Neuronal plasticity and its role in Alzheimer's disease and Parkinson's disease

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From the Contents

Abstract

Neuronal plasticity, the brain's ability to adapt structurally and functionally, is essential for learning, memory, and recovery from injuries. In neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, this plasticity is disrupted, leading to cognitive and motor deficits. This review explores the mechanisms of neuronal plasticity and its effect on Alzheimer's disease and Parkinson's disease. Alzheimer's disease features amyloid-beta plaques and tau tangles that impair synaptic function, while Parkinson's disease involves the loss of dopaminergic neurons affecting motor control. Enhancing neuronal plasticity offers therapeutic potential for these diseases. A systematic literature review was conducted using databases such as PubMed, Scopus, and Google Scholar, focusing on studies of neuronal plasticity in Alzheimer's disease and Parkinson's disease. Data synthesis identified key themes such as synaptic mechanisms, neurogenesis, and therapeutic strategies, linking molecular insights to clinical applications. Results highlight that targeting synaptic plasticity mechanisms, such as long-term potentiation and long-term depression, shows promise. Neurotrophic factors, advanced imaging techniques, and molecular tools (e.g., clustered regularly interspaced short palindromic repeats and optogenetics) are crucial in understanding and enhancing plasticity. Current therapies, including dopamine replacement, deep brain stimulation, and lifestyle interventions, demonstrate the potential to alleviate symptoms and improve outcomes. In conclusion, enhancing neuronal plasticity through targeted therapies holds significant promise for treating neurodegenerative diseases. Future research should integrate multidisciplinary approaches to fully harness the therapeutic potential of neuronal plasticity in Alzheimer's disease and Parkinson's disease.

Key Words: Alzheimer's disease; long-term depression; long-term potentiation; neuroinflammation; neuronal plasticity; Parkinson's disease; synaptic plasticity

Introduction

Neurodegenerative diseases encompass a group of disorders characterized by the gradual loss of neuron function and structure, often resulting in severe cognitive and physical impairments. Central among these diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), which are distinguished not only by their prevalence but also by their debilitating impact on patients' lives. AD is primarily noted for its progressive cognitive decline, typically presenting as memory loss and a decrease in cognitive function, while PD is primarily associated with motor system disorders, notably tremors, and rigidity (Sunderland et al., 2023; Zaib et al., 2023; Adamu et al., 2024). Globally, AD affects approximately 50 million individuals (Escott-Price and Hardy, 2022), making it the most common cause of dementia. PD, although less prevalent, still impacts an estimated 6 million people worldwide (Lampropoulos et al., 2022), with numbers expected to increase as the population ages. The growing prevalence of these diseases poses significant challenges not only to affected individuals and their families but also to healthcare systems, which must adapt to the increasing demand for care and support. The economic impact of neurodegenerative diseases is staggering, with AD and PD accounting for considerable portions of healthcare budgets in both developed and developing countries. In the United States alone, the annual cost of AD (Dauphinot et al., 2022) and PD (Yang et al., 2020b) diseases are projected to be in the billions of dollars, a figure that includes direct medical costs, long-term care, and lost productivity. Moreover, the social implications of neurodegenerative diseases are profound. They not only diminish the quality of life for millions but also place a heavy burden on caregivers, often leading to significant emotional and financial stress. The relevance of these diseases to public health is underscored by their increasing incidence, their chronic nature, and the lack of definitive cures, which amplifies the importance of research into their pathophysiology and treatment options. Understanding the mechanisms and impacts of neurodegenerative diseases like AD (Magalingam et al., 2018) and PD (Marogianni et al., 2020) is thus critical. Research focusing on the pathogenesis and progression of these diseases not only helps in developing effective therapeutic strategies but also plays a key role in prevention and management, ultimately aiming to enhance patient outcomes and reduce the burden on healthcare systems.

Neuronal plasticity, or neuroplasticity, refers to the ability of the nervous system to change and adapt structurally and functionally in response to experience or injury. This adaptability is a fundamental property of the brain and underlies everything from developmental processes during infancy and childhood to learning and memory in adults (Innocenti, 2022; Jahan et al., 2023). At the core of neuroplasticity is the brain's ability to reorganize itself by forming new neural connections. This occurs not only during normal brain activity but also as a compensatory adjustment to changes, injuries, or diseases. Such plastic changes can be seen at various levels—from molecular changes involving new protein synthesis to alterations in the dendritic branches and synaptic connections between neurons (Gulyaeva, 2017). The significance of neuronal plasticity extends across the entire

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lifespan. In early development, it plays a crucial role in shaping the brain's architecture; synaptic connections are formed and refined based on sensory and experiential inputs. This plastic nature of the brain allows for the critical period of development, where the sensory experiences a child encounters determine the strength and formation of neural connections (Schaefers and Teuchert-Noodt, 2016). In adults, neuroplasticity is pivotal for learning and memory. The brain's ability to incorporate new information involves the strengthening of certain synaptic connections and the weakening of others, processes known respectively as long-term potentiation (LTP) and long-term depression (LTD). These processes are vital for the storage and recall of information, allowing individuals to learn new skills, adapt to new environments, and store (Cassilhas et al., 2016). Moreover, neuronal plasticity is crucial for neurological recovery following injury. After events such as stroke or traumatic brain injury, the brain's plasticity can lead to a degree of natural recovery, where undamaged areas of the brain adapt to take over functions from the affected regions. Rehabilitation strategies leverage this plasticity through targeted therapies that aim to enhance recovery by promoting beneficial plastic changes and minimizing maladaptive ones (Braun and Wittenberg, 2021). The therapeutic implications of enhancing neuronal plasticity are vast. Research into neuroplastic mechanisms has led to innovative treatments for neurodegenerative conditions, such as AD and PD, where plasticity-related interventions could potentially slow disease progression or even restore lost functions (Nahum et al., 2013). Understanding and harnessing the power of neuroplasticity thus holds tremendous potential for a wide array of neurological conditions, making it a key area of study in neuroscience and clinical neurology (Flachenecker, 2015).

The extracellular matrix (ECM) plays a fundamental role in the central nervous system (CNS) by providing structural and biochemical support to neurons, aiding in synaptic stability, and promoting neuronal plasticity (Melrose et al., 2021). Composed of molecules like glycoproteins, proteoglycans, and glycosaminoglycans, the ECM creates a microenvironment that regulates synapse formation, maintenance, and plasticity. Recent research highlights the dynamic nature of ECM components, which not only provide a scaffold but also actively participate in synaptic signaling and plasticity processes by modulating interactions between neurons and glial cells (Dzyubenko and Hermann, 2023). In the context of neurodegenerative diseases, such as AD and PD, ECM alterations have emerged as significant factors contributing to disease progression. For instance, the accumulation and altered distribution of chondroitin sulfate proteoglycans (CSPGs) in the ECM have been linked to synaptic dysfunction and impaired plasticity in AD and PD. Studies indicate that increased CSPG expression creates inhibitory barriers around neurons, reducing their ability to form new connections, which is essential for maintaining cognitive and motor functions as neurodegeneration progresses (Lin et al., 2021). Additionally, dysregulation of ECM proteins like reelin and tenascin-R, which influence neuronal growth and synaptic plasticity, further exacerbates synaptic instability in AD and PD, accelerating cognitive and motor deficits. Thus, understanding ECM dynamics provides insight into the molecular disruptions underlying AD and PD, with ECM-targeting therapies offering promising avenues to restore plasticity and potentially mitigate neurodegenerative progression.

Despite extensive research, the precise molecular mechanisms underlying neuronal plasticity in AD and PD remain inadequately understood, often focusing on isolated components rather than multifaceted interactions (Ciurea et al., 2023; Pinky et al., 2023). Many studies are cross-sectional, missing dynamic changes over time, and there is significant variability in experimental models that do not fully replicate human disease states. Research predominantly targets advanced stages, overlooking early pathological changes and biomarkers critical for early diagnosis (Doroszkiewicz et al., 2022). Additionally, the complexity of neuronal plasticity requires multidisciplinary approaches, which are often lacking, leading to fragmented insights. Translational research gaps hinder the application of basic findings in clinical settings, and individual variability in genetic, epigenetic, and environmental factors is underexplored. The role of lifestyle factors like diet, exercise, and social engagement is also under-researched, and current therapeutic strategies show inconsistent results due to methodological variations (Dane and Bhatia, 2023). Addressing these gaps through concerted efforts from the research community, funding agencies, and policymakers can significantly advance understanding and improve therapeutic outcomes for patients with AD and PD. **Table 1** identifies and describes critical research gaps in the study of neuronal plasticity related to AD and PD, highlighting areas, e.g., molecular mechanisms, longitudinal studies, experimental models, early disease stages, multidisciplinary approaches, translational research, personalized medicine, lifestyle factors, and therapeutic interventions. Each gap is explained with references for further reading, aiming to guide future research efforts to enhance understanding and treatment of these neurodegenerative conditions.

Addressing the identified research gaps in neuronal plasticity for AD and PD requires a multifaceted approach (Savelieff et al., 2019). Future research should prioritize longitudinal studies to understand temporal dynamics and integrate findings with advanced imaging and biomarkers. Refining experimental models to better replicate human conditions is crucial, as is shifting the focus to early disease stages for early detection and intervention. Multidisciplinary approaches that combine neuroscience, genetics, bioinformatics, and clinical data are essential for a comprehensive understanding (Dey et al., 2024). Bridging the gap between laboratory findings and clinical applications through rigorous translational research is necessary, alongside personalized medicine to tailor treatments. Incorporating lifestyle factors like diet and exercise into research and standardizing methodologies will enhance the consistency and comparability of findings. Addressing these gaps will advance the understanding and treatment of these neurodegenerative diseases, ultimately improving patient outcomes.

The objectives of this review are to elucidate the critical role of neuronal plasticity in the pathophysiology and therapeutic intervention of neurodegenerative diseases, specifically AD and PD. The review aims to explore both the detrimental and beneficial aspects of plastic changes within the nervous system. It will identify significant gaps in current research, emphasizing the need for comprehensive studies that link molecular mechanisms to clinical outcomes and develop therapeutic strategies to modify these processes. Additionally, the review seeks to advance the understanding of molecular, cellular, and systemic mechanisms of neuronal plasticity, demonstrating how these plastic changes can be harnessed or mitigated to improve the clinical outcomes in patients. It will provide a critical examination of existing therapeutic approaches targeting neuronal plasticity, alongside an exploration of potential future treatments currently under research and development. This includes the assessment of new drugs, advanced genetic tools, and innovative treatment modalities. Furthermore, the review will advocate for increased interdisciplinary collaboration among researchers from neuroscientific, genetic, and clinical domains to enhance research efforts in understanding and manipulating neuronal plasticity for therapeutic benefit. Through a comprehensive analysis, the review intends to offer insights into how AD and PD could potentially be better managed or even prevented through innovative therapeutic strategies.

Literature Retrieval Strategy

To review the role of neuronal plasticity in AD and PD, we conducted a systematic literature search using PubMed, Scopus, Web of Science, and Google Scholar, covering publications up to June 2024. Key search terms included "neuronal plasticity," "neuroplasticity," "Alzheimer's disease," "Parkinson's disease," "molecular mechanisms," "synaptic plasticity," "long-term potentiation," "long-term depression," "neurogenesis," "synaptogenesis," "therapeutic interventions," "early biomarkers," and "lifestyle factors," using Boolean operators (AND, OR) for refinement. Inclusion criteria were peer-reviewed articles, studies involving humans, animal models, or cell cultures, focusing on neuronal plasticity in AD and PD, and published in English. Exclusion criteria were non-relevant studies, non-peer-reviewed articles, and non-English publications. Titles and abstracts were screened for relevance, and full-text articles meeting inclusion criteria were retrieved. Reference lists of selected articles were manually searched for additional studies.

Relevant articles were systematically reviewed using a standardized data extraction form, capturing study design, population, key findings on neuronal plasticity in AD and PD, molecular mechanisms, therapeutic interventions, and methodological details. Extracted data were synthesized to identify common themes and significant findings, and categorized into molecular mechanisms, disease progression impact, therapeutic strategies, early biomarkers, and lifestyle factors. This synthesis provided a comprehensive overview of current research, highlighting agreements and discrepancies, aiming to identify patterns and robust conclusions on neuronal plasticity in these diseases.

Table 1 | **Key research gaps in understanding neuronal plasticity in AD and PD**

Research gap	Description	Current status	Potential impact if addressed	Reference
Limited understanding of molecular mechanisms	Incomplete understanding of how various molecular pathways interact and contribute to disease progression.	Fragmented and isolated studies.	Better targeted therapies and understanding of disease mechanisms.	Gulyaeva, 2017
Insufficient longitudinal studies	Lack of studies tracking neuronal plasticity changes over time to understand disease progression and treatment effects.	Predominantly cross-sectional studies.	Insight into disease progression and potential early intervention strategies.	Gordon et al., 2018; Filippi et al., 2021
Variability in experimental models	Differences in animal and cell culture models leading to inconsistent and non-replicable results.	Wide variability in model systems.	More accurate and translatable research findings.	Pramotton et al., 2024
Inadequate focus on early disease stages	Limited research on initial pathological changes and early biomarkers for timely diagnosis and intervention.	Focus on advanced stages of disease.	Early detection and improved prevention strategies.	Hansson, 2021
Insufficient integration of multidisciplinary approaches	Lack of integration across neuroscience, genetics, bioinformatics, and clinical studies, leading to fragmented insights.	Disciplinary silos.	Holistic understanding and innovative treatment strategies.	Papatzikis et al., 2023
Gaps in translational research	Challenges in translating basic research findings into clinical applications and effective treatments.	Slow progress in clinical translation.	Accelerated development of effective clinical therapies.	Beck and Meyerholz, 2020
Limited exploration of personalized medicine	Insufficient consideration of individual genetic, epigenetic, and environmental factors in treatment strategies.	Generalized treatment approaches.	Tailored treatments improving patient outcomes and reducing side effects.	Strianese et al., 2020
Understudied role of lifestyle and environmental factors	Lack of comprehensive studies on how diet, exercise, and social engagement impact neuronal plasticity and disease progression.	Limited integration in research.	Development of holistic and non-pharmacological interventions.	Phillips, 2017
Inconsistent findings on therapeutic interventions	Variability in study designs, patient populations, and methodologies leading to inconsistent research outcomes.	Inconsistent and conflicting results.	Standardized methodologies leading to more reliable and comparable research findings.	Jovicich et al., 2019

Quality assessment focused on study design, sample size, controls, inclusion/exclusion criteria, experimental procedure descriptions, and statistical analyses. Preference was given to randomized controlled trials, longitudinal studies, and large cohort studies. Studies with larger sample sizes and those replicated by independent groups were rated higher. Efforts to control for confounding factors, such as blinding and randomization, were also considered. Each study was scored based on these criteria, with higher scores indicating more reliable evidence. Reviewer discrepancies were resolved by discussion and consensus, ensuring conclusions were based on high-quality, reliable research for further investigation and clinical application.

Neuronal Plasticity: Concepts and Mechanisms

Types of neuronal plasticity

Neuronal plasticity, or neuroplasticity, is the nervous system's ability to reorganize its structure, function, and connections in response to internal and external stimuli (Dhuriya and Sharma, 2020; Joshua, 2022). This adaptability is essential for brain functions such as learning, memory, and recovery from injury. Neuroplasticity involves various changes that occur at different levels of the nervous system, including synaptic, structural, and functional plasticity.

Synaptic plasticity

Synaptic plasticity is the ability of synapses, the connections between neurons, to strengthen or weaken over time in response to increases or decreases in their activity. This type of plasticity is fundamental for learning and memory formation. Synaptic plasticity is often categorized into two main types: LTP and LTD (Malenka, 1995). LTP is a long-lasting enhancement in signal transmission between two neurons that results from their synchronous stimulation. It is considered a major cellular mechanism underlying learning and memory. During LTP, repeated stimulation of a synapse leads to an increase in synaptic strength, often through the insertion of additional receptors into the postsynaptic membrane, making the neuron more responsive to neurotransmitter release (Bliss et al., 2018). LTD is a long-lasting decrease in synaptic strength that occurs when neurons are less frequently stimulated. LTD is essential for synaptic pruning and the fine-tuning of neural circuits. It often involves the removal of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors from the postsynaptic membrane, reducing the neuron's responsiveness (Sejnowski, 1991).

Structural plasticity

Structural plasticity refers to the brain's ability to change its physical structure in response to learning, experience, or injury (Schmidt et al., 2021). This includes the formation and elimination of synapses, dendritic branching, and axonal sprouting. Synaptogenesis is the formation of new synapses, which occurs throughout life but is particularly prominent during early development. Synaptic pruning, the elimination of less active synapses, refines neural circuits, enhancing the efficiency of brain function. These processes are critical for cognitive development and are influenced by both genetic and environmental factors (Petanjek et al., 2023). Dendritic remodeling involves changes in the shape and number of dendritic spines, which can influence the strength and connectivity of synapses. Axonal remodeling includes the growth of new axonal branches and the formation of new connections, which can help compensate for damaged pathways (Bosch and Hayashi, 2012).

Functional plasticity

Functional plasticity refers to the brain's ability to alter its functional properties, such as changes in neuronal excitability, neurotransmitter release, and receptor sensitivity (Mahncke et al., 2006). This type of plasticity is crucial for adapting to new experiences and recovering from injuries. Changes in the intrinsic excitability of neurons can occur through modifications in ion channel expression or function, influencing how easily a neuron can be activated (Mahon and Charpier, 2012). Adjustments in the release of neurotransmitters and the sensitivity of receptors to these chemicals can modulate synaptic strength and plasticity (Dolphin and Lee, 2020).

Molecular and cellular mechanisms of neuronal plasticity

Long-term potentiation

LTP is a sustained increase in synaptic strength following high-frequency stimulation of a synapse (Figurov et al., 1996; Tan et al., 2022). LTP is widely considered a primary cellular mechanism underlying learning and memory. The process of LTP involves several stages, starting with the activation of glutamate receptors, particularly N-methyl-D-aspartate (NMDA) receptors, which allow calcium ions to enter the postsynaptic neuron (Franchini et al., 2020). This calcium influx activates various kinases, such as calcium/calmodulin-dependent protein kinase II (CaMKII), which phosphorylates proteins and leads to the insertion of additional AMPA receptors into the postsynaptic membrane, enhancing synaptic transmission.

LTP involves induction, expression, and maintenance stages. Induction is triggered by tetanic stimulation, leading to increased synaptic transmission (expression). Maintenance ensures this enhanced transmission persists. Efforts in the '70s and '80s identified AMPA and NMDA receptors in hippocampal synapses (Fukata et al., 2024). AMPA receptors mediate basal transmission, while NMDA receptors, activated by tetanic stimulation, induce a necessary Ca^{2+} influx for LTP induction and AMPA receptor changes (Hayashi, 2022). The site of LTP expression and maintenance is debated. Some studies support presynaptic mechanisms (increased transmitter release), while others support postsynaptic mechanisms (increased glutamate sensitivity). Findings of AMPA receptor acquisition post-LTP induction (unsilencing) suggest decreased synaptic failure rates could be due to postsynaptic changes. If changes are presynaptic, retrograde communication from postsynaptic NMDA receptor activation and Ca^{2+} influx, possibly via messengers like nitric oxide, is required. Reproducibility issues in these studies highlight the need for breakthroughs in LTP research.

Long-term depression

LTD is the opposite of LTP, characterized by a long-lasting decrease in synaptic strength (Bear and Malenka, 1994). LTD occurs following low-frequency stimulation of a synapse and is essential for synaptic pruning and the fine-tuning of neural circuits. The induction of LTD also involves NMDA receptors but results in a lower level of calcium influx compared to LTP (Alkadhi, 2021). This lower calcium concentration activates phosphatases, such as protein phosphatase 1 and calcineurin, which dephosphorylate target proteins and lead to the internalization of AMPA receptors from the postsynaptic membrane, reducing synaptic efficacy. LTD at the parallel fiber-Purkinje cell (PF-PC) synapse, essential for motor learning, involves the simultaneous activation of climbing fiber (CF) and PF inputs to a PC (Hoxha et al., 2016). LTD requires Ca^{2+} influx through P/Q channels from CF depolarization and glutamate release from PFs acting on metabotropic glutamate (mGlu1) and AMPA receptors (**Figure 1A**). Activation of mGlu1 receptors promotes diacylglycerol production and Ca^{2+} release, increasing Ca^{2+} concentration in PC dendritic spines. This activates PKC, which in turn activates kinases like Raf, MEK (MAPK/ERK kinase; MAPK stands for mitogen-activated protein kinase and ERK stands for extracellular signal-regulated kinase), and ERK1/2. PKCα is crucial for LTD; it phosphorylates AMPA receptors at serine-880 on GluA2, leading to their removal via clathrin-mediated endocytosis, reducing synaptic transmission. The activity of PKCα is regulated by diacylglycerol kinase ζ (DGKζ), which metabolizes diacylglycerol. Upon LTD induction, PKCα phosphorylates and releases DGKζ, enhancing AMPA receptor internalization. PKC also activates MEK, ERK1/2, and phospholipase A2, creating a positive feedback loop for sustained LTD maintenance.

Figure 1 illustrates the molecular and cellular mechanisms of synaptic plasticity at the PF-PC synapse in the cerebellum, showcasing three distinct types of modifications. LTD at the PF-PC synapse is induced by low-frequency stimulation and requires the simultaneous activation of parallel fibers (PF) and CF (Hoxha et al., 2016). This dual activation results in Ca^{2+} influx through P/Q channels due to CF depolarization and glutamate release from PFs, activating mGlu1 and AMPA receptors. The mGlu1 receptor activation promotes diacylglycerol production and Ca^{2+} release, which increases Ca^{2+} concentration in PC dendritic spines. This process activates PKC, leading to the phosphorylation of AMPA receptors at serine-880 on the GluA2 subunit and their subsequent internalization via clathrin-mediated endocytosis, ultimately reducing synaptic efficacy. A positive feedback loop involving PKC and the MAPK/ERK pathway (Raf-MEK-ERK1/2) contributes to the sustained maintenance of LTD. LTP at the PF-PC synapse is triggered by brief high-frequency (4–8 Hz) PF stimulation, which raises Ca^{2+} levels in PF terminals. This increase activates Ca^{2+}/calmodulin-dependent adenylyl cyclase, elevating cyclic AMP (cAMP) levels and activating protein kinase A (PKA). PKA then phosphorylates vesicle-release proteins, such as RIM1α and Rab3, enhancing glutamate release from PFs (Hoxha et al., 2016). Endocannabinoids released from the postsynaptic membrane can inhibit this process by acting on cannabinoid receptors in the presynaptic terminals, thus modulating the strength of LTP. Postsynaptic LTP at the PF-PC synapse is evoked by low-frequency (1 Hz) PF stimulation, which promotes the insertion of GluA2-containing AMPA receptors into the postsynaptic membrane. This form of LTP requires lower Ca^{2+} transients and activates protein phosphatases, including protein phosphatase 1, PP2A, and PP2B, which stabilize AMPA receptors at the synapse, enhancing synaptic transmission and contributing to sustained synaptic potentiation (Hoxha et al., 2016). These types of synaptic plasticity underscore the dynamic modulation of synaptic strength at the PF-PC synapse, which plays a significant role in learning, memory, and motor coordination—processes often affected in AD and PD.

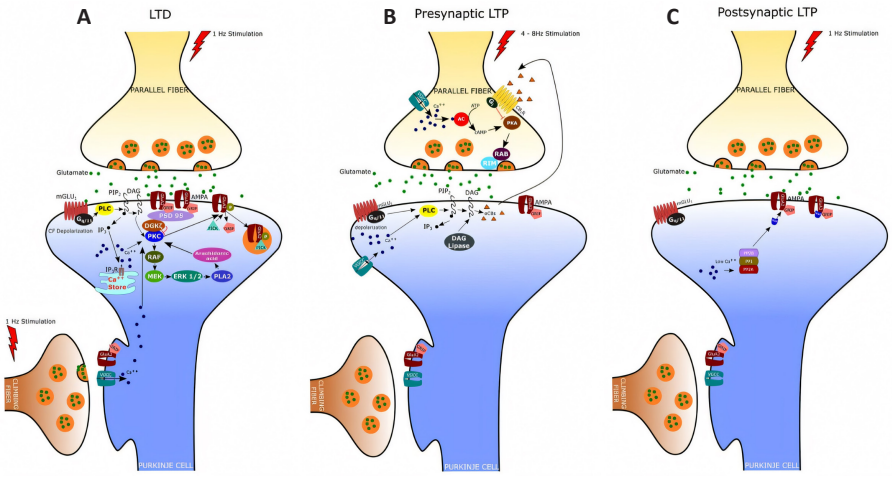

Figure 1 | **Mechanisms of LTD, presynaptic LTP, and postsynaptic LTP.**
(A) LTD is triggered by simultaneous stimulation of parallel and CFs and necessitates an increase in postsynaptic Ca^{2+} levels. (B) Presynaptic LTP can be induced by brief parallel fiber stimulations at 4–8 Hz, regulated by a retrograde signaling mechanism involving cannabinoids. eCBs are released from the postsynaptic membrane following high-frequency bursts of parallel fiber activity, which depend on the activation of postsynaptic mGlu1 receptors. These eCBs then act retrogradely on presynaptic CB1R, leading to a decrease in transmitter release. (C) Postsynaptic LTP can be induced by stimulating parallel fibers at 1 Hz and requires low levels of Ca^{2+} in Purkinje cells. Reproduced with the permission from Hoxha et al. (2016). Published by Frontiers under license CC BY 4.0. CB1R: Cannabinoid 1 receptors; CF: climbing fibers; eCBs: endogenous cannabinoids; LTD: long-term depression; LTP: long-term potentiation.

Immune responses in shaping neuronal plasticity during neurodegeneration

The immune response within the CNS has a dual role in neurodegenerative diseases, where both protective and harmful effects are observed (Zang et al., 2022). Activated microglia, in response to Aβ in AD or α-synuclein (α-Syn) in PD, initially attempt to clear the pathological proteins. However, as the disease progresses, a prolonged immune response becomes detrimental, leading to chronic inflammation that damages healthy neurons and disrupts synaptic connections. This prolonged activation of immune responses affects plasticity mechanisms, reducing synaptogenesis and altering synaptic pruning, critical processes in maintaining cognitive and motor function. The role of immune responses highlights the potential for anti-inflammatory therapies targeting microglial and astrocyte modulation to mitigate the detrimental effects on synaptic plasticity during neurodegeneration (Gao et al., 2023).

Neurogenesis

Neurogenesis is the process through which new neurons are generated from neural stem cells or neural progenitor cells (Bagheri-Mohammadi, 2022). This process is crucial for brain development and continues throughout life in specific regions such as the subventricular zone and the subgranular zone of the hippocampus. Neurogenesis involves several stages: proliferation, differentiation, migration, and integration of new neurons into existing neural circuits (Yao et al., 2016). This process is tightly regulated by a combination of intrinsic genetic programs and extrinsic environmental cues, involving multiple molecular and cellular mechanisms. During embryonic neurogenesis, neuroepithelial cells transform into radial glial cells around embryonic day 14 (E14). Radial glial cells can generate neurons directly or produce intermediate progenitor cells, which then differentiate into neurons (Ohlemacher et al., 2016). Later in development, radial glial cells also give rise to astrocytes and oligodendrocytes. Intrinsic signals, including rapid epigenetic changes, support these transitions, ensuring robust neurogenesis.

In the adult brain, neurogenesis primarily occurs in two regions: the subventricular zone and the subgranular zone of the hippocampus (Jurkowski et al., 2020). In subventricular zone neurogenesis, quiescent radial glia-like neural stem cells can activate and produce intermediate progenitor cells, which then generate neuroblasts. These neuroblasts migrate through the rostral migratory stream to the olfactory bulb, where they differentiate into interneurons. In subgranular zone neurogenesis, radial glia-like neural stem cells produce T-box brain protein 2-expressing intermediate progenitor cells, which then differentiate into neuroblasts. These neuroblasts migrate and integrate into the granule cell layer of the dentate gyrus as dentate granule neurons.

Epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, play crucial roles in regulating neurogenesis by responding to both intrinsic signals and

extracellular cues (Bure et al., 2022). DNA Methylation involves the addition of methyl groups to cytosine residues, typically leading to gene silencing. Enzymes like DNA methyltransferases maintain and establish methylation patterns crucial for neurogenesis. Histone modifications, involving histone acetylation and methylation, dynamically modulate chromatin structure and gene transcription. Enzymes such as histone acetyltransferases and deacetylases regulate these modifications. MicroRNAs and long non-coding RNAs regulate gene expression post-transcriptionally, impacting neurogenesis.

Synaptogenesis

Synaptogenesis is the formation of synapses, the basic units for information processing and storage in the nervous system. This process is essential for neural circuit formation and function. In humans, an increase in synapses is correlated with cognitive abilities. Genes involved in synaptogenesis are also linked to neurological and psychiatric disorders, highlighting the importance of understanding the molecular mechanisms underlying synapse formation. Synaptic proteins are crucial for synapse formation. Pre-synaptic terminals contain vesicles docking on the cytomatrix, while postsynaptic densities (PSDs) are electron-enriched areas in the post-synaptic compartment (Qi et al., 2022). **Figure 2** illustrates the molecular components critical to synaptogenesis, focusing on scaffold proteins that structure synaptic networks essential for neural communication (Qi et al., 2022).

Genetic screenings and homologous cloning have identified various synaptic proteins. For example, Liprin-α interacts with LAR transmembrane proteins and recruits ELKS/CAST to the active zone, facilitating synaptic vesicle docking and neurotransmission (**Figure 3**). CAMs like Syncam1, Neurexin, Neuroligin, and netrin-G ligand-3 are essential for synapse formation (Uchigashima et al., 2023). They interact with scaffold proteins to stabilize synaptic connections. LAR-RPTPs (leukocyte common antigen-related family receptors protein-tyrosine phosphatases) and their ligands, such as netrin-G ligand-3 and synaptic adhesion-like molecules, also play crucial roles in synapse development. The cytoskeleton provides structural support for synapses. Actin cytoskeleton dynamics, regulated by proteins like profilin and cofilin, are vital for the formation and maintenance of dendritic spines and axonal growth cones. Actin remodeling is influenced by neural activity, affecting synaptic structure and plasticity (Qi et al., 2022). Neural activity drives synaptogenesis by promoting the formation and stabilization of synaptic connections (Minegishi et al., 2023). Activity-dependent mechanisms include calcium signaling, protein kinases, transcription factors, and local translation. Studies on the visual system and neuromuscular junctions have demonstrated the importance of neural activity in synapse elimination and refinement. Neural activity regulates the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which mediate synaptic growth and plasticity. BDNF signaling involves Trk receptors and modulates local protein synthesis at synapses. **Figure 3** illustrates the intricate network of synaptic proteins essential for establishing and maintaining excitatory synapses (Qi et al., 2022).

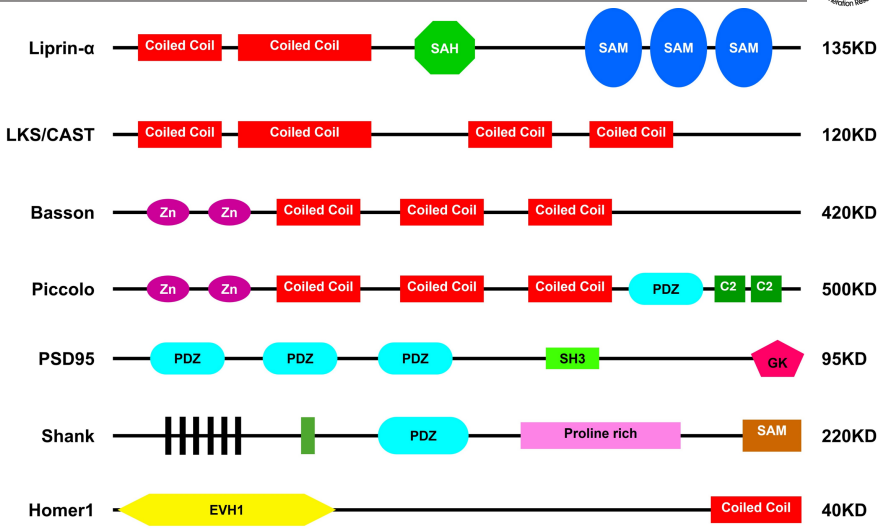

Figure 2 | **Representative illustration of key scaffold proteins and their respective domains.**
The molecular components critical to synaptogenesis, focusing on scaffold proteins that structure synaptic networks essential for neural communication. Highlighted proteins include Liprin-α, ELKS/CAST (ERC1, LIPRIN-α, and SYD-2/CAZ-associated structural protein), Piccolo, Bassoon, and PSD95. These scaffold proteins organize pre-synaptic vesicle docking within the cytomatrix and contribute to the formation of PSDs, electron-dense regions essential for synaptic stability and function. The diagram, though not scaled, provides a detailed view of interactions among these proteins, emphasizing their roles in supporting the architecture and connectivity of synapses, fundamental for information processing and storage in the nervous system. Reproduced with the permission from Qi et al. (2022). Published by Frontiers under license CC BY 4.0. PSD: postsynaptic density.

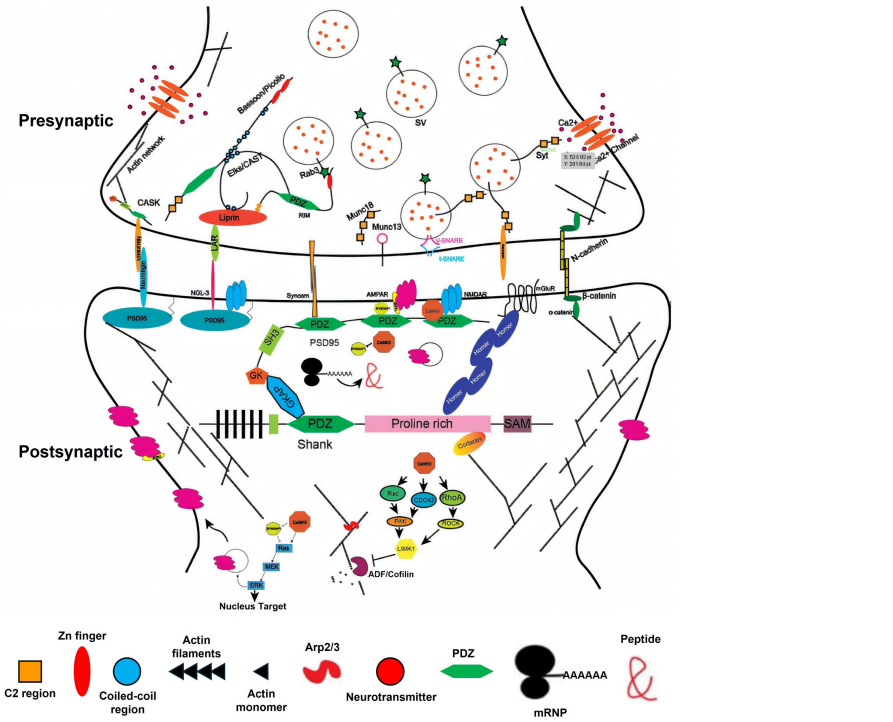

Figure 3 | **Illustration of the protein network within excitatory synapses, emphasizing the interactions among different synaptic proteins and CAMs.**
The figure shows the intricate network of synaptic proteins essential for establishing and maintaining excitatory synapses. Genetic screenings and homologous cloning approaches have identified key players like Liprin-α, which interacts with LAR transmembrane proteins to recruit ELKS/CAST at the active zone, promoting synaptic vesicle docking and efficient neurotransmission. CAMs, including Syncam1, Neurexin, Neuroligin, and NGL-3, serve as critical bridges between pre- and post-synaptic components, aligning and stabilizing synaptic structures through interactions with scaffold proteins. The LAR-RPTPs and their ligands, such as NGL-3 and SALMs, further support synapse formation and stability. Structural integrity is provided by the cytoskeleton, with actin filaments dynamically regulated by proteins like profilin and cofilin, ensuring the formation and maintenance of dendritic spines and axonal growth cones. Actin remodeling, driven by neural activity, significantly impacts synaptic plasticity and structure. Activity-dependent mechanisms involving calcium signaling, protein kinases, transcription factors, and local translation facilitate synaptogenesis by stabilizing synaptic connections. Additionally, neural activity governs the release of neurotrophic factors, particularly BDNF, which modulates synaptic growth and plasticity via Trk receptors and local protein synthesis at synaptic sites. The figure has been reproduced with the permission from Qi et al. (2022). Published by Frontiers under license CC BY 4.0. CAMs: Cell adhesion molecules; LAR-RPTPs: leukocyte common antigen-related protein-tyrosine phosphatases; NGL-3: netrin-G ligand-3; SALMs: synaptic adhesion-like molecules.

Role of neurotransmitters, growth factors, and intracellular signaling pathways

Neurotransmitters, growth factors, and intracellular signaling pathways play pivotal roles in mediating neuronal plasticity (Mattson, 2008). Glutamate, the primary excitatory neurotransmitter in the brain, is critical for synaptic plasticity. Activation of glutamate receptors, such as NMDA and AMPA receptors, is essential for the induction of both LTP and LTD. Gamma-aminobutyric acid, the main inhibitory neurotransmitter, also modulates synaptic plasticity by regulating the excitability of neuronal circuits. Growth factors such as BDNF, nerve growth factor, and fibroblast growth factor 2 (FGF2) are essential for promoting neuronal survival, differentiation, and plasticity. BDNF, in particular, is a key regulator of synaptic plasticity, enhancing synaptic strength and promoting neurogenesis (Yang et al., 2020a). Intracellular signaling pathways activated by neurotransmitters and growth factors are crucial for mediating changes in neuronal plasticity. The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, and the mechanistic target of rapamycin (mTOR) pathway are some of the key signaling cascades involved (Wang et al., 2024b). These pathways regulate various cellular processes, including protein synthesis, cytoskeletal reorganization, and gene expression, which are essential for synaptic plasticity.

Neuronal plasticity encompasses a range of molecular and cellular mechanisms, including LTP, LTD, neurogenesis, and synaptogenesis, all of which are crucial for the brain's adaptability (Chelyshev et al., 2022). Neurotransmitters, growth factors, and intracellular signaling pathways play vital roles in these processes, mediating the changes necessary for learning, memory, and recovery from injury (Nagappan et al., 2020). Understanding these mechanisms is essential for developing therapeutic strategies to treat neurodegenerative diseases and enhance cognitive function.

Interaction between neuroinflammation and synaptic plasticity

Neuroinflammation plays a significant role in the progression of both AD and PD, influencing neuronal plasticity through various molecular pathways (Di Filippo et al., 2008). In neurodegenerative diseases, the activation of microglia and astrocytes—a response to neuronal damage—leads to the release of pro-inflammatory cytokines like interleukin-1β (IL-1β), tumor necrosis factor-α, and chemokines (Brás et al., 2020). These cytokines, while initially intended to manage injury or infection, become chronically elevated and toxic, disrupting synaptic function and weakening synaptic plasticity. Chronic neuroinflammation can impair LTP, a process essential for memory formation and learning, and promote LTD, which can contribute to cognitive and motor deficits in AD and PD. Furthermore, neuroinflammation exacerbates oxidative stress, triggering neurodegenerative cascades that further impair synaptic plasticity. By understanding the interaction between neuroinflammation and synaptic plasticity, researchers can develop novel therapeutic interventions aimed at reducing inflammation to preserve neuronal plasticity and slow neurodegenerative progression.

Role of extracellular matrix dynamics in neuronal plasticity

The ECM in the CNS is a specialized, intricate network composed of proteoglycans, glycoproteins, and fibrous proteins that provide both structural support and dynamic signaling cues to neurons. Unlike ECM in other tissues, the CNS ECM is uniquely adapted to regulate processes essential for neuronal plasticity, such as synapse formation, stability, and remodeling. These characteristics make ECM dynamics a key factor in the adaptability and functional plasticity of neuronal circuits, especially within the context of neurodegenerative diseases like AD and PD (Freitas et al., 2021).

Structural and molecular composition of extracellular matrix in the central nervous system

The ECM of the CNS includes essential components like CSPGs, hyaluronan, tenascins, and laminins (Downs et al., 2023). CSPGs, in particular, form inhibitory perineuronal nets (PNNs) around specific neurons, such as those involved in motor and sensory processing. PNNs restrict synaptic plasticity by stabilizing synapses and limiting dendritic spine formation, which is critical for maintaining neural circuits but can also pose limitations in contexts where neuronal remodeling is beneficial, such as in recovery from injury or neurodegenerative conditions (Sánchez-Ventura et al., 2022).

Extracellular matrix dynamics and synaptic plasticity

In response to various stimuli, ECM undergoes remodeling processes, including the degradation of CSPGs and the upregulation of ECM-modifying enzymes like matrix metalloproteinases (Wei et al., 2020). This dynamic remodeling allows the ECM to act as a regulatory element for synaptic plasticity by controlling the physical and biochemical accessibility of synaptic sites. ECM components influence key aspects of both LTP and LTD, modulating synaptic strength by either facilitating or inhibiting receptor availability and neuronal signaling pathways. Studies have shown that enzymatic degradation of CSPGs can significantly enhance synaptic plasticity, indicating that ECM's structural components can be manipulated to restore synaptic flexibility and promote adaptive responses to neurological stress (Pelucchi et al., 2022; Chapman and Sorg, 2024).

Extracellular matrix dysfunction in Alzheimer's disease and Parkinson's disease

In AD and PD, aberrant ECM dynamics contribute to disease progression through mechanisms that impair plasticity and synaptic integrity. For instance, increased CSPG deposition has been observed in both AD and PD, forming dense barriers around neurons and limiting synaptic reorganization critical for cognitive and motor functions (John et al., 2023). This abnormal ECM buildup correlates with impaired neurogenesis and altered neuronal connectivity, directly contributing to the pathophysiological decline observed in these diseases. Furthermore, the dysregulation of ECM components like reelin and tenascin-R exacerbates synaptic instability, facilitating neurodegenerative progression by hindering compensatory plasticity that might otherwise counterbalance neuronal loss.

Advanced imaging and molecular tools

In studying neuronal plasticity, advanced imaging techniques and molecular tools have become indispensable (Zhumakhanova et al., 2024). These methods provide unprecedented insights into the dynamic processes occurring within the brain, enabling researchers to explore the mechanisms underlying synaptic changes and neurogenesis. This section will elaborate on two pivotal imaging techniques—functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)—as well as discuss the revolutionary genetic tools clustered regularly interspaced short palindromic repeats (CRISPR) and optogenetics, which are instrumental in dissecting the molecular intricacies of neuronal plasticity.

Advanced imaging techniques

Functional magnetic resonance imaging

fMRI is a non-invasive technique that measures brain activity by detecting changes in blood flow. When a brain region is more active, it consumes more oxygen, and fMRI can detect these fluctuations through blood oxygen level-dependent signals. fMRI offers high spatial resolution, allowing researchers to pinpoint areas of the brain involved in specific cognitive functions and to observe the effects of various stimuli on neuronal activity (Enzinger et al., 2016). The application of fMRI in studying neuronal plasticity has provided invaluable insights. For instance, fMRI has been used to observe changes in brain activity patterns in patients with neurodegenerative diseases such as AD (Lajoie et al., 2017) and PD (Wolters et al., 2019). These studies have revealed alterations in connectivity and functional organization, shedding light on how these diseases impact neuronal plasticity and brain function.

Positron emission tomography

PET is another powerful imaging technique used to study brain function (Jin et al., 2023). PET involves the use of radioactive tracers that bind to specific molecules in the brain, allowing researchers to visualize metabolic processes and neurotransmitter activity. PET provides molecular-level information that complements the spatial resolution of fMRI, making it a crucial tool for understanding the biochemical underpinnings of neuronal plasticity. PET has been particularly useful in tracking the progression of neurodegenerative diseases (Sarikaya, 2015). By using tracers that bind to Aβ plaques or tau proteins, researchers can monitor the accumulation of these pathological markers in AD (Wang et al., 2023). Similarly, PET can be used to study dopamine metabolism in PD (Ni, 2023), providing insights into the loss of dopaminergic neurons and its impact on synaptic plasticity.

Molecular tools

Clustered regularly interspaced short palindromic repeats

CRISPR technology has revolutionized genetic research by enabling precise modifications of

the genome. This tool uses a guide RNA to target specific DNA sequences, which are then cut by the Cas9 enzyme. The cell's natural repair mechanisms can be harnessed to introduce or remove genetic material, allowing for the study of specific genes involved in neuronal plasticity (Davis-Anderson et al., 2023). CRISPR has been instrumental in identifying the roles of various genes in synaptic formation and function. For example, knocking out genes related to synaptic proteins can reveal their contribution to synaptic stability and plasticity. Additionally, CRISPR can be used to create animal models of neurodegenerative diseases, enabling the study of disease mechanisms and the development of potential therapies (Rahimi et al., 2024).

Optogenetics

Optogenetics is a technique that uses light to control neurons that have been genetically modified to express light-sensitive ion channels. This method allows for precise temporal and spatial control of neuronal activity, providing insights into the functional connectivity and dynamics of neural circuits (Montagni et al., 2019). In the context of neuronal plasticity, optogenetics has been used to manipulate specific pathways and observe the resulting changes in synaptic strength and structure. For instance, by selectively activating or inhibiting neurons in the hippocampus, researchers can study the mechanisms underlying learning and memory. Optogenetics has also been used to restore function in animal models of neurodegenerative diseases, highlighting its potential therapeutic applications (Mitroshina et al., 2023; El Hajj et al., 2024).

Integration and future directions

The integration of advanced imaging techniques and molecular tools has transformed the study of neuronal plasticity (Minehart and Speer, 2021). Combining fMRI and PET with CRISPR and optogenetics enables a comprehensive approach, linking functional and molecular data to provide a holistic understanding of brain dynamics (Haas et al., 2024). Future research will continue to leverage these technologies to unravel the complexities of neuronal plasticity. Innovations in imaging and molecular biology will enhance our ability to monitor and manipulate neural circuits, paving the way for groundbreaking discoveries and therapeutic interventions in neurodegenerative diseases and beyond. By advancing our knowledge of the brain's plasticity, these tools are not only pushing the boundaries of neuroscience but also opening new avenues for treating neurological disorders, ultimately influencing the scientific community and healthcare practices on a global scale.

Influence of genetic variability on neuronal plasticity and disease

Genetic variability plays a pivotal role in determining individual susceptibility to neurodegenerative diseases, influencing neuronal plasticity and disease progression. Specific gene variants, such as those in APOE for AD and LRRK2 for PD, have been associated with differences in synaptic plasticity, affecting how neurons respond to both normal and pathological stimuli (Boyd et al., 2022). For instance, individuals with the APOE ε4 allele show a predisposition to amyloid accumulation, which impairs plasticity-related mechanisms such as synaptic remodeling and neurogenesis (Teter and Ashford, 2002). Understanding genetic variability provides a foundation for precision medicine approaches that tailor interventions based on individual genetic profiles, potentially improving therapeutic efficacy by targeting pathways most relevant to the patient's genetic makeup. Personalized approaches based on genetic insights may ultimately allow for improved outcomes by addressing the unique plasticity dynamics of each patient.

Neurotechnologies and molecular biology for plasticity modulation

Recent advancements in molecular biology and neurotechnologies provide innovative avenues to manipulate neuronal plasticity in AD and PD. CRISPR gene-editing technology and optogenetics have emerged as promising tools for modulating specific neural pathways to enhance or restore neuroplasticity (Geng et al., 2022). CRISPR, with its precise genome-editing capability, enables targeted modification of genes linked to synaptic function and plasticity, potentially reducing neurodegenerative damage in affected regions. Similarly, optogenetics allows for real-time control of neuronal activity, restoring memory functions by selectively activating synaptic circuits in animal models of AD and PD. These tools offer unprecedented control over neuronal pathways, advancing potential therapies for neurodegeneration by re-establishing synaptic flexibility and cognitive resilience in disease-affected areas.

Table 2 provides a detailed comparison of the advanced imaging techniques (fMRI and PET) and molecular tools (CRISPR and Optogenetics), highlighting their definitions, resolutions, primary uses, applications, advantages, disadvantages, data output, common research uses, integration with other tools, innovative applications, and future directions.

Role of Neuronal Plasticity in Alzheimer's Disease

Pathophysiology and impact on plasticity

Amyloid-beta plaques and their effects on neuronal plasticity

AD is a progressive neurodegenerative disorder characterized by the presence of Aβ plaques and tau tangles, which significantly impact neuronal plasticity (Zhang et al., 2021). Aβ plaques are extracellular deposits primarily composed of Aβ peptides, which are derived from the amyloid precursor protein (APP). The formation of these plaques is a hallmark of AD and plays a critical role in the disruption of neuronal function.

Mechanism of plaque formation

Aβare produced through the sequential cleavage of APP by β-secretase and γ-secretase enzymes. The aggregation of these peptides into oligomers and fibrils leads to the formation of amyloid plaques. These plaques are predominantly found in the hippocampus and cortex, regions crucial for memory and cognitive functions (Takahashi et al., 2017).

Impact on neuronal plasticity

The presence of Aβ plaques disrupts synaptic function and plasticity through various mechanisms. Aβ oligomers interact with synaptic receptors, impairing synaptic signaling, inhibiting LTP, which is essential for learning and memory, and enhancing LTD, resulting in synaptic weakening (Zhang et al., 2022b). Additionally, Aβ plaques activate microglia and astrocytes, causing chronic neuroinflammation. This inflammatory response releases cytokines and reactive oxygen species, further damaging synapses and disrupting neuronal communication. Furthermore, Aβ oligomers cause excessive calcium influx into neurons, disrupting calcium homeostasis. Elevated intracellular calcium levels trigger neurotoxic pathways, leading to synaptic loss and neuronal death.

Tau tangles and their effects on neuronal plasticity

Tau tangles, or neurofibrillary tangles, are intracellular aggregates of hyperphosphorylated tau protein (Nisbet et al., 2015). Tau is a microtubule-associated protein that stabilizes microtubules, which are essential for maintaining neuronal structure and function.

Mechanism of tangle formation

In AD, tau undergoes abnormal hyperphosphorylation, leading to the detachment from microtubules and subsequent aggregation into paired helical filaments and neurofibrillary tangles (Avila, 2006). These tangles accumulate within neurons, particularly in regions associated with cognitive functions such as the hippocampus and entorhinal cortex.

Impact on neuronal plasticity

The formation of tau tangles disrupts neuronal plasticity through several mechanisms. Hyperphosphorylated tau detaches from microtubules, causing their destabilization, which impairs axonal transport essential for delivering synaptic components, thus compromising synaptic function and plasticity (Rawat et al., 2022). Tau pathology also correlates with synaptic loss, a major contributor to cognitive decline in AD. The accumulation of tau tangles in synapses disrupts synaptic architecture and reduces synaptic density, impairing neural communication. Additionally, tau aggregates induce neuroinflammation, where activated microglia and astrocytes release inflammatory mediators that exacerbate synaptic damage and neuronal dysfunction. Furthermore, tau tangles impair mitochondrial function, leading to energy deficits and increased oxidative stress, which affects synaptic activity and plasticity by disrupting the energy supply necessary for synaptic processes.

The pathological features of AD, including Aβ plaques and tau tangles, have profound effects on neuronal plasticity (Kent et al., 2020). These pathologies disrupt synaptic function, induce neuroinflammation, alter calcium homeostasis, destabilize microtubules, cause synaptic loss, and impair mitochondrial function. Understanding these mechanisms provides critical insights into the disease process and highlights potential therapeutic targets for preserving or restoring neuronal plasticity in AD patients. By addressing these pathophysiological aspects, future research

Table 2 | **Comparative overview of advanced imaging and molecular tools in neuroscience research**

Aspect	fMRI	PET	CRISPR	Optogenetics
Definition	Non-invasive imaging technique measuring brain activity through blood flow changes (BOLD signals)	Imaging technique using radioactive tracers to visualize metabolic processes and neurotransmitter activity	Genetic tool enabling precise modifications of the genome using guide RNA and Cas9 enzyme	Technique using light to control neurons genetically modified to express light-sensitive ion channels
Resolution	High spatial resolution, limited temporal resolution	High spatial resolution, moderate temporal resolution	Genetic-level precision, no spatial/temporal resolution in imaging context	High temporal precision, moderate spatial resolution
Primary use	Observing brain activity patterns, functional connectivity	Visualizing metabolic processes, tracking biochemical changes	Gene editing, creating disease models, studying gene function	Controlling neuronal activity, studying neural circuits, functional connectivity
Applications	Neurodegenerative disease progression, cognitive function studies	Tracking neurodegenerative markers (e.g., amyloid plaques, tau proteins), dopamine metabolism	Studying gene roles in plasticity, creating neurodegenerative models, developing therapies	Manipulating specific neural pathways, studying learning/memory mechanisms, potential therapeutic interventions
Advantages	Non-invasive, detailed spatial maps of brain activity	Molecular-level information, specificity to biochemical processes	Precision in genetic modifications, broad applications in gene function and disease studies	Precise control of neuronal activity, high temporal precision, and specificity in targeting neural circuits
Disadvantages	Limited by temporal resolution, indirect measure of neural activity	Involves radiation exposure, expensive tracers, limited by tracer availability	Ethical concerns, off-target effects, challenges in delivery systems	Requires genetic modification, potential for tissue damage from light exposure
Data output	BOLD signal maps indicating active brain regions	Tracer distribution maps indicating metabolic or neurotransmitter activity	Genotypic modifications, phenotypic outcomes, functional assays	Neural activity control and mapping, behavioral outcomes
Common research uses	Functional connectivity in health and disease, brain mapping, cognitive neuroscience	Neurotransmitter studies, neurodegenerative disease progression, receptor binding studies	Investigating roles of specific genes in plasticity, creating precise disease models, gene therapy research	Exploring functional neural circuits, synaptic plasticity, behavior-modulation studies
Integration with other tools	Often combined with electrophysiology, transcranial magnetic stimulation, behavioral studies	Often used alongside MRI, fMRI, biochemical assays	Combined with sequencing, electrophysiology, imaging tools	Often used with fMRI, behavioral assays, calcium imaging
Innovative applications	Real-time fMRI neurofeedback, brain-machine interfaces	Development of new tracers for specific biochemical targets	CRISPR-Cas9 base editing, CRISPR interference, and activation for gene regulation	Development of optogenetic tools with finer control, integration with other neuromodulation technologies
Future directions	Higher temporal resolution techniques, integration with AI for data analysis	Development of more specific tracers, hybrid PET/MRI systems	Improved precision and delivery systems, expanded therapeutic applications	Expansion to more precise optogenetic control, integrating with advanced imaging for real-time analysis

BOLD: Blood-oxygen-level-dependent; CRISPR: clustered regularly interspaced short palindromic repeats; fMRI: functional magnetic resonance imaging; PET: positron emission tomography.

can develop innovative strategies to mitigate the impact of Aβ plaques and tau tangles on neuronal plasticity, ultimately aiming to slow down or prevent the progression of AD. This comprehensive approach aligns with the ongoing efforts to uncover groundbreaking treatments that could transform the clinical management of AD and improve the quality of life for affected individuals.

Role of extracellular matrix alterations on plasticity in Alzheimer's disease

In AD, dysregulated ECM components play a critical role in disease progression by disrupting synaptic plasticity and neuronal connectivity (Sun et al., 2021). The ECM in the CNS, primarily composed of CSPGs, hyaluronan, laminins, and tenascins, is essential for maintaining synaptic stability. However, in AD, ECM composition and dynamics are altered, exacerbating neurodegenerative processes and impairing neuronal plasticity (Anwar et al., 2022).

Extracellular matrix alterations and synaptic impairment

In AD, excessive deposition of CSPGs within the ECM leads to the formation of dense, inhibitory PNNs around neurons (Tewari et al., 2022). These PNNs act as physical barriers that limit synaptic remodeling, impeding neurogenesis and adaptability—both crucial for memory and cognitive function. CSPG accumulation disrupts LTP, a fundamental mechanism of synaptic plasticity required for learning and memory, by restricting receptor mobility and hindering synaptic responsiveness (Dityatev et al., 2010). Consequently, neurons lose their capacity to form new synaptic connections, intensifying cognitive deficits characteristic of AD.

Impact of reelin and tenascin-R dysregulation

In addition to CSPGs, the ECM proteins reelin and tenascin-R, which typically support synaptic plasticity by facilitating synapse formation and stabilization, are dysregulated in AD (Sethi and Zaia, 2017). Reelin, known for modulating synaptic strength and LTP, shows reduced expression in AD, correlating with weakened synaptic signaling and heightened vulnerability to Aβ and tau pathologies. Reelin deficiency disrupts dendritic spine structure, diminishing neural network connectivity and accelerating synaptic loss (Stranahan et al., 2013). Similarly, tenascin-R, which interacts with various ECM components to support structural plasticity, is altered, leading to impaired neuronal signaling and connectivity.

Role of extracellular matrix in inflammatory and oxidative pathways

The dysregulated ECM in AD also promotes neuroinflammatory and oxidative stress pathways, which further impact synaptic plasticity (Sun et al., 2021). Activated by Aβ plaques, reactive glial cells release pro-inflammatory cytokines, which degrade ECM integrity and amplify CSPG deposition. This inflammatory cascade exacerbates ECM rigidity, impeding the synaptic flexibility necessary for neuronal repair and adaptability. The oxidative stress associated with AD pathology damages ECM components directly, compounding the loss of synaptic efficacy and contributing to the progressive neurodegeneration observed in AD patients (Anwar, 2022).

Therapeutic implications of targeting extracellular matrix modulation in Alzheimer's disease

Given the ECM's involvement in AD pathogenesis, therapeutic approaches aimed at ECM modulation have gained interest. Enzymatic treatments, such as chondroitinase ABC, which breaks down inhibitory CSPGs, have shown potential to restore plasticity by enhancing synaptic connectivity and facilitating neurogenesis (Muir et al., 2019). Reelin-targeted therapies are also being explored to strengthen synaptic resilience and counteract the cognitive decline driven by ECM dysregulation in AD.

Current research and therapeutic interventions regarding Alzheimer's disease

Recent studies on Alzheimer's disease

Effects of amyloid-beta on synaptic plasticity

Galanis et al. (2021) found that Aβ oligomers impair LTP by disrupting NMDA receptor function and promote LTD through metabotropic glutamate receptor activation, contributing to cognitive deficits in Alzheimer's disease by weakening synaptic connections. Using tissue cultures from APP-deficient mice, they showed that without APP, dentate granule cells could not strengthen excitatory synapses homeostatically. Interestingly, Aβ, but not the APP ectodomain APPsa, restored homeostatic plasticity, highlighting Aβ's specific role in synaptic regulation. These findings clarify Aβ's dual impact on LTP and LTD, offering insight into its pathogenic role in AD and potential therapeutic approaches.

Tau pathology and synaptic dysfunction

Di et al. (2016) found that abnormal tau protein impairs cognitive function through two mechanisms: synaptic dysfunction at low pH-Tau levels and neuronal loss at high PH-Tau levels. They observed cognitive deficits and synaptic loss at lower levels, while higher levels led to severe neuronal loss and reduced brain size. This study

highlights the role of tau phosphorylation in Alzheimer's, showing that varying tau levels drive different pathological outcomes.

Neuroinflammation's role in synaptic plasticity

Aungst et al. (2014) found that repeated mild traumatic brain injury leads to chronic neuroinflammation, neuronal loss, and impaired synaptic plasticity, particularly in the hippocampus. This neuroinflammation disrupted NMDA receptor-mediated responses, impairing LTP while sparing AMPA receptor function. Rats with repeated mild traumatic brain injury showed cognitive deficits in memory and recognition tasks. These results emphasize the role of neuroinflammation in synaptic and cognitive impairments following mild traumatic brain injury and underscore the potential for therapies targeting neuroinflammatory pathways.

Dopaminergic modulation in Alzheimer's disease

Koch et al. (2014) found that the dopamine agonist rotigotine (RTG) improves LTP-like plasticity in AD patients, which is typically impaired in AD (Koch et al., 2014). While LTP-like plasticity was restored with RTG, neither rivastigmine (RVT) nor placebo showed any effect. LTD-like plasticity remained unchanged in all groups. Both RTG and RVT increased central cholinergic activity. These findings suggest RTG's potential as a therapeutic approach for enhancing synaptic plasticity in AD through dopaminergic stimulation.

Therapeutic strategy targeting neuronal plasticity for Alzheimer's disease

Advances in understanding the mechanisms underlying synaptic plasticity have opened new avenues for therapeutic interventions aimed at mitigating the effects of AD and PD. These treatments focus on enhancing LTP, reducing LTD, and counteracting the pathological impacts of Aβ and tau.

Amyloid-beta-targeting therapies

Crenezumab, a humanized monoclonal antibody, binds monomeric and aggregated forms of Aβ, especially oligomeric Aβ, which are key mediators of neurotoxicity in AD. Two phase 3 studies, CREAD (Crenezumab Alzheimer's Disease) and CREAD2 (Crenezumab Alzheimer's Disease-2), evaluated crenezumab's safety and efficacy in early AD patients (Ostrowitzki et al., 2022). The CREAD and CREAD2 trials evaluated the efficacy of crenezumab, an antibody targeting Aβ, in early AD but found no significant benefit. Despite high dosing, crenezumab did not reduce clinical decline or improve cognitive and functional measures compared to placebo, although it was well tolerated. These results highlight the challenges of targeting Aβ alone and suggest the need for combination therapies that address multiple AD pathologies. This outcome underscores the complexity of translating preclinical successes into clinical benefits in AD treatment.

Tau-targeting therapies

A recent study evaluated the efficacy of an active tau immunotherapy, AADvac1 (an active immunotherapy vaccine developed to target pathological tau protein in AD), in AD patients with amyloid and tau pathologies (Cullen et al., 2024). The ADAMANT (given name of the clinical trial) phase 2 trial evaluated the tau-targeting vaccine AADvac1 in Alzheimer's patients with amyloid and tau pathologies, showing it successfully induced anti-tau antibodies. In the amyloid- and tau-positive (A^+T^+) subgroup, the vaccine was associated with trends toward slower cognitive and functional decline, as well as reduced neurodegeneration markers like plasma NF-L levels and brain atrophy. These findings suggest that AADvac1 may benefit patients with confirmed tau pathology, supporting further trials to validate these effects and explore combination therapies.

Modulating neuroinflammation

Yang et al. (2021) found that low-dose radiation therapy (RT) reduces neuroinflammation in AD by suppressing proinflammatory cytokines (IL-6, CCL6, and IL-1β) and decreasing inflammatory markers. This treatment also reduced amyloid plaque burden and cognitive impairment, with RT attenuating microglial activation, a key factor in AD-related inflammation. These findings suggest low-dose RT as a potential approach for managing neuroinflammation in AD, underscoring the importance of targeting inflammatory processes to slow disease progression and improve outcomes.

Zelcer et al. (2007) found that activating liver X receptors (LXRs) could reduce neuroinflammation and amyloid plaque load in AD. LXRs, which regulate cholesterol and inflammation, suppress inflammatory genes (like iNOS and COX2) and enhance microglial phagocytosis of Aβ deposits. These dual actions—reducing inflammation and promoting Aβ clearance—highlight LXRs as promising therapeutic targets for addressing both inflammatory and amyloid aspects of AD, supporting further investigation of LXR agonists for AD treatment.

Enhancing neurotransmitter systems

Yao et al. (2023) developed a microcapsule-based delivery system to enhance neurotransmitter treatment in Alzheimer's disease, addressing issues like rapid metabolism and low bioavailability seen in traditional drugs. Using microfluidic electrospray technology, the microcapsules provide stability in the stomach and slow release in the intestine, reducing administration frequency to once every 5 days. This approach showed cognitive improvement and reduced Aβ plaque deposition, offering a promising method for more effective drug delivery and improved patient outcomes in AD.

Neurotrophic factors

Neurotrophic factors, such as BDNF, play a crucial role in promoting neuronal survival and plasticity. Wu et al. (2022) demonstrated that acetoacetate, a ketone body, enhances memory in AD by promoting BDNF expression and reducing inflammation. Acetoacetate improved spatial and recognition memory in AD mice while inhibiting the GPR43-pERK pathway, which reduced inflammatory markers (tumor necrosis factor-α and IL-6) in the hippocampus. This treatment also stimulated BDNF expression, suggesting acetoacetate's therapeutic potential for AD through neuroprotection and cognitive enhancement by modulating inflammation and supporting neurotrophic factors.

Lifestyle interventions

Lifestyle interventions, including physical exercise, cognitive training, and dietary modifications, have been shown to positively influence synaptic plasticity. Exercise, in particular, increases BDNF levels and promotes neurogenesis, thereby enhancing LTP and reducing LTD (Xue et al., 2022). Cognitive training stimulates synaptic activity and strengthens neural circuits, while dietary interventions, such as omega-3 fatty acids, provide neuroprotective effects (Gravesteijn et al., 2022).

Beyond pharmacological treatments, lifestyle factors like physical exercise, cognitive training, and diet have demonstrated the potential to enhance neuroplasticity (Maharjan et al., 2020). Physical activity increases BDNF, a key facilitator of synaptic plasticity, while cognitive engagement strengthens neuronal connections and boosts cognitive reserve (Ribeiro et al., 2021). Dietary approaches, such as omega-3 fatty acid intake, further support neuronal health by reducing inflammation. These interventions offer accessible, complementary strategies to conventional therapies, providing holistic support for neuroplasticity and cognitive function.

Impact of physical exercise and cognitive engagement on neuronal plasticity

Lifestyle factors such as physical exercise and cognitive engagement have been shown to positively influence neuronal plasticity, offering non-pharmacological methods to delay the onset and progression of neurodegenerative diseases. Physical exercise, for instance, promotes neurogenesis and synaptic plasticity by increasing levels of BDNF, which enhances LTP and reduces LTD (Bettio et al., 2019). Cognitive engagement similarly strengthens synaptic connections and promotes neuroplasticity by stimulating brain activity, potentially delaying cognitive decline in AD and PD (Petzinger et al., 2013; Mahaman et al., 2021). Emerging evidence suggests that these lifestyle factors activate pathways involved in mitochondrial function and oxidative stress reduction, further supporting neuroprotective mechanisms. As these interventions are accessible and can be customized, they offer practical insights for clinicians seeking to implement holistic treatment approaches that promote neuroplasticity and improve the quality of life for patients.

Critical analysis of conflicting findings

While studies underscore the promise of neuroplasticity-based therapies, conflicting findings highlight the challenges in translating preclinical results to clinical efficacy (Cramer et al., 2011; Lysetskyi et al., 2024). Variability in outcomes across animal models, patient populations, and methodological approaches often complicates comparisons and hinders consensus on therapeutic effectiveness. Such differences stem from variability in genetic, environmental, and experimental factors, which may yield distinct neuroplastic responses. For instance, some interventions show strong efficacy in controlled preclinical settings, but clinical applications often yield less consistent or limited outcomes due to patient-specific factors such as age, disease stage, and genetic predispositions.

This inconsistency suggests the need for more standardized protocols and multidisciplinary approaches in neuroplasticity research (Péran et al., 2020; Kumar et al., 2023; Papatzikis et al., 2023). Standardizing methodology and emphasizing cross-model comparisons could provide a clearer understanding of which interventions might yield reliable, scalable therapeutic options for neurodegenerative diseases. Additionally, more extensive longitudinal studies across diverse cohorts would help clarify the long-term impacts of neuroplasticity-focused interventions and foster translational success. Addressing these research gaps through integrative and standardized approaches will be essential in developing effective, reliable therapies for AD and PD.

Current research on neuronal plasticity in AD and PD has significantly advanced the understanding of the underlying mechanisms and identified potential therapeutic targets (Saha et al., 2022; Prabha et al., 2024). By focusing on enhancing LTP, reducing LTD, and counteracting the pathological effects of Aβ and tau, these treatments offer promising avenues for mitigating cognitive decline and improving patient outcomes. **Table 3** encapsulates the key studies and therapeutic strategies discussed, providing a comprehensive overview of current research and potential treatments for AD.

Future therapeutic directions for Alzheimer's disease

Future therapeutic directions should aim to tackle the complex pathology of AD by targeting multiple mechanisms simultaneously. Advances in understanding the molecular and cellular underpinnings of AD have paved the way for groundbreaking approaches, including CRISPR, optogenetics, multi-target therapies, gene editing, advanced drug delivery systems, neurotrophic factor enhancement, modulation of neuroinflammation, lifestyle interventions, personalized medicine, and the discovery of emerging molecular targets.

Clustered regularly interspaced short palindromic repeats and neuronal circuit modulation

The advent of CRISPR technology has opened groundbreaking possibilities in addressing neurodegenerative diseases like AD at the genetic level. CRISPR, through the Cas9 enzyme complex, enables precise editing of genetic material, allowing targeted interventions on genes involved in neuronal plasticity and neurodegeneration (Bhardwaj et al., 2022). In the context of AD, CRISPR has been employed to disrupt genes associated with Aβ plaque formation and tau protein aggregation, which are central to AD pathology (Rohn et al., 2018). By precisely excising or modifying specific genetic sequences, CRISPR can reduce or prevent the production of pathogenic proteins, thereby potentially reversing synaptic damage that impairs neuronal plasticity. Recent advancements in CRISPR technology, such as base editing and prime editing, allow for even more precise single-base modifications, minimizing off-target effects (Klinkovskij et al., 2023). Such refinements improve the potential of CRISPR in modulating plasticity, as they enable the restoration of genes involved in synaptic signaling and neuronal survival without the collateral damage observed in earlier gene-editing methods (Banazadeh et al., 2024). Moreover, by targeting genes that regulate neurotrophic factors like BDNF, CRISPR can enhance synaptic plasticity and neurogenesis in AD models, further supporting neuronal resilience and functional recovery (Wang et al., 2024a).

Optogenetics and precision control of neuronal activity

Optogenetics represents another transformative approach to modulating neuronal circuits with high specificity. By introducing light-sensitive ion channels, such as channelrhodopsins into neurons, optogenetics allows for the control of neuronal firing patterns through light exposure, providing unprecedented precision in activating or inhibiting specific neuronal pathways associated with memory and learning (Mirzayi et al., 2022). In animal models of AD, optogenetic stimulation has demonstrated significant potential in restoring hippocampal-dependent memory functions by selectively activating circuits impaired by Aβ and tau pathology. Optogenetics can be tailored to target neuronal subtypes involved in LTP, a cellular correlate of memory formation, and LTD, which is involved in synaptic pruning (Speranza et al., 2021). By modulating these pathways, optogenetics can correct imbalances in synaptic signaling caused by neurodegeneration, thereby restoring cognitive functions compromised in AD. Furthermore, advances in wireless optogenetic systems now enable minimally invasive approaches, which are promising for potential human applications.

Potential applications and future directions

Incorporating CRISPR and optogenetics within AD therapeutic strategies offers a dual-modality approach to both prevent pathological protein aggregation and enhance neuronal circuit functionality (Yin et al., 2023). These technologies provide precise control over genetic and neural circuit elements, promoting plasticity and neuroregeneration in ways traditional pharmacotherapies cannot achieve. Future applications of these technologies will likely involve combined gene and optogenetic therapies for an integrative intervention that targets both molecular and cellular dysfunctions in AD. The continued development of these cutting-edge technologies, alongside innovations in delivery methods, such as viral vectors and nanocarrier systems, will be crucial for their clinical translation. As ethical and safety considerations remain paramount, particularly with gene-editing technologies, robust preclinical studies are essential to evaluate off-target effects and long-term outcomes, laying the groundwork for future therapeutic avenues in AD. By leveraging such advanced approaches, the future of AD therapy promises to be transformative, potentially altering the landscape of treatment for this complex neurodegenerative condition.

A deeper engagement with CRISPR and optogenetics, paired with lifestyle interventions like exercise and cognitive engagement, offers a cutting-edge perspective on AD treatment (Lu et al., 2021). CRISPR enables precise genetic modifications, allowing researchers to target genes associated with AD pathology, such as those involved in Aβ and tau protein production. By correcting genetic anomalies, CRISPR can potentially reduce toxic protein aggregation, enhancing neuronal survival and supporting synaptic plasticity essential for cognitive resilience. Optogenetics complements this approach by modulating specific neural circuits involved in memory and cognition. Using light-sensitive ion channels, optogenetics can restore disrupted pathways, thereby improving synaptic signaling and promoting neuroplasticity in affected brain regions (Ning et al., 2022). Integrating these advanced technologies with lifestyle factors like physical exercise and mental stimulation—both shown to boost neurotrophic factors such as BDNF—creates a comprehensive approach. Exercise and cognitive engagement enhance neurogenesis and synaptic strength, contributing to cognitive improvement and delaying AD progression. This integrative strategy thus combines genetic, circuit-level, and lifestyle-based interventions, offering a holistic and transformative approach to AD therapy.

Table 4 provides a comprehensive, comparative, and inclusive overview of these future therapeutic directions, highlighting key findings and their potential impacts on AD treatment.

Role of Neuronal Plasticity in Parkinson's Disease

Pathophysiology and impact on plasticity

PD is primarily characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a significant decrease in dopamine levels in the striatum. This loss of dopaminergic neurons disrupts the delicate balance of the basal ganglia circuitry, which plays a crucial role in regulating motor control, learning, and synaptic plasticity. Understanding the pathophysiological mechanisms underlying this neuronal degeneration is vital for developing effective therapeutic strategies (Zhou et al., 2023).

Loss of dopaminergic neurons and the resultant effects on plasticity

The degeneration of dopaminergic neurons in PD is a complex process involving multiple cellular and molecular mechanisms. Oxidative stress, mitochondrial dysfunction, proteasomal impairment, and neuroinflammation are among the key factors contributing to neuronal loss. α-Syn aggregation, a hallmark of PD, forms Lewy bodies that disrupt cellular functions and promote neuronal death (Maiti et al., 2017).

Impact on synaptic plasticity

The loss of dopaminergic neurons severely affects synaptic plasticity, particularly in the striatum. Dopamine is a critical modulator of synaptic plasticity, influencing both LTP and LTD, which are essential for motor learning and cognitive functions. In the striatum, dopamine regulates the activity of medium spiny neurons through dopamine receptors D1 and D2, promoting LTP in the direct pathway and LTD in the indirect pathway, respectively (Bullock, 2016).

Disruption of basal ganglia circuits

In PD, the reduction in dopamine levels disrupts the normal functioning of the basal ganglia circuits. The direct pathway, which facilitates movement,

Table 3 | **Key studies and therapeutic strategies in AD**

Study/strategy	Focus	Key findings	Therapeutic implications
Study 1: effects of Aβ on synaptic plasticity	Impact of Aβ on synaptic plasticity	Aβ oligomers impair LTP by disrupting N-methyl-D-aspartate receptor function and promote LTD through metabotropic glutamate receptors.	Understanding Aβ's role in synaptic weakening; targeting Aβ to enhance synaptic function.
Therapeutic strategy 1: Aβ-targeting therapies	Crenezumab in early AD	No significant difference in clinical outcomes with Crenezumab; trends towards cognitive benefits in A+T+ subgroup.	Highlights the need for combination therapies and further research on Aβ targeting.
Study 2: Tau pathology and synaptic dysfunction	Impact of tau on synaptic function	Low levels of PH-Tau lead to cognitive deficits and synaptic loss; high levels cause neuronal loss.	Targeting tau phosphorylation and aggregation to preserve synaptic function.
Therapeutic strategy 2: Tau-targeting therapies	AADvac1 immunotherapy	Induced anti-tau antibodies; trends towards cognitive benefits in amyloid- and tau-positive patients.	Supports the potential of tau-targeting therapies, warrants further large-scale trials.
Study 3: the role of neuroinflammation in synaptic plasticity	Role of neuroinflammation in AD	Chronic neuroinflammation impairs LTP and promotes LTD; linked to cognitive deficits post-mTBI.	Targeting neuroinflammatory pathways to enhance synaptic plasticity and cognition.
Therapeutic strategy 3: modulating neuroinflammation	Low-dose RT in 5 × FAD mice	Suppressed proinflammatory cytokines, reduced amyloid plaques, and improved cognition.	Promising potential of low-dose RT to manage neuroinflammation in AD.
Study 4: dopaminergic modulation in AD	Dopamine agonist rotigotine on cortical plasticity	Rotigotine improved LTP-like plasticity in AD patients; rivastigmine and PLC had no effect.	Highlights the potential of dopaminergic modulation to restore synaptic plasticity.
Therapeutic strategy 4: enhancing neurotransmitter systems	Microcapsule delivery of cholinergic drugs	Improved drug bioavailability and cognitive function in AD mouse models; reduced administration frequency.	Innovative drug delivery systems to enhance compliance and therapeutic efficacy.
Study 5: neurotrophic factors	Role of BDNF in cognitive improvement	Acetoacetate improved memory and increased BDNF expression; inhibited inflammation in AD mice.	Potential of BDNF modulation to enhance neuroprotection and cognitive function.
Therapeutic strategy 5: neurotrophic factors	Acetoacetate in AD	Enhanced BDNF expression, reduced inflammation, and improved cognitive outcomes.	Supports targeting BDNF pathways for therapeutic intervention in AD.

AD: Alzheimer's disease; BDNF: brain-derived neurotrophic factor; LTD: long-term depression; LTP: long-term potentiation; PD: Parkinson's disease.

Table 4 | **Comparative overview of future therapeutic directions in AD**

Therapeutic direction	Description	Key findings	Potential impact	Reference
Multi-target therapies	Combining therapies targeting amyloid-beta and tau proteins.	Shown to reduce amyloid plaques and tau tangles more effectively, improving cognitive outcomes in models.	Offers a more holistic treatment approach by addressing multiple pathological features of AD.	Busche and Hyman, 2020
Gene editing and therapy	Utilizing CRISPR-Cas9 to edit genes involved in amyloid-beta production and tau phosphorylation.	Gene therapy targeting amyloid precursor protein or presenilin 1 genes and reducing tau pathology has shown significant cognitive improvements in models.	Addresses the root causes of AD at the genetic level, providing a potentially curative approach.	Bhardwaj et al., 2022
Advanced drug delivery systems	Nanoparticle-based and microcapsule delivery systems to enhance drug bioavailability.	Improved drug stability, targeted delivery, sustained release, and reduced dosing frequency were demonstrated in models.	Enhances therapeutic outcomes, improves patient compliance, and reduces side effects.	Hernando et al., 2023
Neurotrophic factor enhancement	Increasing levels of BDNF promote neurogenesis and synaptic plasticity.	Acetoacetate stimulates BDNF expression, reduces neuroinflammation, and improves memory in AD mouse models.	Promotes neuroprotection and cognitive function, offering a supportive treatment strategy.	Choi et al., 2018
Modulating neuroinflammation	Targeting neuroinflammation with therapies like low-dose RT and anti-inflammatory drugs.	Low-dose RT suppressed proinflammatory cytokines, reduced amyloid plaques, and improved cognition in models.	Reduces neuroinflammation, protects synaptic function, and supports overall brain health.	Yang et al., 2021
Lifestyle and non-pharmacological interventions	Physical exercise, cognitive training, and dietary modifications.	Exercise increases BDNF levels and neurogenesis; cognitive training enhances neural circuits; dietary interventions provide neuroprotective effects.	Complements pharmacological treatments, contributing to a holistic and sustainable AD care approach.	Thunborg et al., 2024; Zhou et al., 2024
Personalized medicine	Tailoring therapies to individual genetic, epigenetic, and biomarker profiles.	Advances in precision medicine allow for customized therapeutic regimens based on specific AD subtypes.	Ensures more effective treatments, potentially improving therapeutic outcomes and reducing adverse effects.	Fessel, 2024; Siafarikas, 2024
Emerging molecular targets	Discovering new pathways involved in synaptic function, mitochondrial health, and cellular metabolism.	Drugs targeting these pathways are in development, showing potential for novel therapeutic interventions.	Offers fresh opportunities for innovative treatments and future breakthroughs in AD therapy.	Dhapola et al., 2022

AD: Alzheimer's disease; BDNF: brain-derived neurotrophic factor.

becomes underactive, while the indirect pathway, which inhibits movement, becomes overactive. This imbalance leads to the characteristic motor symptoms of PD, such as bradykinesia, rigidity, and tremors (Blandini et al., 2000).

Synaptic plasticity and motor symptoms

The impairment of LTP and LTD in the striatum due to dopaminergic neuron loss has profound implications for motor symptoms in PD. Reduced dopaminergic signaling decreases the plasticity of corticostriatal synapses, impairing the ability to form and maintain motor memories. This synaptic dysfunction contributes to the difficulty PD patients experience in initiating and executing voluntary movements (Cousineau et al., 2022).

Neuroinflammation and plasticity

Neuroinflammation plays a significant role in PD pathophysiology, exacerbating neuronal loss and synaptic dysfunction (Wang et al., 2024c). Activated microglia and astrocytes release pro-inflammatory cytokines that disrupt synaptic function and plasticity (Cornell et al., 2022). These inflammatory responses further impair LTP and LTD, leading to the progressive decline in motor and cognitive functions observed in PD patients.

Role of extracellular matrix alterations on plasticity in Parkinson's disease

In PD, alterations in the ECM significantly influence disease progression by impacting the structural and functional plasticity of neuronal circuits, particularly within the basal ganglia (De Luca et al., 2020). The ECM, comprising proteoglycans, glycoproteins, and various structural proteins, maintains the neuronal microenvironment essential for synaptic stability and plasticity. However, dysregulation of ECM components in PD creates a microenvironment that is hostile to neuronal survival and adaptability, exacerbating the motor deficits and cognitive decline associated with this disease (Chapman and Sorg, 2024).

Chondroitin sulfate proteoglycan accumulation and synaptic rigidity

One of the primary ECM changes in PD involves the abnormal accumulation of CSPGs, which are crucial in maintaining synaptic structure but

become inhibitory when overexpressed (Lin et al., 2021). In PD, excessive CSPG deposition forms rigid PNNs around dopaminergic neurons, particularly in the substantia nigra and striatum. These PNNs restrict the neuronal flexibility needed for synaptic reorganization, making it difficult for the dopaminergic system to adapt to neuron loss. This rigidity directly impacts LTP and LTD in the striatum, which are vital for motor learning and adjustment to new motor patterns (Cousineau et al., 2022).

Tenascin-C and neuroinflammatory response

In addition to CSPGs, tenascin-C, another ECM glycoprotein, is markedly upregulated in PD and is closely linked to neuroinflammatory responses (Heindryckx and Li, 2018) . Tenascin-C modulates the immune response within the ECM, and its overexpression triggers the release of pro-inflammatory cytokines from glial cells, leading to sustained neuroinflammation. This inflammatory state disrupts normal synaptic function by inducing oxidative stress, which damages dopaminergic neurons and impedes synaptic plasticity. Neuroinflammation thus accelerates ECM degradation, further destabilizing the neural circuits responsible for motor control and exacerbating PD symptoms (Jakovcevski et al., 2013).

Reelin deficiency and dopaminergic dysregulation

Reelin, a glycoprotein that plays a key role in synaptic plasticity by promoting dendritic spine growth and synaptic stabilization, is reduced in PD (Levy et al., 2014). This deficiency weakens dopaminergic signaling, essential for motor coordination and learning. Reelin loss in PD disrupts synaptic plasticity within the striatal and cortical circuits, making it challenging for the brain to compensate for the progressive loss of dopaminergic neurons (Hethorn et al., 2015). Without adequate reelin, the structural integrity and adaptability of synapses are compromised, exacerbating motor symptoms and impairing the formation of new motor memory.

Therapeutic implications of extracellular matrix modulation in Parkinson's disease

Understanding ECM alterations in PD opens avenues for therapeutic interventions aimed at modulating ECM components to restore neuronal plasticity. Targeting CSPGs with enzymatic treatments like chondroitinase ABC has shown promise in reducing synaptic rigidity and enhancing plasticity. Additionally, anti-inflammatory therapies aimed at reducing tenascin-C-mediated inflammation could mitigate neuroinflammation's impact on the ECM. Reelin-based therapies also offer the potential to stabilize synaptic structures, supporting dopaminergic transmission and mitigating motor symptoms (Jakovcevski et al., 2013; Fletcher et al., 2019).

Current research and therapeutic interventions

Recent studies

Recent research in PD has significantly advanced our understanding of the disease's effect on neuronal plasticity and potential therapeutic interventions. These studies explore various mechanisms and treatments aimed at preserving and restoring synaptic plasticity, crucial for motor and cognitive functions.

Role of synaptic proteins

Schechter et al. (2020) investigated the role of α-Syn in synaptic plasticity and PD. They found that α-Syn enhances axon elongation and arborization by regulating phosphatidylinositol 4,5-bisphosphate (PI4,5P2) levels. In cultured neurons, α-Syn promoted axonal growth and arborization, which was confirmed in transgenic mouse models and human PD brains. The study also observed increased corticostriatal glutamatergic plasticity in early PD, suggesting the compensatory role of α-Syn. Furthermore, a higher density of thin axons and evidence of axonal injury were noted in symptomatic α-Syn transgenic mice. These findings highlight the dual role of α-Syn in neurodegeneration and plasticity, emphasizing its importance in PD pathophysiology.

Neurotrophic factors and plasticity

Virachit et al. (2019) examined the roles of various neurotrophic factors in the hippocampus of PD patients, focusing on glial cell line-derived neurotrophic factor (GDNF), cerebral dopamine neurotrophic factor, and FGF2. The study found altered levels of neurotrophic factors in the hippocampus of PD patients: decreased GDNF and increased cerebral dopamine neurotrophic factor and FGF2. Reduced GDNF may affect neuronal morphology and neuroplasticity, while elevated cerebral dopamine neurotrophic factor suggests a protective response against stress-related apoptosis, and increased FGF2 is linked to neuroinflammation and synaptic regulation. These findings highlight the potential of these factors as therapeutic targets for addressing cognitive decline in PD.

Gene therapy approaches

Björklund et al. (2000) investigated gene therapy for PD using adenovirus (Ad), adeno-associated virus, and lentivirus vectors to deliver GDNF to the nigrostriatal system in animal models. Their research demonstrated that gene therapy using adeno-associated virus and lentivirus vectors to deliver GDNF effectively promotes neuroprotection and functional recovery in dopamine neurons in PD. GDNF delivery to the nigrostriatal system prevented neuron degeneration and, in long-term studies, provided sustained neuroprotection and improved function in PD models. These findings highlight adeno-associated virus and lentivirus vectors as promising tools for developing neuroprotective treatments in PD, with potential for clinical applications.

Neuroinflammation and synaptic plasticity

Wahner et al. (2007) examined the role of neuroinflammation and its impact on synaptic plasticity in PD. Their study highlighted that neuroinflammation, indicated by activated microglia and increased proinflammatory cytokines, is prevalent in PD. Their population-based study showed that regular use of non-aspirin nonsteroidal anti-inflammatory drugs was linked to a significantly reduced risk of developing PD, likely due to the inhibition of cyclooxygenase, reduction of oxidative stress, and protection against glutamate toxicity. These findings suggest a potential therapeutic role for anti-inflammatory strategies in PD management and highlight the need for further research into nonsteroidal anti-inflammatory drug-mediated neuroprotection.

Current treatments improving plasticity

Current therapeutic interventions for PD aim to alleviate symptoms, slow disease progression, and enhance neuronal plasticity. These treatments range from pharmacological approaches to advanced therapeutic techniques.

Dopamine replacement therapy

Wu et al. (2024) explored the impact of dopamine replacement therapy (DRT) on cortical structure in PD patients. The study found that DRT in PD patients is associated with significant cortical atrophy, particularly in the prefrontal cortex, with reductions in cortical thickness and volume in regions like the superior frontal and rostral anterior cingulate cortices. These structural changes correlated negatively with DRT duration and dosage, suggesting that prolonged DRT may have adverse effects on brain structure. The study emphasizes the need for careful dose management to balance symptomatic relief with potential impacts on cortical integrity.

Neuroprotective agents

Wang et al. (2020) conducted a study on neuroprotective agents targeting PD via the Nrf2/Keap1 (Nrf2 stands for Nuclear factor erythroid 2-related factor 2 and Keap1stands for Kelch-like ECH-associated protein 1) pathway. They identified a piperine analogue, compound 3b, as a promising neuroprotective candidate for PD by targeting the Nrf2/Keap1 pathway. Compound 3b activated Nrf2, boosting antioxidant enzymes like HO-1 and NQO1, which protected neuron-like cells from oxidative damage. *In vivo*, 3b improved PD-related behaviors and preserved dopaminergic neurons in a mouse model, highlighting its potential as a treatment for oxidative stress in PD.

Deep brain stimulation

Dong et al. (2024) investigated the efficacy of deep brain stimulation (DBS) compared to drug therapy alone on the progression of PD. The study involved 77 patients with PD, divided into a DBS therapy group and a drug therapy group, followed over two years (Dong et al., 2024). They found that DBS provided greater motor function improvement and quality of life benefits for PD patients compared to drug therapy alone, with reduced medication needs and family burden. However, DBS patients experienced faster motor symptom progression in the "off" state. While DBS showed significant motor and quality of life benefits, it did not notably impact cognitive or psychiatric symptoms.

Exercise and physical therapy

Mak et al. (2017) investigated the long-term effects of exercise and physical therapy in individuals with PD. Their research demonstrated that long-term exercise and physical therapy provide lasting benefits for PD patients, improving muscle strength, balance, gait, and mobility. Strength and aerobic training reduced fall risk and enhanced postural stability, with balance exercises like tai chi offering sustained improvements. Exercise also promoted neuroplasticity, potentially influencing disease progression through increased BDNF levels and brain structure changes. The study supports integrating structured exercise programs into standard PD care for significant long-term benefits.

Emerging therapies

Dong-Chen et al. (2023) reviewed emerging therapies in PD, focusing on innovative approaches targeting α-Syn aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. They highlighted gene therapy using viral vectors and neuroprotective agents from medicinal plants as promising strategies. The study emphasized the necessity for multifaceted treatments due to the complex pathogenesis of PD and underscored the need for continued research to develop effective therapies that go beyond symptomatic relief provided by traditional treatments like L-DOPA (levodopa).

Innovative drug delivery systems

Storm et al. (2021) explored the emerging therapies in PD and highlighted various innovative approaches being investigated. The study reviewed emerging therapies for PD, highlighting gene therapy, cell-based therapies, and advanced drug delivery systems. Gene therapy focuses on delivering neuroprotective genes to support neuron survival, while stem cell transplantation aims to restore motor function by replacing lost dopaminergic neurons. Novel delivery systems, such as nanoparticles and liposomes, were developed to enhance treatment efficacy and reduce side effects. These innovative approaches show promise in improving PD management, though further research and trials are needed to confirm their safety and effectiveness for widespread clinical use.

Table 5 summarizes the key studies and neuroprotective strategies in PD discussed in the current review. It includes findings related to synaptic proteins, neurotrophic factors, gene therapy approaches, neuroinflammation, dopamine replacement therapy, neuroprotective agents, DBS, exercise and physical therapy, emerging therapies, and innovative drug delivery systems. Each entry outlines the main findings, mechanisms or approaches used, and the impact or conclusions drawn from the studies. This comprehensive overview highlights the multifaceted therapeutic strategies being explored to address the complex pathogenesis of PD and improve clinical outcomes for patients.

Future therapeutic directions

Gene editing and clustered regularly interspaced short palindromic repeat technology

CRISPR technology, with its high precision and adaptability, has transformed therapeutic strategies for neurodegenerative diseases, including PD. The application of CRISPR in PD involves precise targeting and modification of genetic sequences to address mutations associated with neuronal degeneration. Key targets include genes implicated in the misfolding and aggregation of α-Syn, a hallmark of PD pathology, as well as genes affecting dopamine synthesis and mitochondrial function (Mansour and El-Khatib, 2023). By excising or modifying such genes, CRISPR holds the potential to reduce toxic protein aggregation and enhance dopamine production, critical for restoring synaptic plasticity and function in dopaminergic neurons. Advanced CRISPR techniques like base editing and prime editing offer enhanced precision, allowing single-nucleotide changes without creating double-stranded breaks, which minimizes off-target effects and improves safety—an essential consideration for genetic therapies targeting the CNS. Preclinical studies employing CRISPR in PD models have shown improvements in motor functions and reduced α-Syn pathology, supporting its potential as a powerful tool for modulating synaptic and structural plasticity in PD (Mathur and Seamon, 2024).

Luo et al. (2019) utilized the CRISPR-Cas9 gene-editing system to investigate the neuroinflammatory and neuropharmacological mechanisms involved in PD. Their study used CRISPR-Cas9 to explore neuroinflammatory and neuropharmacological mechanisms in PD, demonstrating its potential to advance PD research. By creating PD models (such as Parkin, DJ-1, and PINK1 triple knockout pigs) and dissecting pathways like PKCδ and Prokineticin-2 signaling, the study highlighted the role of CRISPR in identifying complex disease mechanisms and therapeutic targets. These findings underscore CRISPR's transformative impact on neurodegenerative disease research and its potential to pave the way for innovative PD treatments.

Optogenetics and circuit-specific modulation in Parkinson's disease

Optogenetics, a groundbreaking technology that combines genetics and optics, enables precise modulation of neuronal activity through light-sensitive ion channels like channelrhodopsins. This method facilitates the control of neural circuits implicated in PD, especially within the basal ganglia circuitry responsible for motor function regulation. In PD, where dopaminergic neuronal loss disrupts the balance between the direct and indirect pathways of the basal ganglia, optogenetics provides a highly targeted approach to restoring motor function by selectively activating or inhibiting these pathways (Zhang et al., 2022a). Optogenetic stimulation has shown significant potential to enhance plasticity within these motor circuits by restoring LTP in the direct pathway and balancing the activity of medium spiny neurons, which are often dysregulated in PD. Experimental models have demonstrated that activating specific pathways within the striatum and cortex can partially compensate for dopamine deficiency, restoring motor coordination and improving synaptic efficacy (Shen et al., 2022). With continued advancements in wireless and minimally invasive optogenetic delivery systems, this technology shows promise for future human applications, allowing targeted restoration of plasticity and synaptic function with minimal intervention.

CRISPR and optogenetics provide a dual approach to PD by addressing genetic and circuit-level dysfunctions. CRISPR can correct dopamine-related mutations, while optogenetics restores synaptic balance, tackling both root causes and symptoms of PD. Advances in viral vectors and nanoparticles enhance the precision and safety of these therapies, aiding targeted delivery to

Table 5 | Key studies and neuroprotective strategies in PD

Study/strategy	Key findings	Mechanism/approach	Impact/conclusion
Study 1: role of synaptic proteins	α-Synuclein enhances axon elongation and arborization through PI4,5P2 regulation.	Promotes axonal growth and compensatory plasticity in early PD stages.	Highlights the dual role of α-synuclein in neurodegeneration and plasticity.
Study 2: neurotrophic factors	GDNF levels decreased in PD, while CDNF and FGF2 levels increased.	Promotes neuronal survival and plasticity via neurotrophic factor upregulation.	Emphasizes the potential of neurotrophic factors in addressing cognitive decline in PD.
Study 3: gene therapy approaches	AAV and LV vectors delivering GDNF promoted neuroprotection and recovery.	Viral vectors used for sustained GDNF delivery to dopaminergic neurons.	Demonstrates the promise of gene therapy for long-term neuroprotection in PD.
Study 4: neuroinflammation and plasticity	Elevated pro-inflammatory cytokines associated with synaptic dysfunction.	Anti-inflammatory treatments reduce neuroinflammation and preserve synaptic integrity.	Supports targeting neuroinflammation as a therapeutic strategy to enhance synaptic plasticity in PD.
Dopamine replacement therapy	Chronic dopamine replacement therapy linked to cortical atrophy, impacting motor and cognitive functions.	Replenishes dopamine but may lead to adverse structural changes in the brain.	Highlights the need for careful dose management to balance benefits and potential adverse effects.
Neuroprotective agents	Piperine analogues activated Nrf2/Keap1 pathway, protecting dopaminergic neurons.	Antioxidant and anti-inflammatory properties to combat oxidative stress.	Shows the potential for neuroprotective agents to slow PD progression and improve motor function.
DBS	DBS improved motor function and quality of life but did not significantly affect cognitive symptoms.	Modulates neural activity in specific brain regions.	Indicates DBS as an effective intervention for enhancing motor performance in PD patients.
Exercise and physical therapy	Long-term exercise interventions improved strength, balance, and neuroplasticity.	Promotes neuroplasticity and motor function through sustained physical activity.	Emphasizes the importance of incorporating exercise programs into PD management for lasting benefits.
Emerging therapies	Targeted α-synuclein aggregation, oxidative stress, and gut-brain axis regulation.	Multifaceted therapeutic approaches to address complex pathogenesis of PD.	Highlights the need for continued research to develop comprehensive and effective therapies for PD.
Innovative drug delivery systems	Improved delivery and efficacy of therapeutic agents using nanoparticles and liposomes.	Enhances drug bioavailability and minimizes side effects.	Demonstrates the potential of advanced delivery systems to optimize PD treatment outcomes.

DBS: Deep brain stimulation; FGF2: fibroblast growth factor 2; GDNF: glial cell line-derived neurotrophic factor; PD: Parkinson's disease.

neurons and supporting clinical potential. This combined approach offers a transformative path for PD therapy, promoting neuroplasticity and regeneration beyond traditional treatments, with rigorous safety measures remaining a priority.

Stem cell therapy

Doi et al. (2020) conducted a pre-clinical study on the safety and efficacy of induced pluripotent stem cell–derived dopaminergic progenitors (DAPs) for treating PD. Their research evaluated the safety and efficacy of induced pluripotent stem cell-derived DAPs for PD. *In vitro*, DAPs showed no genetic abnormalities, and *in vivo* studies in mice demonstrated no tumor formation or toxicity. Transplantation into PD-model rats led to significant behavioral improvements, supporting the clinical potential of induced pluripotent stem cell-derived DAPs, which are now in trial for PD treatment.

Neuroprotective agents therapy

Elesawy et al. (2024) investigated the neuroprotective potential of ezetimibe in a rat model of PD induced by rotenone. Their study demonstrated that ezetimibe, an antihyperlipidemic drug, provides neuroprotective effects in PD by improving motor function, restoring dopamine levels, and activating the AMPK/SIRT1/PGC1α pathway. Ezetimibe treatment enhanced autophagy and reduced apoptosis in the brain, effects confirmed by AMPK inhibition. These findings suggest the potential of ezetimibe as a therapeutic option for PD management.

Immunotherapy for Parkinson's disease

Immunotherapy, which has shown success in treating cancers and autoimmune diseases, is now being explored as a treatment for PD. Zhao et al. (2023) investigated the role of immunotherapy in PD by focusing on neurotrophic factor-related gene signatures. They explored immunotherapy in PD by analyzing neurotrophic factor-related genes, identifying four key genes—EN1, IRF7, PLOD3, and LOXL1—that play roles in PD progression and glioblastoma prognosis. These neurotrophic factor-related genes correlated with immune cell infiltration and responses to immune checkpoint inhibitors, indicating their potential as immunotherapy targets for both PD and GBM. The study highlights the importance of personalized medicine that leverages genetic and immunological profiles to enhance treatment strategies for neurodegenerative diseases.

Lifestyle and non-pharmacological interventions

Emerging research is also focusing on the role of lifestyle factors and non-pharmacological interventions in managing PD. Regular physical exercise, cognitive training, and dietary modifications have been shown to have neuroprotective effects and improve the quality of life for PD patients. Veronese et al. (2024) evaluated the independent associations of various nutritional components, physical activity, sedentary behavior, and metabolic factors with the risk of PD in a population-based prospective cohort study using data from the United Kingdom Biobank. The study of 502,017 individuals followed for 12.8 years, vigorous physical activity, low sitting time, high sleep quality, moderate coffee intake, and current smoking were linked to a reduced risk of PD, while alcohol intake increased risk. Protective effects were also noted for plasma vitamin D and uric acid, while LDL cholesterol, triglycerides, and C-reactive protein were risk factors. The study suggests that lifestyle interventions like exercise, sleep quality, moderate coffee, and vitamin D may serve as neuroprotective strategies for the prevention of PD.

Integrating CRISPR and optogenetics with lifestyle interventions, such as exercise and cognitive engagement, offers a cutting-edge approach to PD treatment. CRISPR allows precise gene editing to target α-Syn and dopamine regulation genes, addressing root causes of PD, while optogenetics provides targeted control of motor circuits, restoring function and supporting plasticity. Exercise and cognitive engagement further enhance resilience by boosting neurotrophic factors and supporting dopamine release, creating a comprehensive strategy that combines genetic, circuit-based, and lifestyle interventions for more effective PD management.

Comparative Analysis of Neuronal Plasticity in Alzheimer's Disease and Parkinson's Disease

Shared and distinct mechanisms

Neuronal plasticity, the ability of the nervous system to adapt and reorganize itself, plays a crucial role in both AD and PD. Despite the differences in their primary pathological features—Aβ plaques and tau tangles in AD, and dopaminergic neuronal loss in PD—both diseases exhibit alterations in neuronal plasticity that contribute to cognitive and motor deficits (Yuan et al., 2020). Understanding the shared and distinct molecular pathways affecting neuronal plasticity in these diseases is essential for developing effective therapeutic strategies.

Shared mechanisms

Synaptic dysfunction

Both AD and PD exhibit synaptic dysfunction as a common early feature. In AD, synaptic loss is closely associated with Aβ oligomers, which disrupt synaptic function by impairing LTP and promoting LTD (Shankar and Walsh, 2009). Similarly, in PD, the loss of dopaminergic neurons leads to reduced dopaminergic signaling, impairing synaptic plasticity and leading to motor and cognitive deficits (Picconi et al., 2012).

Neuroinflammation

Chronic neuroinflammation is a hallmark of both diseases, contributing to neuronal damage and impaired plasticity. In AD, microglia activation by Aβ plaques induces a pro-inflammatory state, exacerbating neuronal damage (Sobue et al., 2023). In PD, activated microglia release pro-inflammatory cytokines that damage dopaminergic neurons and disrupt synaptic plasticity (Isik et al., 2023).

Oxidative stress

Increased oxidative stress is a common pathological feature in both AD and PD. In AD, oxidative stress is primarily induced by Aβ and tau pathology, leading to neuronal damage and impaired plasticity (Chen and Zhong, 2014). In PD, the degeneration of dopaminergic neurons results in elevated levels of reactive oxygen species, further impairing neuronal plasticity and function (Chang and Chen, 2020).

Distinct mechanisms

Molecular pathways

In AD, the amyloid cascade hypothesis posits that the accumulation of Aβ peptides initiates a cascade of events leading to tau hyperphosphorylation, neurofibrillary tangles, and synaptic loss (Kepp et al., 2023). Conversely, in PD, the pathogenesis is primarily driven by the aggregation of α-Syn into Lewy bodies, resulting in dopaminergic neuron degeneration and disrupted neuronal networks (Calabresi et al., 2023).

Neurotrophic factors

In AD, BDNF levels are reduced, contributing to synaptic loss and cognitive decline (Gao et al., 2022). In PD, GDNF plays a critical role in the survival and function of dopaminergic neurons, with reduced GDNF levels leading to neuronal degeneration and impaired plasticity (Kakoty et al., 2024).

Insights from comparative studies

Comparative studies on plasticity-based therapies in AD and PD have provided valuable insights into their potential efficacy and underlying mechanisms (Yuan et al., 2020). These studies highlight the importance of targeting shared pathways, such as neuroinflammation and oxidative stress, while also addressing disease-specific mechanisms to enhance therapeutic outcomes.

Synaptic plasticity enhancement

Therapies aimed at enhancing synaptic plasticity, such as NMDA receptor modulators and synaptic activity stimulators, have shown promise in both AD and PD. For instance, NMDA receptor antagonists like memantine have been used to mitigate synaptic dysfunction in AD (Liu et al., 2019). In PD, dopaminergic therapies such as levodopa and dopamine agonists help restore synaptic plasticity and improve motor function (Zhuang et al., 2013).

Neurotrophic factor therapy

Administering neurotrophic factors has been explored as a therapeutic strategy in both diseases. In AD, BDNF delivery has shown potential in promoting synaptic plasticity and cognitive function (Gao et al., 2022). In PD, GDNF delivery aims to protect and restore dopaminergic neurons, enhancing motor function and neuronal survival (Kirik et al., 2004).

Anti-inflammatory treatments

Given the role of neuroinflammation in both diseases, anti-inflammatory treatments are being investigated for their potential to protect neuronal function and plasticity. Nonsteroidal anti-inflammatory drugs and specific cytokine inhibitors are being tested to reduce neuroinflammation and improve outcomes in AD and PD (Chopade et al., 2023).

Table 6 compares the mechanisms of neuronal plasticity in AD and PD. It highlights shared features like synaptic dysfunction, neuroinflammation, and oxidative stress, and contrasts specific pathways such as the amyloid cascade in AD and α-Syn aggregation in PD. The table also discusses neurotrophic factors, with BDNF in AD and GDNF in PD, and outlines therapeutic strategies, including NMDA receptor modulators, neurotrophic factor delivery, and anti-inflammatory treatments. This summary emphasizes the need for multifaceted therapies targeting both common and unique pathways in AD and PD.

Discussion and Future Directions

Summary of key findings

The comprehensive analysis of neuronal plasticity in AD and PD reveals several shared and distinct mechanisms affecting neuronal function and plasticity. Key findings highlight that both AD and PD exhibit synaptic dysfunction, neuroinflammation, and oxidative stress as common pathological features. In AD, Aβ oligomers and tau tangles are the primary culprits, leading to impaired LTP and increased LTD. In PD, the degeneration of dopaminergic neurons and the aggregation of α-Syn into Lewy bodies result in disrupted dopaminergic signaling and synaptic plasticity.

A comparative study indicates that targeting neurotrophic factors such as BDNF in AD and GDNF in PD can enhance neuronal survival and plasticity (Nasrolahi et al., 2022). Therapeutic strategies aimed at modulating synaptic plasticity, reducing neuroinflammation, and addressing oxidative stress have shown promise in both diseases. For instance, NMDA receptor modulators, neuroprotective agents, and anti-inflammatory treatments have demonstrated efficacy in preclinical and clinical studies.

Implications for clinical practice and future research

The findings from this review have significant implications for clinical practice and future research. The identification of shared mechanisms such as synaptic dysfunction and neuroinflammation underscores the potential of developing unified therapeutic strategies that can address both AD and PD. Clinicians should consider integrating treatments that enhance synaptic plasticity and reduce neuroinflammation as part of a comprehensive management plan for patients with these neurodegenerative diseases. Future research should focus on the development of multifaceted therapies that target both common and disease-specific pathways. For example, combining NMDA receptor modulators with neurotrophic factor delivery and anti-inflammatory agents could offer synergistic benefits. Additionally, personalized medicine approaches that consider the genetic, epigenetic, and biomarker profiles of patients can optimize treatment efficacy and minimize adverse effects. Emerging technologies such as gene editing and stem cell therapy hold promise for transforming the treatment landscape of AD and PD. Gene editing techniques like CRISPR-Cas9 can correct genetic mutations associated with these diseases, while stem cell therapy can replace lost neurons and restore neuronal function. Continued research and clinical trials are essential to validate the safety and effectiveness of these innovative treatments.

While existing therapies offer promising interventions, future research should aim to further enhance treatment efficacy by exploring combinatorial and stage-specific approaches. Key areas for exploration include:

• Combinatorial Therapies: Investigating the integration of synaptic plasticity modulation with gene therapy or neuroinflammatory inhibitors may yield more comprehensive therapeutic outcomes. For instance, combining neurotrophic factor therapies with gene-editing techniques could enhance the durability and precision of treatment effects.

Table 6 | Comparative analysis of neuronal plasticity mechanisms

Mechanism	AD	PD	Shared mechanism
Synaptic dysfunction	Aβ oligomers impair long-term potentiation and promote long-term depression	Loss of dopaminergic neurons reduces synaptic plasticity	Both exhibit early synaptic dysfunction
Neuroinflammation	Microglia activation by Aβ plaques	Activated microglia release pro-inflammatory cytokines	Chronic neuroinflammation contributes to neuronal damage
Oxidative stress	Induced by Aβ and tau pathology	Elevated ROS levels from dopaminergic neuron degeneration	Increased oxidative stress in both diseases
Molecular pathways	Amyloid cascade, tau hyperphosphorylation	Alpha-synuclein aggregation into Lewy bodies	
Neurotrophic factors	Reduced BDNF levels	Reduced GDNF levels	
Therapeutic strategies	NMDA receptor modulators, BDNF delivery	Dopaminergic therapies, GDNF delivery	Anti-inflammatory treatments explored in both

AD: Alzheimer's disease; Aβ: amyloid-beta; BDNF: brain-derived neurotrophic factor; GDNF: glial cell line-derived neurotrophic factor; PD: Parkinson's disease.

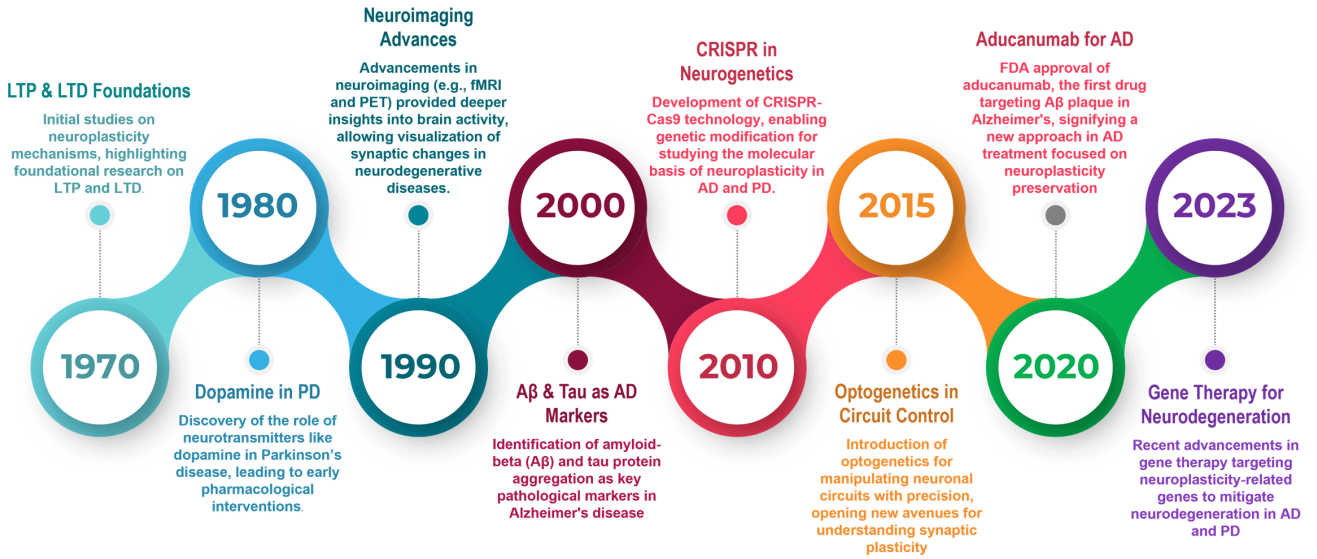

Figure 4 | Timeline of historical milestones in the study of neuronal plasticity, AD, and PD.
The figure illustrates key advancements from the foundational studies on neuroplasticity mechanisms in the 1970s through the discovery of pathological markers in AD, to recent developments in gene therapy aimed at preserving neuronal plasticity in neurodegenerative diseases. This visual progression highlights the evolution of research and therapeutic approaches over five decades, emphasizing the contributions of neuroimaging, genetic engineering, and precision medicine in understanding and combating AD and PD. AD: Alzheimer's disease; Aβ: amyloid-beta; LTD: long-term depression; LTP: long-term potentiation; PD: Parkinson's disease.

• Stage-Specific Interventions: Tailoring interventions to early, middle, and late stages of neurodegeneration could optimize therapeutic responses by addressing the disease's progression dynamics. This stratified approach could offer customized interventions for patients at different stages of AD and PD.

• Genetic and Environmental Interactions: Research on how environmental and genetic factors influence synaptic resilience could provide insights into non-drug interventions that may bolster synaptic strength and delay neurodegenerative decline. This includes examining the impact of lifestyle factors like diet, exercise, and cognitive engagement on synaptic plasticity.

Ethical and clinical considerations

The development and implementation of new therapies for AD and PD must be guided by ethical and clinical considerations. Ensuring patient safety and informed consent is paramount, particularly with novel treatments such as gene editing and stem cell therapy. Researchers and clinicians must adhere to rigorous ethical standards to protect patient rights and well-being. Clinical considerations include the need for comprehensive patient education and support throughout the treatment process. Patients and their families should be well-informed about the potential risks and benefits of new therapies, as well as the expected outcomes. Additionally, ongoing monitoring and assessment are crucial to evaluate the long-term safety and efficacy of these treatments. Finally, the integration of lifestyle and non-pharmacological interventions, such as exercise, cognitive training, and dietary modifications, should be considered as part of a holistic approach to patient care. These interventions have been shown to have neuroprotective effects and can complement pharmacological treatments, enhancing overall therapeutic outcomes.

Limitations

This review article has some inherent limitations. It primarily discusses neuronal plasticity in AD and PD, focusing on experimental findings and technological advancements without delving into the theoretical framework of neuroplasticity or offering a comprehensive overview of the aesthetic theories related to neuronal function and plasticity. Additionally, the paper does not provide an exhaustive examination of processing methods for aesthetic data within neuroplasticity studies. Moreover, while the review extensively covers Western perspectives and findings, it lacks a global outlook, particularly insights from Eastern approaches or cultural influences on neuroplasticity, which might offer alternative views or complementary findings. Future reviews could benefit from including these theoretical and cultural perspectives to enhance the scope and depth of understanding in the field.

Conclusions

Understanding neuronal plasticity is crucial in addressing neurodegenerative diseases such as AD and PD. This review has elucidated the critical role of neuronal plasticity in the pathophysiology and therapeutic intervention of these conditions. Neuronal plasticity encompasses various mechanisms, including synaptic plasticity, neurogenesis, and synaptogenesis, which are vital for learning, memory, and recovery from injury. In AD, the presence of Aβ plaques and tau tangles disrupts synaptic function and induces neuroinflammation, significantly impairing neuronal plasticity. In PD, the loss of dopaminergic neurons leads to a severe disruption in basal ganglia circuits, affecting motor control and synaptic plasticity. The review also highlighted current research on therapeutic interventions targeting neuronal plasticity, such as gene editing, neurotrophic factors, and advanced drug delivery systems, emphasizing their potential to mitigate disease progression and improve patient outcomes.

Future research should prioritize a comprehensive and interdisciplinary approach to further unravel the complexities of neuronal plasticity in neurodegenerative diseases. Emphasis should be placed on early diagnosis and intervention, leveraging advanced imaging techniques and molecular tools to monitor disease progression and therapeutic efficacy. Collaborative efforts across neuroscience, genetics, bioinformatics, and clinical practice are essential to develop holistic treatment strategies. Moreover, lifestyle interventions, including regular physical exercise and dietary modifications, should be integrated into standard care practices, given their demonstrated neuroprotective effects. Ethical considerations and patient-centered care must guide the development and implementation of new therapies. By fostering interdisciplinary collaboration and innovative research, we can enhance our understanding of neuronal plasticity and develop transformative therapies to improve the quality of life for individuals affected by AD and PD.

This review suggests future research directions to better understand how emerging neurotechnologies and lifestyle interventions may synergistically support neuronal plasticity. For instance, combining CRISPR-mediated gene modifications with lifestyle interventions could amplify plasticity-promoting effects, potentially delaying cognitive decline. Such integrated approaches warrant further exploration to identify optimal treatment combinations and assess their long-term efficacy in AD and PD populations.

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