on Brain Plasticity	Effect on Neurodegenerative Diseases	Therapeutic Strategies
Microglial Activation	Chronic low-level neuroinflammation	Impairs synaptic function and plasticity in Alzheimer's	Anti-inflammatory drugs
Decreased Neurogenesis	Reduced plasticity in the hippocampus and cortex	Accelerates Alzheimer's and Parkinson's progression	Exercise, cognitive training
Reduced Neurotrophic Factor Levels	Less support for neuronal survival and synaptic plasticity	Contributes to cognitive decline in aging	Supplementation with neurotrophic factors

synaptic remodeling, further limiting the brain's ability to counteract age-related functional decline.

These epigenetic changes not only impair neuroplasticity and neurotransmitter signaling but also increase susceptibility to neurodegeneration. However, since epigenetic modifications are reversible, they present a promising therapeutic avenue for modulating brain plasticity and mitigating the effects of aging and neurodegenerative diseases. Interventions targeting epigenetic mechanisms, such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase (DNMT) modulators, have shown potential in enhancing synaptic plasticity, reducing neuroinflammation, and slowing neurodegeneration in preclinical models (6, 33).

3. Neuroplasticity Across Major Neurodegenerative Disorders

3.1. Neuroplasticity in Alzheimer's Disease: Compensatory Mechanisms or Pathological Changes?

In AD, neuroplasticity serves as an essential mechanism in early-stage compensation but becomes increasingly disrupted as the disease progresses. In the initial stages, the brain attempts to counteract neuronal loss through synaptic remodeling, circuit reorganization, and recruitment of alternative neural pathways to sustain cognitive function. These adaptive mechanisms enable patients to maintain cognitive abilities despite accumulating pathological changes, delaying the onset of severe symptoms (34).

However, as the disease advances, progressive synaptic dysfunction and neurodegeneration weaken the brain's ability to compensate. The accumulation of amyloid-β plaques and hyperphosphorylated tau tangles disrupts normal synaptic transmission and impairs network plasticity (35, 36). Neuroinflammation, oxidative stress, and mitochondrial dysfunction further compromise synaptic resilience, leading to loss of dendritic spines, impaired neurotransmission, and irreversible cognitive decline.

The aging brain is particularly vulnerable to these neuroplasticity disruptions. Age-related declines in neurotrophic factor signaling, reduced synaptic remodeling capacity, and weakened neuronal metabolism limit the efficacy of compensatory plasticity (37). Additionally, chronic neuroinflammation and vascular dysfunction exacerbate synaptic degradation and neuronal network instability, accelerating Alzheimer's progression (38). This interplay between aging, neuroplasticity decline, and disease pathology highlights why older individuals experience faster cognitive deterioration once AD-related changes begin.

Given the evolving nature of neuroplasticity in AD, therapeutic interventions have focused on enhancing compensatory mechanisms while preventing pathological disruptions. Pharmacological approaches such as cholinesterase inhibitors and NMDA receptor modulators aim to stabilize synaptic function, while BDNF-targeted therapies and neurotrophic factor modulation seek to reinforce synaptic resilience. Additionally, neuromodulatory techniques, including TMS and tDCS, have shown potential in reactivating neural networks and supporting functional recovery.

3.2. The Dual Role of Neural Plasticity in Parkinson's Disease: Protective or Maladaptive?

PD is primarily characterized by progressive degeneration of dopaminergic neurons in the substantia nigra, leading to motor deficits such as tremors, rigidity, and bradykinesia (9). In response to dopaminergic loss, the brain initially engages compensatory plasticity mechanisms, including increased sprouting of remaining dopaminergic terminals, upregulation of dopamine receptor sensitivity, and recruitment of alternative neural pathways to sustain motor function (39). These adaptive responses help delay symptom onset and maintain motor control in early stages of PD.

However, not all neuroplastic changes are beneficial. As the disease progresses, excessive or uncoordinated synaptic remodeling can lead to maladaptive plasticity, exacerbating disease symptoms and treatment-related complications (40). A well-documented example is L-DOPA-induced dyskinesia (LID), a side effect of prolonged L-DOPA therapy. While L-DOPA temporarily restores dopamine signaling, the abnormal sprouting and excessive sensitivity of dopaminergic terminals contribute to involuntary and uncontrolled movements, significantly impairing quality of life (41,42). Additionally, maladaptive plasticity in basal ganglia-thalamocortical circuits disrupts motor coordination and learning, further complicating disease management.

Beyond the intrinsic plasticity changes within PD, aging-related declines in neuroplasticity further reduce the brain's ability to compensate for dopaminergic loss. The aging brain exhibits diminished synaptic remodeling capacity, reduced neurotrophic factor availability, and impaired neuronal network reorganization, all of which accelerate disease progression and worsen symptom severity (43). Furthermore, chronic neuroinflammation and oxidative stress exacerbate synaptic dysfunction and maladaptive circuit remodeling, making older individuals less responsive to compensatory plasticity-driven mechanisms (44).

Thus, the role of neuroplasticity in PD is inherently dual-faceted. In early-stage disease, it delays functional decline by reorganizing neural networks and maintaining dopaminergic signaling. However, as neuronal loss becomes more severe, these same plasticity mechanisms become dysregulated, leading to maladaptive consequences that contribute to treatment resistance and motor complications. Understanding this delicate balance between beneficial and harmful plasticity changes is essential for designing therapies that enhance compensatory mechanisms while preventing maladaptive outcomes. Emerging interventions such as targeted neuromodulation (e.g., deep brain stimulation), pharmacological strategies aimed at stabilizing dopamine signaling, and neurotrophic factor-based therapies hold promise for managing both adaptive and maladaptive neuroplasticity in PD.

3.3. Huntington's Disease and Synaptic Remodeling: Insights into Cognitive Decline

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by the degeneration of medium spiny neurons (MSNs) in the striatum, a region critical for integrating cortical and subcortical inputs involved in motor control and cognition (45). In the early stages of the disease, the brain initiates compensatory plasticity mechanisms, attempting to counteract neuronal loss through synaptic remodeling, enhanced excitatory drive, and neural circuit reorganization (46). These adaptive responses help delay the onset of severe clinical symptoms by maintaining functional connectivity between striatal and cortical networks.

However, as HD progresses, ongoing neuronal degeneration, disrupted synaptic plasticity, and dysregulated neurotransmitter dynamics impair these compensatory mechanisms, leading to worsening cognitive and motor deficits (47). The loss of MSNs particularly affects glutamatergic and dopaminergic signaling, causing excessive cortical hyperexcitability, imbalanced inhibitory-excitatory control, and maladaptive synaptic remodeling. These pathological changes contribute to the hallmark symptoms of HD, including chorea, cognitive impairment, and psychiatric disturbances.

Aging further compounds neuroplasticity deficits in HD. The age-related decline in neurotrophic support, diminished synaptic adaptability, and increased neuroinflammation weaken the brain's ability to reorganize neural connections in response to neurodegenerative damage (48). As a result, the brain's intrinsic plasticity mechanisms become progressively insufficient, leading to more severe and rapid functional decline in older individuals (38). This interplay between disease progression, synaptic dysfunction, and aging-related plasticity reductions accelerates cognitive and motor deterioration.

4. Treatment Methods and Brain Plasticity

4.1. Pharmacological Enhancement of Neural Plasticity: A Therapeutic Avenue for Neurodegenerative Diseases

Pharmacological interventions targeting neural plasticity mechanisms have gained increasing attention as potential strategies for delaying cognitive decline and enhancing functional recovery in neurodegenerative diseases (36). Several classes of drugs have been investigated for their ability to modulate synaptic plasticity, protect neurons from degeneration, and facilitate compensatory neural reorganization.

One of the primary therapeutic targets is glutamatergic and GABAergic neurotransmission, which play a fundamental role in synaptic strength, learning, and memory processes. NMDA receptor modulators, such as memantine, have demonstrated efficacy in stabilizing excitatory-inhibitory balance and preventing excitotoxicity, a key contributor to neurodegeneration in AD (49, 50). Similarly, GABAergic modulation strategies, including GABA agonists and benzodiazepine-based compounds, have been explored for their ability to enhance inhibitory control and protect against abnormal network hyperactivity seen in PD and HD.

Beyond neurotransmitter-based interventions, neuroinflammation-targeting therapies have emerged as promising approaches for preserving neural plasticity. Chronic inflammation disrupts synaptic remodeling, neurotrophic factor signaling, and neurogenesis, thereby accelerating cognitive decline. Anti-inflammatory agents such as NSAIDs, COX-2 inhibitors, and monoclonal antibodies against pro-inflammatory cytokines (e.g., TNF-α inhibitors) have shown potential in mitigating inflammation-induced synaptic dysfunction and improving adaptive plasticity responses (6).

Another significant avenue of research focuses on epigenetic regulation of neuroplasticity. HDAC inhibitors and DNMT modulators have demonstrated neuroprotective effects by enhancing synaptic plasticity, reversing transcriptional repression of neurotrophic genes, and restoring memory function in animal models of neurodegeneration (51,52). These findings suggest that targeting epigenetic modifications may provide long-term benefits by reprogramming neuronal gene expression to support adaptive plasticity mechanisms.

Neurotrophic factors such as BDNF, NGF, and GDNF are also being investigated for their ability to promote neuronal survival, synaptogenesis, and circuit reorganization. However, challenges such as limited blood-brain barrier permeability and short half-life have hindered their clinical translation. Efforts to develop small-molecule mimetics, gene therapy-based delivery systems, and biomaterial-based sustained-release formulations are ongoing to optimize their therapeutic potential (18).

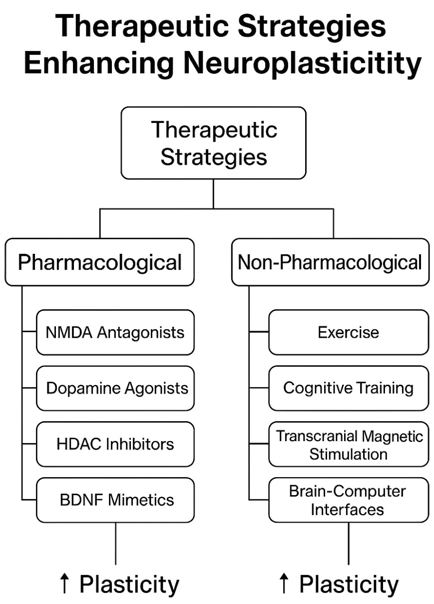

Figure 3

Therapeutic Strategies Enhancing Neuroplasticity in Neurodegenerative Diseases.

*This flowchart categorizes the principal therapeutic approaches aimed at enhancing neuroplasticity into pharmacological and non-pharmacological domains. Pharmacological strategies include neurotransmitter modulators, neurotrophic factor mimetics, and epigenetic agents, while non-pharmacological strategies encompass physical exercise, cognitive training, and brain stimulation techniques such as TMS. This classification highlights the need for multimodal interventions to effectively support synaptic resilience and functional recovery in neurodegenerative conditions. Figure created by the author.

While pharmacological approaches offer significant promise, their effectiveness is often enhanced when integrated with non-pharmacological interventions. Cognitive training, aerobic exercise, TMS, and deep brain stimulation (DBS) have demonstrated complementary effects by activating neuroplasticity pathways and facilitating long-term functional improvements (53,54). Future research should focus on developing personalized, multimodal treatment strategies that combine pharmacological agents with targeted neurostimulation and behavioral interventions, optimizing their efficacy based on disease stage and individual plasticity potential. A classification of the principal therapeutic strategies enhancing neuroplasticity is summarized in Figure 3.

4.2. Non-Pharmacological Approaches to Modulating Brain Plasticity in Neurodegeneration: Exercise, Diet, and Cognitive Training

Non-pharmacological interventions have gained increasing attention as effective strategies for enhancing brain plasticity and mitigating neurodegenerative processes (55). These approaches, which include physical exercise, dietary modifications, and cognitive training, leverage the brain's inherent capacity for synaptic remodeling, neurogenesis, and network reorganization, making them valuable adjuncts to pharmacological treatments in neurodegenerative diseases.

Regular physical exercise has been shown to stimulate neurogenesis, enhance synaptic function, and promote the release of neurotrophic factors, particularly BDNF, which plays a crucial role in synaptic plasticity (5). Exercise-induced increases in hippocampal neurogenesis and cortical connectivity have been linked to improvements in cognitive function, motor coordination, and emotional resilience, particularly in conditions such as AD and PD (56). Additionally, aerobic and resistance training have been associated with reduced neuroinflammation and oxidative stress, further supporting neuronal survival and functional reorganization.

Dietary interventions, particularly the Mediterranean diet, have also been implicated in enhancing neuroplasticity and protecting against neurodegenerative decline. These effects are largely attributed to the diet's anti-inflammatory, antioxidant, and neurotrophic-enhancing properties, which contribute to reduced neuronal apoptosis, improved mitochondrial function, and stabilization of synaptic integrity (57). Specific nutrients such as omega-3 fatty acids, polyphenols, and flavonoids have been found to upregulate BDNF expression, modulate neurotransmitter levels, and support synaptic plasticity mechanisms in the aging brain.

Cognitive training, including activities such as problem-solving tasks, memory exercises, and skill learning, has been demonstrated to trigger neuroplasticity-related processes, strengthen neural connections, and improve cognitive reserve (58,59). Longitudinal studies suggest that structured cognitive engagement may delay cognitive decline in AD and improve executive function in PD by reinforcing synaptic connectivity, increasing cortical thickness, and promoting compensatory neural network activation.

4.3. The Role of Transcranial Magnetic Stimulation (TMS) in Enhancing Brain Plasticity in Neurodegenerative Disorders

TMS is a non-invasive neuromodulation technique capable of influencing neuronal excitability and synaptic plasticity. By applying repetitive magnetic pulses to specific cortical areas, TMS has been investigated for its potential to counteract cognitive and functional decline in neurodegenerative diseases by modulating cortical network activity and facilitating adaptive neuroplasticity processes (60).

TMS exerts its effects by inducing LTP and LTD, two fundamental mechanisms underlying synaptic remodeling and neuronal network reorganization (61). Through these processes, TMS facilitates synaptic strengthening, enhances neuronal connectivity, and reorganizes neural circuits, potentially compensating for neurodegenerative damage and promoting functional recovery (62).

In PD, TMS has been explored for its ability to modulate cortico-striatal and motor cortical pathways, promoting compensatory plasticity in response to dopaminergic neuron loss. Studies have shown that high-frequency TMS (≥5 Hz) over the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) can improve motor coordination, gait function, and bradykinesia, likely by enhancing dopaminergic neurotransmission and reorganizing motor networks (63). Additionally, TMS applied to non-motor areas has demonstrated promise in improving executive function and mood disturbances associated with PD.

In AD, TMS has been investigated for its ability to enhance cognitive function, delay disease progression, and modulate plasticity-related processes. Research suggests that repetitive TMS (rTMS) applied to the DLPFC, posterior parietal cortex, and hippocampal-related networks can enhance working memory, attention, and processing speed, potentially by stimulating neurotrophic factor expression, reducing beta-amyloid burden, and restoring disrupted neural synchrony (64). These findings highlight the potential of TMS as an adjunct therapy for preserving cognitive function in early-stage AD.

5. Brain Plasticity and the Neuroimmune Relationship

5.1. Neuroinflammation and Synaptic Plasticity in Neurodegeneration

The interaction between neuroinflammation and synaptic plasticity plays a pivotal role in the pathogenesis of neurodegenerative diseases, influencing both disease progression and neuronal function (65). Neuroinflammation, which is marked by the activation of microglia and astrocytes, can have both beneficial and detrimental effects on brain plasticity. While inflammation is traditionally viewed as harmful in the context of neurodegeneration, recent studies have emphasized its complex dual role, acting as both a protective mechanism and a contributor to disease progression (66).

On the one hand, the release of pro-inflammatory mediators such as cytokines (e.g., TNF-α, IL-1β), chemokines, and ROS by activated glial cells can disrupt synaptic function and impair synaptic plasticity mechanisms. Chronic inflammation impairs neurotrophic factor signaling, synaptic strength, and neurogenesis, which can accelerate cognitive decline and impair motor function in diseases such as AD, PD, and HD (8). This persistent inflammatory state contributes to synaptic loss, network instability, and progressive neuronal degeneration, further compounding the damage caused by neurodegeneration. Table 4 shows the key mediators of neuroinflammation, including cytokines, ROS, and chemokines, and their specific effects on synaptic plasticity.

On the other hand, controlled and transient inflammatory responses can have a beneficial effect by stimulating the production of neurotrophic factors, promoting synaptic remodeling, and enhancing neuronal network reorganization. For example, activated microglia can secrete neuroprotective molecules like BDNF, which aid in the recovery of neuronal circuits and synaptic strength. Similarly, astrocytes play a role in maintaining homeostasis during inflammation by regulating neurotransmitter levels and supporting neuronal survival (67, 68).

The complex nature of this neuroimmune relationship underscores the importance of targeting both inflammatory pathways and plasticity-related processes in developing effective therapeutic strategies. Pharmacological approaches, such as anti-inflammatory drugs (e.g., NSAIDs, TNF-α inhibitors), immunomodulatory agents, and neuroprotective compounds, are being investigated to reduce neuroinflammation and enhance synaptic plasticity (24). Furthermore, non-invasive techniques such as TMS offer a promising approach to modulating both inflammation and plasticity, providing an avenue for therapeutic intervention in neurodegenerative diseases (36).

5.2. Immune Modulation of Brain Plasticity: Potential Therapeutic Strategies for Neurodegenerative Diseases

Emerging research on the interaction between the immune system and neuronal plasticity suggests that modulating immune responses may offer a novel therapeutic avenue for treating neurodegenerative diseases (69). Microglia and astrocytes, the

Table 4 Neuroinflammation and Its Effects on Synaptic Plasticity

Inflammatory Agent	Effect on Synaptic Function	Impact on Neurodegeneration	Therapeutic Approaches
Cytokines (IL-1, IL-6)	Disrupt synaptic function, impair plasticity	Accelerates neurodegeneration	Immune-modulatory therapies
Reactive Oxygen Species (ROS)	Impair synaptic signaling and plasticity	Contributes to neuronal death in neurodegenerative diseases	Antioxidant therapy
Chemokines	Enhance microglial activation, promote neuroinflammation	Damages synaptic plasticity	Targeting chemokine pathways for neuroprotection

principal immune cells in the brain, play a key role in regulating neuroinflammation and modulating synaptic plasticity. Through careful regulation of the inflammatory response, these glial cells can promote neurogenesis, synaptic reshaping, and neuronal network reorganization, helping the brain compensate for neurodegenerative damage (24). This positive, short-term inflammatory response can enhance neuroplasticity and support functional recovery, highlighting the potential of immune modulation as a therapeutic approach to counteract the detrimental effects of chronic neuroinflammation in neurodegenerative diseases.

In neurodegenerative conditions such as AD, PD, and HD, persistent neuroinflammation and excessive microglial activation are thought to accelerate neuronal loss and disrupt neuroplasticity. However, carefully modulating these immune responses holds the potential to restore the balance between neuroinflammation and synaptic plasticity. For instance, pharmacological interventions that target pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) or specific immune pathways involved in microglial activation have shown promise in reducing harmful inflammation while preserving or enhancing synaptic function (66). Selective immune modulation may therefore provide a way to alleviate the neurodegenerative process by promoting the restoration of adaptive neuroplasticity without exacerbating chronic inflammation.

Additionally, mesenchymal stem cell (MSC) transplantation has been explored as a therapeutic strategy with anti-inflammatory and neuroprotective properties. MSCs are known to modulate immune responses, reduce neuroinflammation, and promote synaptic plasticity through the secretion of neurotrophic factors. Studies suggest that MSC transplantation may not only preserve neural plasticity but also support functional recovery in neurodegenerative diseases by promoting tissue repair and enhancing neuronal survival (70). This approach represents a promising cell-based therapy aimed at enhancing both neuroinflammation regulation and neuroplasticity to improve cognitive and motor function in patients with neurodegenerative disorders.

6. Plasticity Research with Technological Advances

6.1. Advances in Imaging Brain Plasticity in Neurodegenerative Diseases

Advancements in neuroimaging technologies have revolutionized the study of brain plasticity in the context of neurodegenerative diseases (71). Functional magnetic resonance imaging (fMRI), diffusion-tensor imaging (DTI), and positron emission tomography (PET) are among the most sophisticated techniques that enable researchers to observe and measure dynamic changes in brain structure, function, and connectivity. These imaging methods are pivotal in monitoring neurodegenerative processes and assessing how the brain responds to therapeutic interventions, providing insights into plasticity mechanisms in the context of diseases such as AD, PD, and HD (72).

Functional MRI (fMRI) has been widely used to evaluate cognitive and behavioral processes by capturing neural correlations and monitoring how the brain compensates for neurodegeneration. By observing changes in brain activity, researchers have gained a deeper understanding of how neural circuits reorganize in response to neuronal loss and dysfunction, aiding in the identification of regions involved in cognitive compensation (73).

Similarly, diffusion-tensor imaging (DTI) has proven invaluable in assessing the structural integrity of white matter pathways, which are often disrupted in neurodegenerative diseases. DTI allows for the visualization and quantification of changes in axon fibers and white matter tracts, offering a way to track neuronal connectivity and monitor therapeutic effects on neural networks (74). In diseases like Parkinson's, DTI helps track the degeneration of dopaminergic pathways and assess the effectiveness of treatments aimed at preserving neuronal communication.

Positron emission tomography (PET), particularly with specialized radiotracers, offers a unique ability to visualize and quantify neuroinflammatory processes, which are critical to understanding the interaction between neuroinflammation and synaptic plasticity. PET imaging has been used to study beta-amyloid accumulation in Alzheimer's and dopamine receptor availability in Parkinson's, providing insights into neuroinflammatory signaling and neuronal damage (75,24). Moreover, PET can reveal synaptic integrity and track changes in neurotransmitter systems, providing key information on how inflammation impacts brain function.

These advanced imaging techniques have also proven essential in studying the spatial and temporal patterns of neuroplasticity across different stages of neurodegenerative diseases (76, 77). By evaluating longitudinal changes in neural function, white matter integrity, and regional metabolic activity, researchers can gain a comprehensive understanding of the dynamics of brain plasticity and how the brain adapts to progressive damage. Such information helps in developing personalized therapeutic strategies (6). By observing unique brain restructuring models in individual patients, clinicians can develop targeted interventions aimed at mitigating the harmful effects of neurodegeneration, improving both cognitive function and motor abilities (78).

6.2. Omics Technologies and Their Role in Understanding Synaptic Plasticity in Neurodegeneration

High-efficiency omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, have significantly advanced our understanding of the molecular mechanisms underlying synaptic plasticity in neurodegenerative diseases (79). These technologies provide a comprehensive approach to studying the genetic, biochemical, and molecular factors that regulate synaptic function and neuronal plasticity, offering unprecedented insights into how these processes are disrupted in conditions like AD, PD, and HD (80).

Genomics and transcriptomics have identified key genes involved in synaptic signaling, neurotransmitter release, and synaptic plasticity. These studies have also revealed the spatiotemporal expression patterns of these genes, providing a more detailed map of how neuronal circuits are affected in neurodegenerative diseases. For instance, transcriptomic studies have highlighted the dysregulation of genes such as BDNF, APP, and synaptic vesicle proteins, which are central to synaptic maintenance and plasticity (81).

Moreover, proteomics and metabolomics have provided valuable insights into the biochemical molecules involved in synaptic function. These include neurotransmitters, neuromodulators, and synaptic proteins, all of which play a critical role in synaptic composition and dynamics (82). For example, proteomic analyses have highlighted alterations in the expression and post-translational modifications of key proteins such as synaptic vesicle proteins and neurotransmitter receptors, which are often dysregulated in neurodegenerative diseases (83).

The integration of multi-omics data has facilitated the identification of specific molecular signatures and biomarkers that are associated with neurodegenerative diseases. This approach has also illuminated complex molecular networks and pathways involved in synaptic function and plasticity, providing a more comprehensive understanding of the factors driving neurodegeneration (84,85). By elucidating the molecular pathways and signaling cascades involved in regulating synaptic plasticity, researchers can identify potential therapeutic targets for intervention and personalized treatment strategies aimed at mitigating neuroplastic impairments in diseases like Alzheimer’s and Parkinson’s.

Table 5 highlights various imaging and omics technologies that are used to study synaptic plasticity and their specific applications in neurodegenerative research. For example, fMRI and PET imaging provide insights into neural activity and neuroinflammation, while genomics and proteomics identify genetic and protein-level changes associated with synaptic function in neurodegenerative conditions. By combining these technologies, researchers can gain a holistic view of the dynamics of brain plasticity and develop more precise therapeutic strategies.

Table 5 Imaging and Omics Technologies for Studying Synaptic Plasticity

Technology	Purpose in Brain Plasticity Research	Application in Neurodegeneration	Key Findings
fMRI (Functional Magnetic Resonance Imaging)	Measures brain activity and connectivity	Evaluates compensatory neural circuits in Alzheimer’s	Reveals reorganization of neural networks
PET (Positron Emission Tomography)	Measures metabolic activity and neuroinflammation	Assesses neuroinflammation in **PD**	Detects early neuroinflammatory changes
Genomics	Analyzes genetic changes affecting synaptic plasticity	Identifies genetic markers in Alzheimer’s	Discovers mutations affecting neuroplasticity
Proteomics	Studies of protein changes in synaptic plasticity	Identifies biomarkers for neurodegenerative diseases	Reveals altered protein expression patterns

6.3. Brain-Computer Interfaces as Tools for Enhancing Plasticity in Neurodegenerative Disorders

BCIs have emerged as an innovative therapeutic approach for improving brain plasticity in individuals with neurodegenerative diseases (86). These technologies provide a direct link between the brain and external devices, allowing for real-time modulation of neural activity. By creating a dynamic interface with the brain, BCIs can stimulate adaptive neuroplasticity processes, improve cognitive, sensory, and motor functions, and facilitate rehabilitation in individuals with neurodegenerative conditions such as Alzheimer's, Parkinson's, and stroke (87).

BCIs work by modulating brain activity and reinforcing neuroplastic changes through feedback-driven stimulation. They enable the real-time control and regulation of neural circuits, thereby supporting functional recovery in patients by actively engaging them in the rehabilitation process (88). Feedback provided by BCIs helps reinforce adaptive behaviors and motor learning, offering therapeutic benefits in terms of retraining neural networks and enhancing cognitive and motor functions. This approach is particularly valuable in neurodegenerative disorders, where brain regions responsible for motor control or cognitive processes are damaged and require reorganization (89).

BCIs can also operate in closed-loop systems, where they monitor neural activity and provide adaptive stimulation to optimize functional outcomes. These systems have been shown to improve motor function, reduce cognitive decline, and enhance sensory perception, promoting neuroplasticity in regions like the motor cortex and prefrontal cortex (90). This makes BCIs a powerful tool in personalized treatment plans, enabling clinicians to tailor interventions based on the specific needs and neural patterns of individual patients.

As shown in Table 6, BCI technologies—such as EEG-based, fNIRS-based, and TMS-based systems—have demonstrated significant therapeutic potential. These technologies facilitate neuroplasticity promotion and support recovery in neurodegenerative and neurorehabilitation contexts.

Conclusion

In conclusion, neuroplasticity plays a dual role in neurodegenerative diseases—acting as a protective mechanism in the early stages of disease progression yet potentially contributing to maladaptive changes as the disease advances. The interaction between neuroinflammation and synaptic plasticity is central to the pathophysiology of these diseases, and modulating immune responses presents a promising therapeutic strategy to enhance plasticity while mitigating the harmful effects of neurodegeneration. Technological advances, including BCIs and neuroimaging techniques, have provided valuable insights into real-time changes in brain function and plasticity, paving the way for personalized interventions that can better target affected neural circuits. The integration of multi-omics data offers an unprecedented opportunity to identify molecular biomarkers for early detection and intervention. As our understanding of the molecular and cellular mechanisms behind synaptic plasticity continues to evolve, multimodal approaches, combining pharmacological treatments with non-pharmacological

Table 6 BCIs Technologies in Neurodegenerative Diseases

BCI Technology	Application	Neuroplastic Effects	Therapeutic Potential
EEG-based BCIs	Non-invasive interface for cognitive control	Promotes neural reorganization in response to brain injury	Helps with motor recovery in **PD**
fNIRS-based BCIs	Measures brain activity using near-infrared spectroscopy	Enhances motor function and cognitive recovery	Assists in the rehabilitation of stroke and ALS patients
TMS-based BCIs	Combines transcranial magnetic stimulation with BCI	Induces long-term potentiation and plasticity	Improves cognitive function in Alzheimer's and motor function in Parkinson's

interventions, hold great promise in improving clinical outcomes for individuals with neurodegenerative disorders. Future research should focus on optimizing treatment protocols, identifying new molecular targets, and combining therapeutic strategies that enhance the brain's adaptive potential, ultimately aiming to slow or even reverse the course of these debilitating diseases.

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AAP: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Supervision; Validation; Writing-review & editing.

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