

ENHANCING NEUROPLASTICITY AND NEUROREPAIR IN NEURODEGENERATIVE DISEASES PHARMACOLOGICAL STRATEGIES AND FUTURE DIRECTION

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Abstract

Neurodegenerative diseases are marked by gradual neuron loss, brain cell connection problems, and the brain's limited ability to fix itself. Enhancing neuroplasticity and promoting neurorepair have therefore emerged as promising therapeutic strategies to slow disease progression and restore neurological function. Pharmacological approaches targeting neurotrophic signaling pathways, synaptic remodeling, neurogenesis, and inflammatory modulation have shown encouraging outcomes in preclinical and early clinical studies. Agents such as neurotrophin mimetics, modulators of neurotransmitter systems, anti-inflammatory drugs, and small molecules influencing epigenetic and mitochondrial function have demonstrated the ability to support neuronal survival and circuit reorganization. However, clinical translation remains challenging due to disease heterogeneity, limited drug delivery across the blood–brain barrier, and the complexity of neural repair mechanisms. Future directions emphasize combination therapies, biomarker-guided patient stratification, and the integration of pharmacological strategies with regenerative and neuromodulatory approaches. Advancing these strategies may significantly improve therapeutic outcomes and quality of life in patients with neurodegenerative disorders.

Keywords

Neuroplasticity; Neurorepair; Neurodegenerative diseases; Pharmacological strategies; Neuroprotection; Synaptic remodeling; Future therapeutics

Introduction

Numerous millions of people worldwide suffer from a variety of mostly related to age known as neurodegenerative diseases, that can be defined by the progressive destruction of neurons. Though environmental and genetic factors could significantly raise the risk, Age is the primary risk factor neurodegenerative illnesses. As life expectancy rises, so does the prevalence of these illnesses, which increases the socioeconomic burden of neurodegenerative diseases (1). Named for the German psychiatrist Alois Alzheimer, Alzheimer's disease (AD), the leading cause of dementia, is a neurodegenerative disorder characterized by amyloid-beta buildup, forming plaques and tangles in key brain regions. According to the 2019 Worldwide Cost of Disease Study (GBDS), there will be an astounding 166% increase in dementia evaluations between 2019 2050. affecting the lives of 152.8 million people globally (2). Parkinson's disease (PD), which affecting more than 1.5% of people over 65 worldwide, is The second leading neurodegenerative disorder and one of the most frequent chronic progressive neurological disorders . The motor symptoms of Parkinson's disease (PD) are typically caused by striatal dopamine insufficiency, which results from decreased dopamine production as a result of dopaminergic cell death in the substantia nigra of the midbrain (3). The central nervous system is influenced by the severe neurodegenerative disease amyotrophic lateral sclerosis (ALS), which can be difficult to diagnose, especially in its early stages. Physicians usually emphasize more prevalent diseases because of their rarity, which causes delays in identification(4).

Neurodegenerative disorders that include multiple sclerosis, Parkinson's, and Alzheimer's disease benefit from neuroplasticity-based therapies. As a result of these problems, brain tissues slowly deteriorate, impairing movement, impairing cognitive function, and generating other unpleasant symptoms (5).

A interruption in the blood supply to the brain results in functional restrictions and neurological damage, which is the main cause of stroke, the leading cause of long-term disability (6). Despite the initially devastating consequences, recovery and functional restoration may be feasible due to the brain's inherent capacity for neuroplasticity. The mechanics of neurological injury and the brain's capacity for healing must be taken into account while developing effective rehabilitation strategies (7). These mechanisms serve in neurorehabilitation to recover function and involvement following neurological disorders through organized, task-specific practice. When administered with sufficient dosage, intensity, and specificity, targeted therapies can promote experience-dependent change and aid in recovery(8). This phenomenon becomes especially important in the context of neurorehabilitation when treating disorders like stroke, traumatic brain injury, or neurodegenerative diseases. Important procedures supporting rehabilitation include

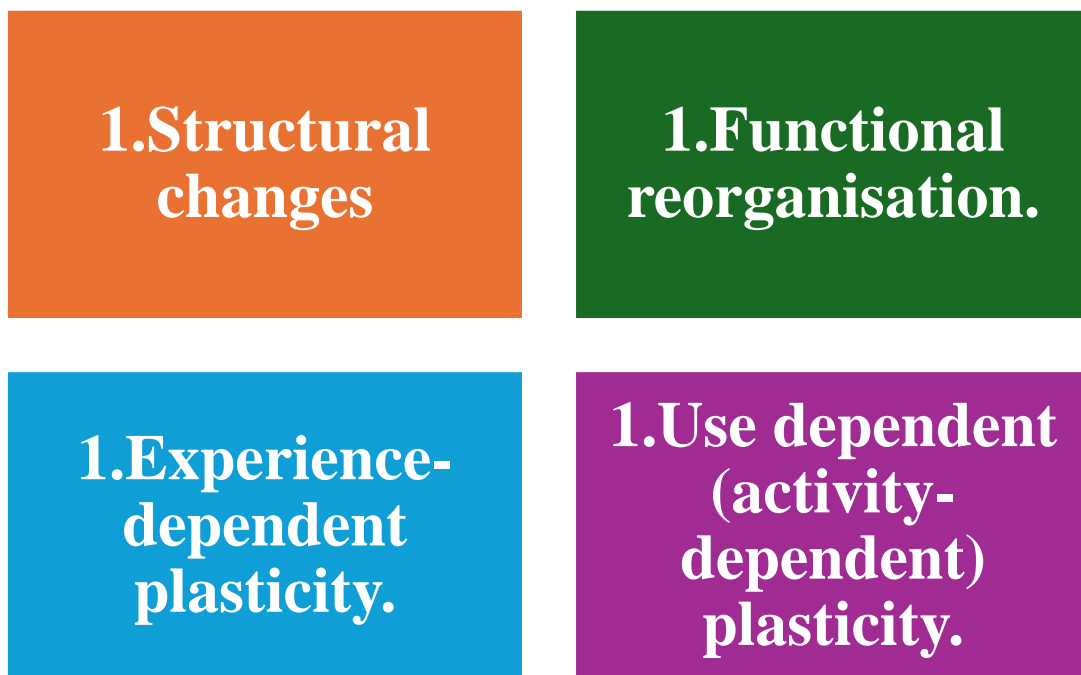


Fig No 1- Some Important procedure for rehabilitation

The pharmaceutical treatment of neurodegenerative diseases is still restricted despite intensive research efforts, with a primary Targets symptoms rather than disease progression. Current therapies for AD, PD, HD, and ALS are frequently inadequate and only slightly improve symptom control. One of the fundamental problems in neurodegenerative medicine is the absence of efficient, disease-modifying treatments. For instance, NMDA receptor antagonists and acetylcholinesterase inhibitors only provide symptomatic relief in Alzheimer's disease; they do not decrease the illness's progression. Similarly, levodopa and other Parkinson's disease medications can reduce motor symptoms but do not address the underlying neurodegenerative process (9).

2. Neuroplasticity

The brain can rewire itself based on what we do and learn or damage" While some neural processes seem to be hardwired in particular, isolated areas of the brain, some neural networks are modular and perform specialized tasks while still having the ability to change course and reorganize themselves. Therefore, neuroplasticity is widely regarded as a complex, multidimensional, essential feature of the brain (10) .

Types of Neuroplasticity

Although the expression "neuroplasticity" refers to the general process of brain reorganization and adaptation, there are two primary subtypes. These kinds are referred to as functional and structural plasticity. Both of these types produce stronger and new brain connections, but they do so in different ways.

1] Structural Neuroplasticity

When brain connections alter their real structure to form more effective networks as a result of learning and experience, this is known as structural plasticity. Neural pathways organize themselves and become stronger with frequent use as an individual develops and has their own distinct experiences. Unused paths are either trimmed or discarded (11).

2] Functional Neuroplasticity

Although functional plasticity is a process that results from brain damage or trauma, it is a little more complicated than structural plasticity. In essence, neurons from a healthy part of the brain go into the damaged area to replace the lost functions. In certain situations, neurons that would not normally be used can do the required tasks [3]. An illustration of this would be the recovery of motor function following a stroke. Functional plasticity can be divided into four main categories(12).

Mechanism of Neurorepair

- **Axonal Regeneration**

Axonal loss is a major issue in brain and spinal cord damage. Neurotoxins and disorders can hurt axons, disrupting connections and hindering repair. But, neurons can regenerate, which helps fix damaged axons (13). Axonal regeneration is a fundamental mechanism of neurorepair that enables damaged neurons to re-establish functional connections after injury. Following axonal damage, the distal segment undergoes Wallerian degeneration, while the proximal stump initiates a regenerative response characterized by activation of regeneration-associated genes and formation of a growth cone. This growth cone navigates the extracellular environment using cytoskeletal remodeling and molecular guidance cues, including neurotrophic factors such as proteins like NGF and BDNF that help nerves grow and survive. In the nerves outside the brain and spinal cord, Schwann cells play a crucial supportive role by clearing inhibitory debris, secreting growth-promoting factors, and forming Bands of Büngner that guide axonal elongation toward target tissues. In contrast, axonal regeneration in the adult central nervous system is limited due to intrinsic neuronal growth constraints, the presence of myelin-associated inhibitory molecules, and the formation of a glial scar. Understanding these mechanisms has informed the development of therapeutic strategies aimed at enhancing axonal regrowth and functional recovery in neurodegenerative and traumatic nervous system disorders (14).

- **Remyelination**

Synaptic plasticity, the brain's way of rewiring itself, is key to learning and memory. Thousands of synapses make up each neuron, creating complex networks of proteins that control circuit activity. Memory consolidation depends on plasticity, which calls for both long-term alterations in gene transcription and protein synthesis as well as short-term synaptic changes like increased glutamate release and receptor activation. By encouraging synaptic development and stability, important signaling pathways like MAPK and PKA activation of CREB are essential for encoding long-term memory (15) Symptoms appear as neurons die. In AD, the hippocampus is affected early; in Parkinson's, significant dopamine neuron loss (70-80%) in substantia nigra precedes symptoms. can tremor, bradykinesia, and postural instability be detected in a normal clinical trial for Parkinson's disease (PD). However, in multiple sclerosis, the myelin sheaths of neurons are attacked by activated immunological responses (microglia), which results in demyelination and impairs neuronal signal conduction. Additionally, they are accountable for a number of mental health issues (16).

3. Pharmacological Strategies to Enhance Neuroplasticity and Neurorepair

3.1 Neurotrophic Factor and Glutamatergic Mimetics

BDNF and TrkB are prevalent in brain regions like the hippocampus. Research (Scharfman et al., 1997) showed BDNF (25-100 ng/mL) triggers neuronal hyperexcitability through TrkB signaling. At two to three months of age, this hyperexcitability causes learning and memory problems, and at six months, it causes seizures (17).

Cholinergic and glutamatergic modulators

There is communication between glutamatergic neurons. The subcortical structures receive projections from pathways like cortico-cerebellar, cortico-striatal, and cortico-thalamic, which regulate glutamate activity. Glutamate's key in learning, memory, and brain adaptability due to its widespread connections. Synaptic plasticity is determined by the capacity of Glutamate receptors (ionotropic and metabotropic) help regulate LTP and LTD in the hippocampus. Synaptic plasticity involves actin changes and local protein production, often relying on calcium (18).

3.2 Monoamine Modulator

Enzyme inhibition in the brain, which raises extracellular dopamine levels, is largely responsible for the symptomatic effectiveness of MAOB inhibitors in Parkinson's disease (PD) (19). There are three MAOB inhibitors: safinamide, rasagiline, and selegiline (20). These medications alleviate MAOB inhibitors help control motor symptoms and fluctuations with levodopa treatment. Selegiline and rasagiline are effective early on and may address non-motor symptoms in Parkinson's. (21).

3.3 Anti-inflammatory and Immunomodulatory agent

During sepsis, immune cells like microglia express TLR4, which detects pathogens and triggers inflammation (22). In sepsis-associated brain injury (SAE), microglia drive neuroinflammation. TLR4's role is context-dependent - it can be protective or harmful. LPS from Gram-negative bacteria activates TLR4, contributing to brain inflammation in sepsis (23)

3.4 Natural compound and Nutraceuticals

Polyherbal extracts could boost curcumin's effectiveness by improving its absorption. A study tested Brainoil, a supplement containing curcumin (600mg) (24), Coenzyme Q10 (100mg), Bacopa monnieri (300mg), Withania somnifera, and Centella asiatica (250mg), plus piperine (1mg) for better absorption and Coenzyme Q10 for mitochondrial support (25).

4 .Preclinical Evidences

Preclinical evidence from animal models has been crucial in elucidating the role of neuroinflammation in neuroinflammatory and neurodegenerative diseases. these pathways - cortico-cerebellar, cortico-striatal, and cortico-thalamic - control glutamate activity. Glutamate's crucial for learning, memory, and brain flexibility because of its far-reaching connections. triggers microglial and astrocytic activation, leading to demyelination and progressive neurological deficits. Similarly, lipopolysaccharide (LPS)-induced neuroinflammation models reveal that systemic or intracerebral activation of innate immune pathways elevates pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6, leading to neuronal damage and impaired synaptic function . In Parkinson's disease models, neurotoxins such as MPTP and 6-hydroxydopamine induce dopaminergic neuronal loss accompanied by sustained microglial activation, indicating that inflammation contributes to disease progression rather than being a mere secondary response(25). Transgenic Alzheimer's disease models further show that amyloid- β accumulation provokes chronic microglial activation, which exacerbates tau pathology and cognitive decline. Collectively, these animal studies provide strong mechanistic evidence that persistent neuroinflammation plays a central role in neuronal degeneration and offers translational targets for therapeutic approach for neuroinflammation (26).

Several clinical trials are actively investigating immunomodulatory and anti-inflammatory strategies to target neuroinflammation in neurodegenerative diseases, reflecting the translational bridge from preclinical evidence to potential therapeutic benefit. In Alzheimer's disease (AD), a range of agents aimed at modulating innate and adaptive immune responses are being evaluated, including monoclonal antibodies targeting TREM2 and inhibitors of pro-inflammatory kinases such as tyrosine kinase (e.g., masitinib) in Phase II/III studies, as well as immunomodulatory approaches involving interleukin-2 and sTNF inhibition that seek to reduce microglial and cytokine-driven inflammation. Several of these studies are scheduled to complete in the mid-2020s, contributing to the understanding of how immune modulation impacts cognitive and functional outcomes in AD (27). In parallel, glucagon-like peptide-1 receptor agonists such as semaglutide are under investigation for their anti-inflammatory and neuroprotective properties, with emerging clinical data showing biomarker modulation consistent with reduced CNS inflammation. Additionally, observational clinical studies, such as imaging protocols in patients with multiple sclerosis and related neuroinflammatory disorders, aim to quantify inflammatory burden and correlate it with structural alterations over time. Research efforts beyond AD also include trials assessing cannabinoid modulation of neuroinflammation in conditions exacerbated by HIV-associated inflammatory pathways. Together, these ongoing clinical trials represent a multi-modal effort to translate insights from animal models into human therapeutics by targeting neuroinflammation as a core pathological process in neurodegenerative diseases (28).

Challenges and Limitation

Despite significant progress, several challenges and limitations hinder the successful translation of neuroinflammation-targeted therapies in ongoing clinical trials. One major limitation is the complex and heterogeneous nature of neuroinflammatory responses, which vary across diseases, disease stages, and individual patients, making it difficult to identify uniform therapeutic targets. Many anti-inflammatory agents that show robust efficacy in animal models fail to demonstrate meaningful clinical benefit in humans due to species differences, simplified disease modeling, and timing of intervention, as neuroinflammation may play both protective and detrimental roles depending on disease progression. Additionally, the lack of reliable and disease-specific biomarkers limits accurate patient stratification, monitoring of treatment response, and assessment of target engagement in clinical settings. Safety concerns also pose challenges, as long-term immune modulation can increase susceptibility to infections or systemic adverse effects. Furthermore, clinical trials often rely on cognitive or functional endpoints that progress slowly, requiring long trial durations and large sample sizes, which increases cost and dropout rates. Collectively, these limitations underscore the need for improved biomarkers, better patient selection strategies, and precision-based approaches to effectively target neuroinflammation in neurodegenerative diseases.

Conclusion

Neuroinflammation plays a vital role in the development and progression of neuroinflammatory and neurodegenerative diseases, as evidenced by extensive preclinical and clinical research. Animal studies have clarified key inflammatory mechanisms, while ongoing clinical trials aim to translate these findings into effective therapies. However, challenges such as disease heterogeneity, limited biomarkers, and translational gaps remain. Continued advances in precision medicine and biomarker-driven approaches are essential to successfully target neuroinflammation in clinical practice.

References

1. Ricci C. Neurodegenerative disease: from molecular basis to therapy. *International Journal of Molecular Sciences*. 2024 Jan 12;25(2):967.
2. Kadam SR, Kale SS, Shinde GK, Devidas C, Upasani AB. Novel interventions for Alzheimer's disease. *Journal of Pharmaceutical and Biological Sciences*. 2024;13(1):4-12.
3. Kaur R, Mehan S, Singh S. Understanding multifactorial architecture of Parkinson's disease: pathophysiology to management. *Neurological Sciences*. 2019 Jan;40(1):13-23.
4. Alotaibi S, Alfayez L, Alkhudhair M. Parkinson's disease: current treatment modalities and emerging therapies. *Cureus*. 2024 Dec 13;16(12).
5. Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *Journal of Neuroscience*. 2004 Jan 21;24(3):628-33.
6. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature Reviews Neuroscience*. 2006 Sep 1;7(9):697-709.
7. Antonenko D, Fromm AE, Thams F, Grittner U, Meinzer M, Flöel A. Microstructural and functional plasticity following repeated brain stimulation during cognitive training in older adults. *Nature Communications*. 2023 Jun 2;14(1):3184.
8. Shaffer J. Neuroplasticity and clinical practice: Building brain power for health. *Frontiers in psychology*. 2016 Jul 26;7:205377.
9. Pache M, Kedar H, Kond S, Jadhav P, Kedar T. Pharmacological Management of Neurodegenerative Disorders Current and Future Approaches. *International Journal of Scientific Research and Technology*. 2025 Mar 24.
10. Marzola P, Melzer T, Pavesi E, Gil-Mohapel J, Brocardo PS. Exploring the role of neuroplasticity in development, aging, and neurodegeneration. *Brain sciences*. 2023 Nov 21;13(12):1610.
11. Vance DE, Roberson AJ, McGuinness TM, Fazeli PL. How neuroplasticity and cognitive reserve: protect cognitive functioning. *Journal of psychosocial nursing and mental health services*. 2010 Apr 1;48(4):23-30.
12. Kaczmarek BL. Current views on neuroplasticity: what is new and what is old?. *Acta neuropsychologica*. 2020 Feb 26;18(1):1-4.
13. Sutherland TC, Geoffroy CG. The influence of neuron-extrinsic factors and aging on injury progression and axonal repair in the central nervous system. *Frontiers in cell and developmental biology*. 2020 Mar 25;8:190.
14. Filbin MT. Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. *Nature Reviews Neuroscience*. 2003 Sep 1;4(9):703-13.
15. Wiesner T, Bilodeau A, Bernatchez R, Deschênes A, Raulier B, De Koninck P, Lavoie-Cardinal F. Activity-dependent remodeling of synaptic protein organization revealed by high throughput analysis of STED nanoscopy images. *Frontiers in neural circuits*. 2020 Oct 15; 14:57.
16. Gadhav DG, Sugandhi VV, Jha SK, Nangare SN, Gupta G, Singh SK, Dua K, Cho H, Hansbro PM, Paudel KR. Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance. *Ageing research reviews*. 2024 Aug 1; 99:102357.
17. Perpetuini AC, Mathoux J, Kennedy BN. The potential of small molecule brain-derived neurotrophic factor: mimetics to treat inherited retinal degeneration. *Neural regeneration research*. 2019 Jan 1;14(1):85-6.
18. Brito-Moreira J, C. Paula-Lima A, R. Bomfim T, F. Oliveira F, J. Sepulveda F, G. De Mello F, G. Aguayo L, Panizzutti R, T. Ferreira S. A β oligomers induce glutamate release from hippocampal neurons. *Current Alzheimer Research*. 2011 Aug 1;8(5):552-62.
19. Abbruzzese G, Kulisevsky J, Bergmans B, Gomez-Esteban JC, Kägi G, Raw J, Stefani A, Warnecke T, Jost WH, SYNAPSES Study Investigators Group. A European observational study to evaluate the safety and the effectiveness of safinamide in routine clinical practice: the SYNAPSES trial. *Journal of Parkinson's disease*. 2021 Feb 2;11(1):187-98.
20. Ahmari M, Sharafi A, Mahmoudi J, Jafari-Anarkoli I, Gharbavi M, Hosseini MJ. Selegiline (1-deprenyl) mitigated oxidative stress, cognitive abnormalities, and histopathological change in rats: alternative therapy in transient global ischemia. *Journal of Molecular Neuroscience*. 2020 Oct;70(10):1639-48.

21. Alborghetti M, Nicoletti F. Different generations of type-B monoamine oxidase inhibitors in Parkinson's disease: from bench to bedside. *Current neuropharmacology*. 2019 Sep 1;17(9):861-73.
22. Itoh K, Tsutani H, Mitsuke Y, Ikawa M, Iwasaki H. Potential strategies for combination therapy involving medicines with differential signal transduction regulation effects and the mechanism of action of minocycline in septic neuroinflammation. *Frontiers in Pharmacology*. 2025 Oct 9;16:1691613.
23. Hosseini M, Bardaghi Z, Askarpour H, Jafari MM, Golkar A, Shirzad S, Rajabian A, Salmani H. Minocycline mitigated enduring neurological consequences in the mice model of sepsis. *Behavioural Brain Research*. 2024 Mar 12;461:114856.
24. Chico L, Ienco EC, Bisordi C, Lo Gerfo A, Petrozzi L, Petrucci A, Mancuso M, Siciliano G. Amyotrophic lateral sclerosis and oxidative stress: a double-blind therapeutic trial after curcumin supplementation. *CNS & Neurological Disorders-Drug Targets-CNS & Neurological Disorders*. 2018 Dec 1;17(10):767-79.
25. Bonella F, Spagnolo P, Ryerson C. Current and future treatment landscape for idiopathic
26. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nature immunology*. 2015 Mar;16(3):229-36.
27. Tommasin S, Gianni C, De Giglio L, Pantano P. Neuroimaging techniques to assess inflammation in multiple sclerosis. *Neuroscience*. 2019 Apr 1;403:4-16.
28. Fu X, Cai H, Quan S, Ren Z, Xu Y, Jia L. Immune cells in Alzheimer's disease: insights into pathogenesis and potential therapeutic targets. *Medical Review*. 2025 Jun 13;5(3):179-202.

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