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Synaptic Plasticity in Alzheimer's Disease: Bridging Molecular Data and Computational Models

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Abstract

Neurodegenerative disorders, most notably Alzheimer's disease (AD), are marked by progressive cognitive decline and widespread neuronal loss. A growing body of evidence indicates that synaptic dysfunction occurs early in AD and serves as a key driver of memory impairment rather than a secondary symptom. Central to this dysfunction is synaptic plasticity (SP)—the ability of synapses to modify their strength in response to patterns of neuronal signaling. By strengthening or weakening connections, SP enables the brain to encode experience, support flexible behavior, and maintain cognitive adaptability. Disruption of SP has therefore been identified as a core pathological mechanism underlying AD progression. This review aims to first summarize the basic mechanisms of synaptic plasticity and then synthesize recent findings on how SP is regulated and dysregulated in Alzheimer's disease. By highlighting current knowledge gaps and unresolved questions, it seeks to identify key directions for future research. Clarifying how major forms of SP are altered in AD may offer crucial insight into the mechanisms of memory impairment and potential therapeutic targets.

Keywords

Alzheimer's Disease, Synaptic Plasticity, Synaptic Dysfunction, Neurodegeneration, Computational Modeling

1. Introduction

1.1. Synaptic Structure and Function in Neural Communication

Neurons communicate through specialized junctions called synapses, where chemical signals are passed from one neuron to another [1]. When an electrical sig-

nal—known as an action potential (AP)—reaches the pre-synaptic terminal, it triggers the opening of voltage-gated calcium channels and the influx of Ca^{2+} ions. This Ca^{2+} entry initiates the release of neurotransmitters, which diffuse across the synaptic cleft and bind to receptors on the post-synaptic membrane [2]. This process allows neurons to transmit, integrate, and respond to information throughout the nervous system. The efficiency of this transmission is not fixed—it can change over time depending on how often and how strongly neurons are activated [3]. This ability of synapses to adjust their strength is known as synaptic plasticity (SP), a fundamental process that enables the brain to learn, adapt, and store information [4] [5]. Because synaptic failure is one of the earliest detectable changes in Alzheimer's disease—as well as a major contributor to cognitive decline—understanding the mechanisms that govern synaptic plasticity is critical for identifying how and why these processes break down during AD progression.

Synaptic plasticity (SP) can be broadly categorized into short-term and long-term forms: short-term plasticity involves temporary, reversible changes in synaptic strength lasting milliseconds to minutes, while long-term plasticity produces more enduring modifications that support memory formation and learning (see **Figure 1**) [6] [7].

1.2. Synaptic Plasticity and Human Cognition

Synaptic plasticity (SP) is the capacity of synapses to undergo enduring modifications in their efficacy, transmission reliability, or structural organization in response to patterns of neuronal firing and synaptic signaling [3] [4]. SP is considered at both the cellular level—where it governs processes such as neurotransmitter release, receptor trafficking, and dendritic spine remodeling—and at the system level, where these changes translate into adaptive cognitive functions. This adaptability underlies not only the acquisition and consolidation of long-term memory but also maintenance of short-term and working memory, as well as the flexible recall of episodic and semantic memory [5] [8] [9]. At the neural level, SP translates patterns of electrical signaling into persistent modifications in synaptic efficacy and network function [3] [10]. Early theoretical work proposed the principle that "cells that fire together wire together", provided a foundational framework linking experience-driven neuronal activity with lasting changes in synaptic efficacy.

1.3. Synaptic Plasticity as a Foundation of Learning and Memory

Since the 1970s, experimental studies have established that synaptic plasticity (SP) is more than a crucial mechanism underlying memory and learning; it represents a biological mechanism closely associated with learning and memory [4]. In animal studies, scientists have found that long-term potentiation (LTP)—a lasting increase in the strength of connections between neurons after repeated activity—occurs in the hippocampus and helps with forming and storing spatial memories. When re-

searchers block NMDA receptor activity, which is needed for this process, memory formation becomes weaker [1] [6]. LTP is often seen as one of the main ways the brain strengthens pathways that are used during learning. In contrast, long-term

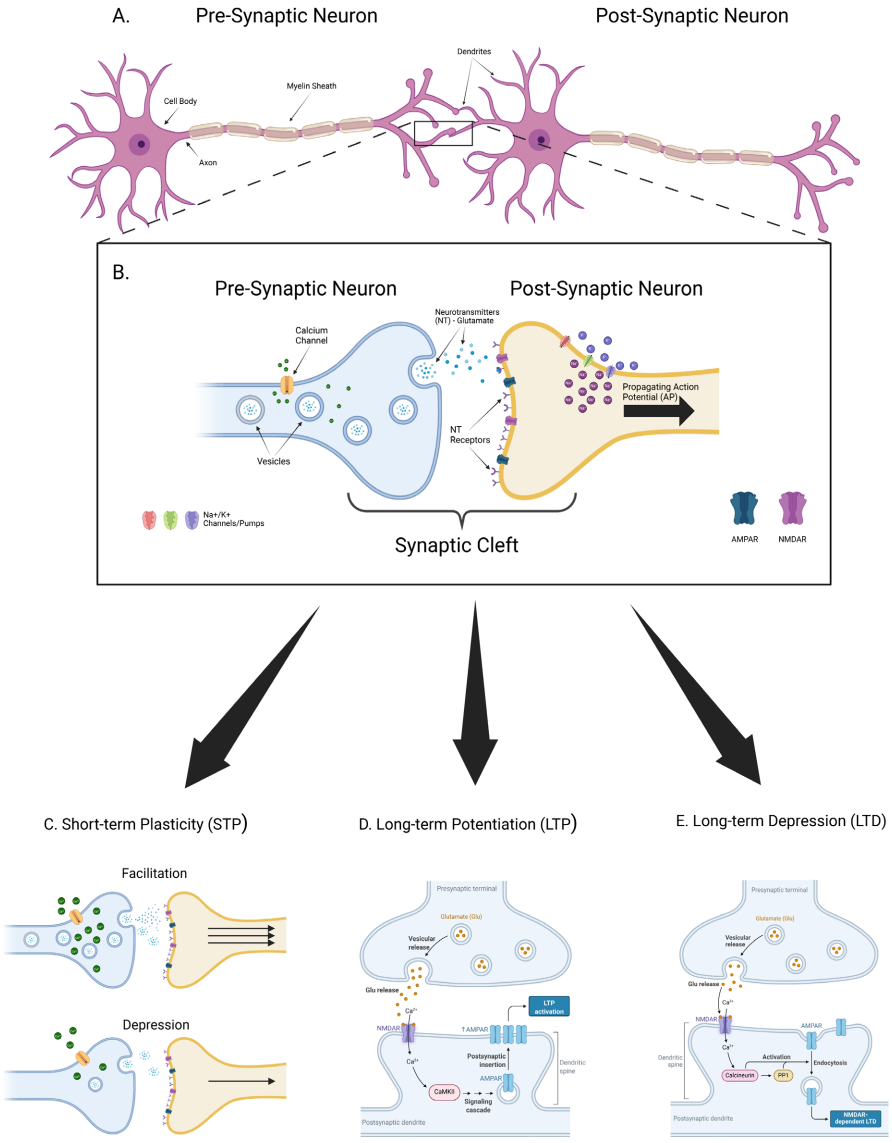

Figure 1. Overview of synaptic transmission and mechanisms of synaptic plasticity. (A) depicts the anatomical relationship between a pre-synaptic and post-synaptic neuron, illustrating the axon terminals of the pre-synaptic cell forming a synapse with the dendritic spines of the post-synaptic neuron. (B) zooms in on the synaptic cleft, showing neurotransmitter release from the pre-synaptic terminal, calcium influx through voltage-gated calcium channels, and receptor activation on the post-synaptic membrane. Three major forms of synaptic plasticity are illustrated below: (C) STP, which includes transient facilitation and depression resulting from pre-synaptic calcium dynamics and vesicle cycling [3]; (D) LTP, characterized by NMDA receptor activation, calcium entry, and AMPA receptor phosphorylation and insertion into the post-synaptic membrane [1]; and (E) LTD, involving reduced calcium signaling, activation of phosphatases, and AMPA receptor internalization. Together, these processes represent the spectrum of synaptic modifications that underlie neural communication, learning, and memory [6].

depression (LTD) is the opposite process—it weakens the connection between neurons and helps with clearing out old information or improving motor skills [3]. Together, LTP and LTD balance each other, allowing the brain to strengthen useful connections while weakening unnecessary ones, which keeps learning flexible and efficient. These findings show strong links between changes in synaptic strength and memory, although they do not prove cause and effect. In humans, brain imaging and electrical studies have also shown that activity-dependent changes in brain plasticity happen during learning, skill development, and problem-solving [8] [11]. Overall, these discoveries suggest that SP provides the foundation for how the brain changes at the cellular level to support learning, memory, and flexible thinking [2] [5] [9].

2. Short-Term Synaptic Plasticity: Mechanisms That Underlie Immediate and Reversible Changes in Regulating Rapid Information Transferred

During fast cognitive processes—such as speech recognition, working memory, or sensory perception—neurons must rapidly adjust how they communicate [7]. Short-term synaptic plasticity (STP) enables this by allowing synaptic strength to change temporarily in response to recent activity [3]. These adjustments typically last from milliseconds to minutes and arise from alterations in neurotransmitter release probability at the pre-synaptic terminal [7]. A general overview of synaptic organization and the relationship between pre- and post-synaptic components is illustrated in **Figure 1**. While STP does not provide a lasting substrate for memory, it plays an essential role in filtering incoming signals, enhancing relevant stimuli, and maintaining stable communication during bursts of neural activity [8]. In this way, STP supports the ability of the brain to rapidly encode and process dynamic information before longer-lasting forms of plasticity occur [4] [7].

The mechanism of STP is rooted in pre-synaptic calcium dynamics and vesicle cycling [3] [7]. When an AP reaches the pre-synaptic terminal, voltage-gated calcium channels open and allow Ca^{2+} influx. Normally, intracellular buffering and pumps clear this Ca^{2+} rapidly, but if successive APs occur within tens of milliseconds, residual calcium remains [4]. This accumulation increases the probability that synaptic vesicles will fuse with the pre-synaptic membrane on the next spike. The elevated release probability manifests as facilitation, in which post-synaptic responses grow larger with closely spaced stimuli. Facilitation is thus driven almost entirely by residual Ca^{2+} acting on the release machinery.

In contrast, depression occurs when repeated stimulation depletes the readily releasable pool of vesicles. If vesicle recycling cannot keep pace, fewer vesicles are available to release, leading to diminished post-synaptic responses, post-tetanic potentiation (PTP), both relying on pre-synaptic Ca^{2+}-dependent modulation of vesicle priming proteins [4]. These mechanisms illustrate how Ca^{2+} accumulation and vesicle pool dynamics transiently regulate synaptic efficacy, tuning information flow in a way that reflects the immediate history of pre-synaptic activity on pre-syn-

aptic Ca^{2+}-dependent modulation of vesicle priming proteins [4]. These mechanisms illustrate how Ca^{2+} accumulation and vesicle pool dynamics transiently regulate synaptic efficacy, tuning information flow in a way that reflects the immediate history of pre-synaptic activity [3].

3. Long-Term Synaptic Plasticity: Mechanisms Regulating Long-Term Plasticity and Establish Lasting Circuit Changes

3.1. Long-Term Potentiation (LTP) Strengthens Synaptic Connections

Long-term potentiation (LTP) is a persistent strengthening of synaptic efficacy, typically induced by high-frequency or burst stimulation that generates a large and rapid NMDAR-mediated Ca^{2+} influx into the post-synaptic spine [1] [6]. This strong elevation of intracellular Ca^{2+} activates protein kinases such as CaMKII, PKA, and PKC, which phosphorylate AMPA receptors to increase their conductance and promote the rapid insertion of additional AMPARs into the post-synaptic membrane [3] [5]. The increase in receptor number enhances synaptic transmission, while long-term structural changes such as dendritic spine enlargement and actin cytoskeleton remodeling further stabilize synaptic strengthening [3]. These mechanisms make LTP essential for memory encoding, experience-dependent plasticity, and the long-term storage of learned information within neural circuits [5] [7].

3.2. Long-Term Depression (LTD) Weakens Synaptic Connections

In contrast, long-term depression (LTD) is a persistent weakening of synaptic efficacy, typically induced by prolonged low-frequency stimulation [1] [6]. LTD also depends on NMDAR-mediated Ca^{2+} influx, but in this case, the calcium signal is smaller and slower than that which induces LTP. Rather than activating kinases, this modest Ca^{2+} elevation preferentially recruits protein phosphatases such as PP1 and calcineurin, leading to the dephosphorylation and internalization of AMPA receptors from the post-synaptic membrane [3] [6]. The reduction in receptor number decreases synaptic transmission, while long-term structural changes such as dendritic spine shrinkage further stabilize synaptic weakening (see **Figure 1**) [3]. These mechanisms make LTD important for adaptive forgetting, synaptic refinement, and the prevention of runaway excitability [5] [7].

While LTP and LTD describe the strengthening or weakening of synaptic connections, the precise timing of neuronal activity plays a critical role in determining which outcome occurs. This timing-dependent regulation is captured by spike-timing-dependent plasticity (STDP), which can be understood as a temporally refined mechanism underlying both LTP and LTD.

3.3. Spike-Timing-Dependent Plasticity (STDP) Links Learning to Neural Firing Timing

Spike-timing-dependent plasticity (STDP) is not a distinct category of plasticity,

but rather a mechanism that determines whether LTP or LTD occurs based on the precise relative timing of neuronal firing. In STDP, the order and timing of pre-synaptic and post-synaptic spikes play a critical role in shaping synaptic outcomes. Unlike STP, which involves transient, millisecond-scale changes in neurotransmitter release due to residual calcium buildup, STDP reflects long-lasting, timing-dependent modifications in synaptic strength that can persist for minutes to hours [3] [6] [7]. If a pre-synaptic spike precedes a post-synaptic spike within tens of milliseconds, NMDA receptor-mediated Ca^{2+} influx is rapid and large, favoring LTP. Conversely, if the post-synaptic neuron fires before the pre-synaptic input, Ca^{2+} entry is weaker or delayed, biasing signaling toward LTD [3].

In this way, STDP provides a temporally refined rule that encodes causal relationships between neuronal firing patterns: synapses that reliably predict post-synaptic activity are strengthened, while those that do not are weakened. This temporal learning mechanism fine-tunes connectivity, supporting processes such as sensory coding, motor learning, and network synchronization [9]. This dynamic regulation of synaptic strength underlies normal cognitive and motor functions, and disruptions in these mechanisms contribute to the pathophysiology of neurodegenerative disorders such as AD.

4. Alzheimer's Disease Progress and Pathology

4.1. Alzheimer's Disease Progresses through Widespread Neural Degeneration

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual decline in memory, cognition, and behavior [12]. Early symptoms often include short-term memory loss, which not only emerges early but also worsens the disease progresses, eventually leading to profound impairments in long-term memory as well. Patients may also have trouble with word recall and disorientation in familiar environments [12]. As AD advances, impairments broaden to include reasoning deficits, personality changes, mood disturbances, and reduced ability to carry out daily tasks independently. These clinical features reflect widespread brain damage, particularly within the hippocampus, amygdala, and cerebral cortex, which are critical for memory consolidation, emotion, and executive function [12].

As demonstrated in **Figure 2** Panel (A). At the cellular and molecular level, AD pathology is primarily driven by the abnormal accumulation of protein that disrupts neuronal function. A major hallmark is the extracellular deposition of amyloid-beta (Aβ) plaques, which form when amyloid precursor protein (APP) is cleaved abnormally by β- and γ-secretases, producing insoluble Aβ fragments that aggregate outside neurons and interfere with synaptic communication [12] [13]. Inside neurons, hyperphosphorylated tau aggregates into neurofibrillary tangles, destabilizing microtubules and impairing axonal transport [14]. The relative importance of these two pathological processes remains a subject of debate: some models propose that Aβ plaque accumulation initiated the disease cascade, while

others emphasize that tau pathology correlates more directly with neuronal dysfunction and cognitive decline [4] [6]. In addition, both Aβ and tau aggregates trigger synaptic dysfunction, impairing long-term potentiation, and drive neuroinflammation. Activated microglia and astrocytes release cytokines and reactive oxygen species that exacerbate injury, ultimately leading to hippocampal and cortical atrophy and the progressive worsening of cognitive and behavioral symptoms [15] [16].

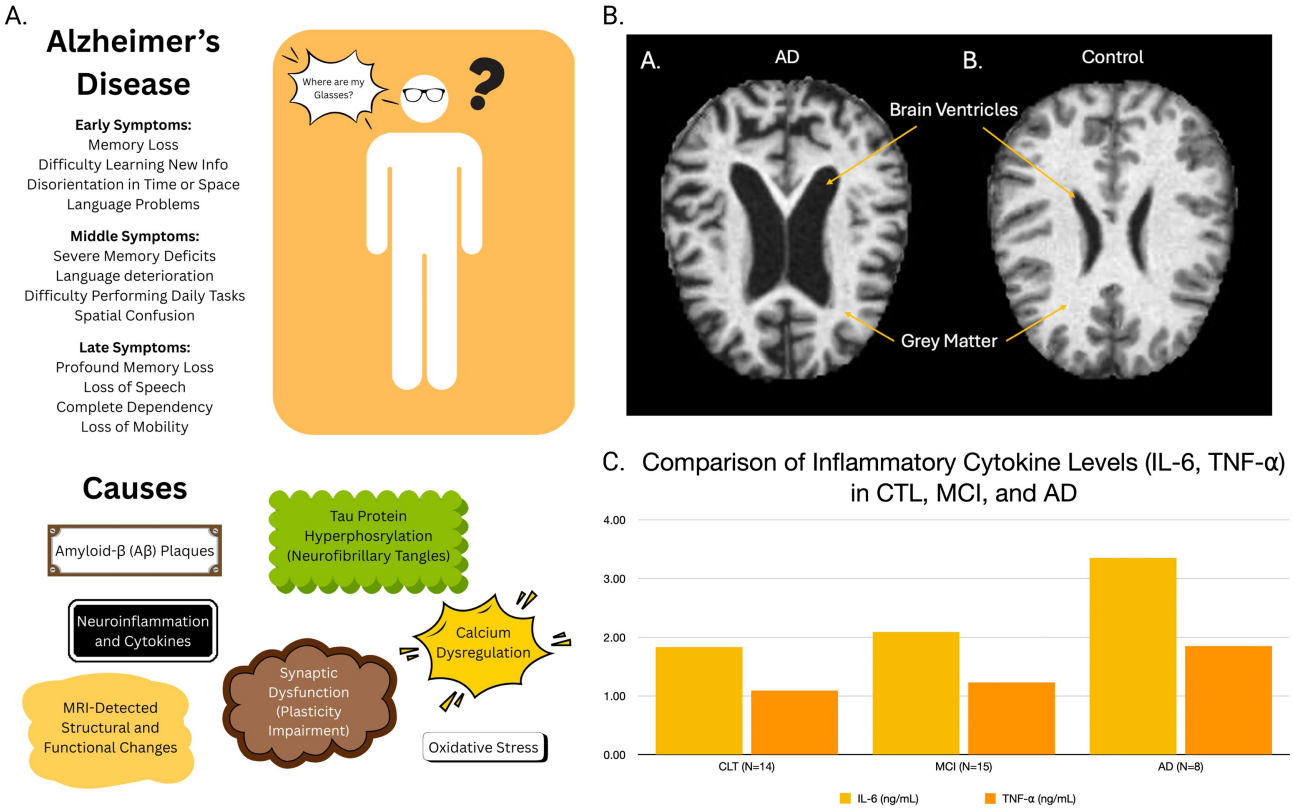

Figure 2. Overview of Alzheimer's disease (AD): clinical symptoms, pathological mechanisms, structural degeneration, and inflammatory profiles. (A) Summary of Alzheimer's disease symptoms and major causative mechanisms. Early symptoms include mild memory loss, disorientation, and language difficulty, which progress to severe memory deficits, spatial confusion, and complete dependency in late stages. Key pathological drivers include amyloid-β (Aβ) plaque accumulation, tau protein hyperphosphorylation, calcium dysregulation, neuroinflammation, oxidative stress, and resulting synaptic dysfunction and MRI-detectable structural changes. (B) MRI scans comparing an Alzheimer's disease (AD) brain (A) with a healthy control (B). In AD, enlarged ventricles and reduced grey matter volume indicate widespread neuronal loss and cortical atrophy. Images adapted from Falah (2023) [18], Dataset_Alzheimer, Kaggle. (C) Comparison of inflammatory cytokine levels (IL-6, TNF-α) among control (CTL), mild cognitive impairment (MCI), and AD groups. Progressive increases in both cytokines indicate escalating neuroinflammation correlating with cognitive decline. Reproduced from [16], Inflammatory Cytokines and Cognition in Alzheimer's Disease and Its Prodrome.

This review examines how disruptions in synaptic plasticity underlie the cognitive decline characteristic of AD. While STP and LT plasticity normally support information processing and memory formation, evidence from electrophysiological, molecular, and transcriptomic studies shows that these processes are profoundly impaired in Alzheimer's models and patient brains. Reduction in LTP, exaggerated

LTD, and altered receptor expression provide experimental confirmation that the disease directly targets the cellular substrates of learning. In the following sections, we integrate findings from both experimental datasets and computational models to highlight how Aβ, tau, and neuroinflammation disrupt plasticity mechanisms, and to explore how these insights inform potential therapeutic strategies [2] [3] [5] [12]-[14] [17].

4.2. Brain Atrophy Reflects Structural Degeneration in Alzheimer's Disease

Magnetic resonance imaging (MRI) is a non-invasive technique that uses strong magnetic fields and radio waves to generate detailed images of brain structures. It is frequently used in Alzheimer's disease (AD) research to detect anatomical changes associated with neurodegeneration. Key structures examined in MRI scans include grey matter, which is composed of neuronal cell bodies and synaptic connections, and the brain ventricles, which are fluid-filled spaces within the brain. Alterations in these regions provide insight into the structural progression of AD.

As illustrated in **Figure 2** Panel (B), the MRI scans reveal characteristic changes in the AD brain. In Panel (A), representing an AD patient, enlarged ventricles and reduced grey matter volume are evident when compared to the healthy control in Panel (B). Ventricular enlargement reflects brain atrophy, as the loss of neural tissue creates additional space within the cranial cavity. At the same time, thinning the grey matter corresponds to the loss of neuronal cell bodies, synaptic connections, and overall brain mass. These changes provide a visible correlate to the cognitive deficits observed in AD patients, as reduced grey matter particularly impacts memory-related regions [18].

4.3. Progressive Increase in IL-6 and TNF-α Levels across Cognitive Decline Stage

Figure 2 Panel (A) visualizes a progressive increase in interleukin (IL)-6 and tumor necrosis factor (TNF)-α concentrations across the control (CTL), mild cognitive impairment (MCI), and Alzheimer's disease (AD) groups. Notably, IL-6 shows a marked elevation in AD patients compared to both CTL and MCI, suggesting that chronic inflammation intensifies as cognitive decline advances. TNF-α also rises, though less dramatically, reinforcing the idea that multiple inflammatory pathways contribute to neurodegeneration. These findings align with evidence that neuroinflammation is not merely a consequence of AD pathology but may actively accelerate synaptic dysfunction and neuronal death. The stepwise increase from CTL to MCI to AD underscores the potential of IL-6 and TNF-α as biomarkers for early detection and progression monitoring [16].

4.4. Electrophysiological Evidence of Impaired Synaptic Plasticity in APP/PS1 Mice

As shown in **Figure 3**, electrophysiological recordings from hippocampal slices of

APP/PS1 mice—transgenic mice expressing human amyloid precursor protein (APP) and presenilin-1 (PS1) mutations associated with familial Alzheimer's disease—provide direct evidence for early synaptic responses. Studies in synaptic plasticity showed changes at hippocampal connections linking CA3 pyramidal neurons to CA1 neurons (**Figure 3(A)**) in 6-month-old wild-type and APP/PS1 mice, recording excitatory post-synaptic currents to assess differences [19]. Paired-pulse ratio (PPR) measurements, which test pre-synaptic release probability, showed no significant differences between genotypes, suggesting that pre-synaptic glutamate release remained intact.

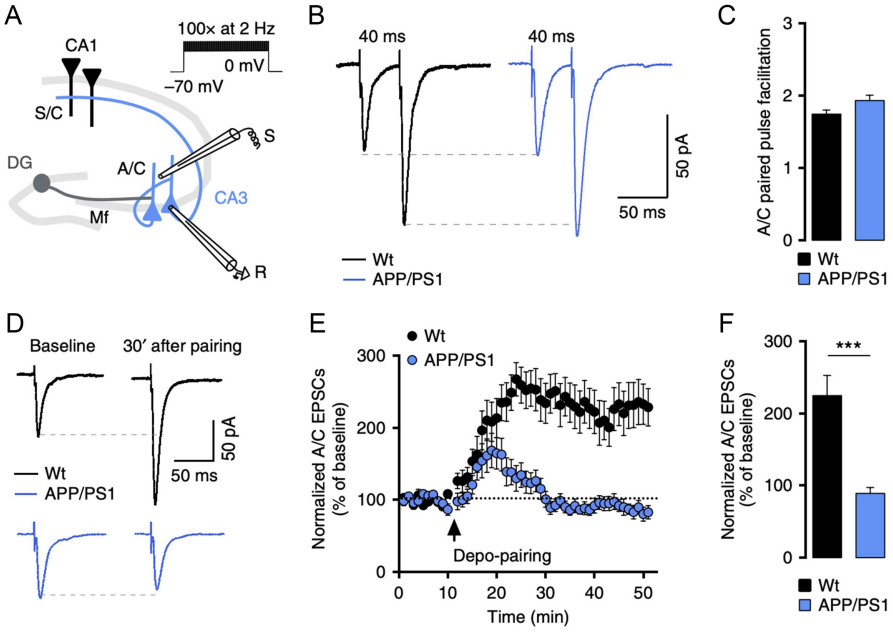

Figure 3. Early changes in synaptic function in 6-month-old APP/PS1 mice. (A) Diagram of the hippocampal CA3 region showing where stimulation and recordings were made. ((B) - (C)) Paired-pulse facilitation, which tests short-term synaptic plasticity, was similar between wild-type (WT) and APP/PS1 mice, suggesting normal pre-synaptic function. ((D) - (F)) In contrast, long-term potentiation (LTP) was strongly reduced in APP/PS1 mice compared to WT. The traces (D) and time-course plot (E) show that WT neurons maintained strong LTP, while APP/PS1 neurons did not.

In contrast, when LTP was induced using an NMDA receptor-dependent depolarization-pairing protocol, wild-type slices exhibited robust potentiation, with EPSCs increasing to approximately 200% - 250% of baseline, whereas APP/PS1 slices failed to potentiate and remained near baseline levels. These findings suggest that while pre-synaptic function appears unaffected, post-synaptic potentiation is reduced in APP/PS1. However, this relationship is correlational rather than causational: impaired LTP in this model occurs alongside, but does not directly prove, the functional deficits observed in AD. Together, these findings indicate that synaptic alterations can emerge early in the disease process, prior to widespread neuronal loss, supporting the hypothesis that disrupted plasticity contributes to the progression of memory decline in AD [15] [19].

4.5. Mathematical Modeling of Neuronal Learning to Explore Trends in SP

Computational models provide an important complementary perspective for understanding synaptic plasticity impairments in AD [20]. At their core, models such as the Hopfield network and other associative memory architectures implement synaptic learning rules to capture how neural circuits encode and retrieve memory patterns [20]. A classic example is the Hebbian weight update rule:

$$\Delta w_{\{ij\}} = \frac{1}{N} \xi_i^p \xi_j^p \tag{1}$$

where, Δw_{ij} represents the change in synaptic weight between neuron i and neuron j, N is the total number of neurons, and ξ_i^p and ξ_j^p represent the activity states of the two neurons in a stored memory pattern p. This formulation reflects Hebbian learning, where the strength of a synaptic connection increases when two neurons are co-active and decreases when their activity is uncorrelated or opposed [3].

This formula is used in Hopfield networks, a type of recurrent neural network that models associative memory by allowing neurons to update their activity based on the collective state of the network (**Figure 4(A)**). In Hopfield networks, the synaptic weight w_{ij} represents the strength of the concentration from neuron j to neuron i. By construction, these models impose a symmetry such that $w_{ij} = w_{ji}$ (**Figure 4(B)**). This assumption ensures that the network converges toward stable attractor states, which are steady patterns of neural activity that the network settles into to represent stored memories. However, in Alzheimer's disease, this idea of perfect symmetry doesn't hold true. When certain brain cells degenerate or become damaged, and when sticky Aβ plaques form in specific areas, soluble oligomers that accompany their formation cause cytotoxic effects, weakening some connections between neurons more than others. This makes the connections uneven. One neuron might send a strong signal to another, but not receive an equally strong signal back, these unbalanced connections make it harder for the network to stay stable and remember stored patterns. When asymmetry or stochastic weakening is introduced into such models, the network exhibits reduced memory capacity and unstable dynamics, sometimes converging on spurious or chaotic attractors [3] [21].

By simulating these disruptions, computational models highlight how even modest changes in plasticity rules or synaptic connectivity can scale up to produce network-level dysfunction, mirroring the memory retrieval failures seen clinically in AD. More detailed biophysical models go further, incorporating receptor-level impairments (e.g., NMDA conductance changes) or altered STDP. These frameworks not only generate testable predictions—for example, thresholds of synaptic loss that precipitate cognitive decline—but also allow in silico exploration of therapeutic strategies aimed at restoring plasticity and stabilizing network dynamics.

Overall, the inclusion of Hebbian learning rules and their extensions within computational models illustrates how fundamental principles of synaptic plasticity can be mathematically formalized, tested, and perturbed to reveal insights into the network-level consequences of Alzheimer's pathology [13] [20]-[24].

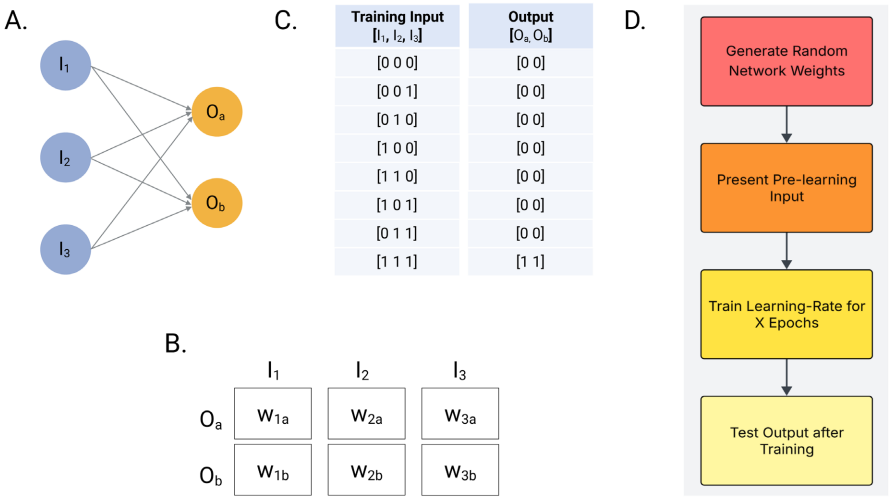

Figure 4. Simplified Hebbian neural network model and training procedure. (A) Diagram of a feedforward Hebbian network showing three input neurons (I_1 - I_3) connected to two output neurons (O_a, O_b) through weighted synapses (w_{ij}). (B) Weight matrix representation, where each cell corresponds to the synaptic strength from an input neuron to an output neuron. (C) Training dataset consisting of binary input patterns and corresponding output targets used to simulate learning. (D) Flowchart summarizing the training process: random initialization of weights, pre-learning input presentation, iterative Hebbian learning across X epochs, and post-training.

4.6. Modeling Synaptic Strengthening through Hebbian Learning

To further test how neurons strengthen their connections through repeated activity, we developed a toy Hebbian learning model with three input neurons and two output neurons. The model applied the Hebbian learning rule to adjust synaptic weights based on input-output coactivation. Weights were initialized randomly and normalized after each update to prevent instability [20] [24]. The structure and training process of this model are illustrated in **Figure 4(C)** and **Figure 4(D)**.

We tested three learning rates—0.05, 0.005, and 0.0005—across 100 training epochs to examine how the speed of learning influences synaptic adaptation (**Figure 5**). In the plots, the x-axis and y-axis represent two neurons that initially produce different output levels (arbitrary units). The black dots show their activity outputs before training, while the red dots show their outputs after training. Each black-to-red connection line represents the change in activity of the two neurons after Hebbian learning was applied.

At the lowest rate, 0.0005, weight changes were minimal, showing reinforcement between neurons (**Figure 5(A)**). When the rate was increased to 0.005, weight updates became faster and more consistent (**Figure 5(B)**). At the highest learning rate (0.05), the model exhibited rapid and large-magnitude weight changes—reflecting more substantial updates in both strengthening and weakening connections. This led to faster convergence toward accurate output representations and more efficient reinforcement of input-output associations (**Figure 5(C)**).

This model demonstrates how Hebbian learning produces stronger connections through repeated coactivation—confirming the principle that "neurons that fire

together wire together". In the context of AD, this process could be altered by impaired NMDA receptor function, which reduces Ca^{2+} signaling and mimics Hebbian learning. In the model, this could be represented by lowering the learning rate, leading to weaker or incomplete pattern reinforcement between neurons, similar to the reduced synaptic strengthening seen in AD. However, there are limitations to the current model. The learning rate increases linearly without any upper limit, which can cause unrealistically large weight growth over time. In future versions, we will incorporate a cap on the learning rate to simulate biological saturation, preventing excessive synaptic strengthening. We also plan to explore the role of additional parameters, such as inhibitory feedback, to better represent the balance between excitation and inhibition, as well as the complexity of real neuronal networks. Overall, the simulation illustrates the basic behavior of Hebbian adaptation while laying the foundation for a more biologically accurate model that connects computational rules with real-world neural dynamics, such as the case of Alzheimer's disease.

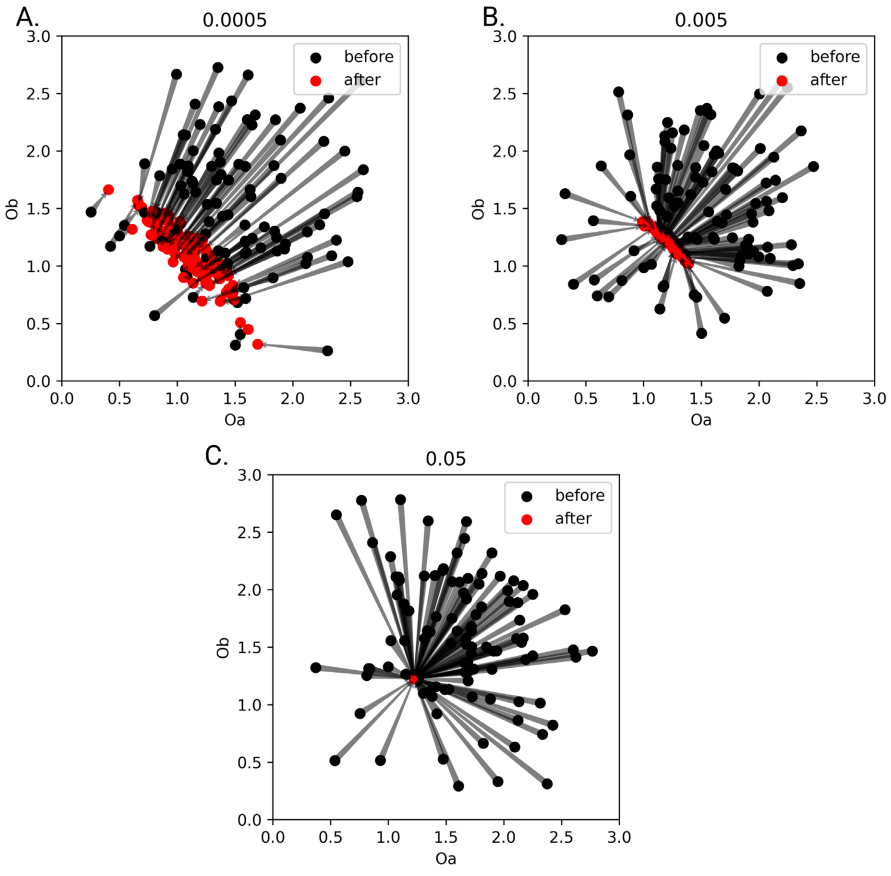

Figure 5. Hebbian network simulation showing how changes in synaptic weights affect convergence behavior under three learning rates: (A) $\eta = 0.0005$, (B) $\eta = 0.005$, and (C) $\eta = 0.05$ over 100 epochs. Higher learning rates led to faster apparent convergence toward similar output patterns and stronger reinforcement, while lower rates produced slower and more variable changes, modeling reduced neural plasticity. However, the simulation did not determine the minimum number of epochs required for convergence or whether these results reflect local versus global minima.

5. Discussion

The findings of this review highlight how disruptions in synaptic plasticity—particularly through Aβ accumulation, tau hyperphosphorylation, and receptor dysregulation—underlie much of the cognitive decline observed in Alzheimer's disease. Moving forward, multimodal research pipelines that align synaptic biomarkers with structural imaging and predictive computational tools will be essential for designing effective combination therapies [5] [9] [11]. Ultimately, restoring synaptic plasticity may not only slow the progression of AD but also preserve the very neural adaptability that underlies memory and self-identity [3] [21] for LTP, drugs that modulate NMDA or AMPA receptors could help restore that signal. Similarly, tau hyperphosphorylation weakens the stability of microtubules and slows transport in neurons. Kinase inhibitors, which block enzymes such as glycogen synthase kinase 3β (GSK-3β) and cyclin-dependent kinase 5 (Cdk5) that add phosphate groups to tau, may help reduce this over-phosphorylation [25]. By slowing this process, these inhibitors could help keep microtubules stable, maintain transport inside neurons and prevent synapses from being cut off. As shown in **Figure 6**, these pharmacological strategies directly target the molecular mechanisms—Aβ aggregation, tau hyperphosphorylation, and receptor dysfunction—that underlie synaptic impairment in AD. Anti-amyloid therapies, which aim to clear or neutralize Aβ therapies, which aim to clear or neutralize Aβ, could also reduce one of the earliest triggers of these plasticity problems [4] [12] [13].

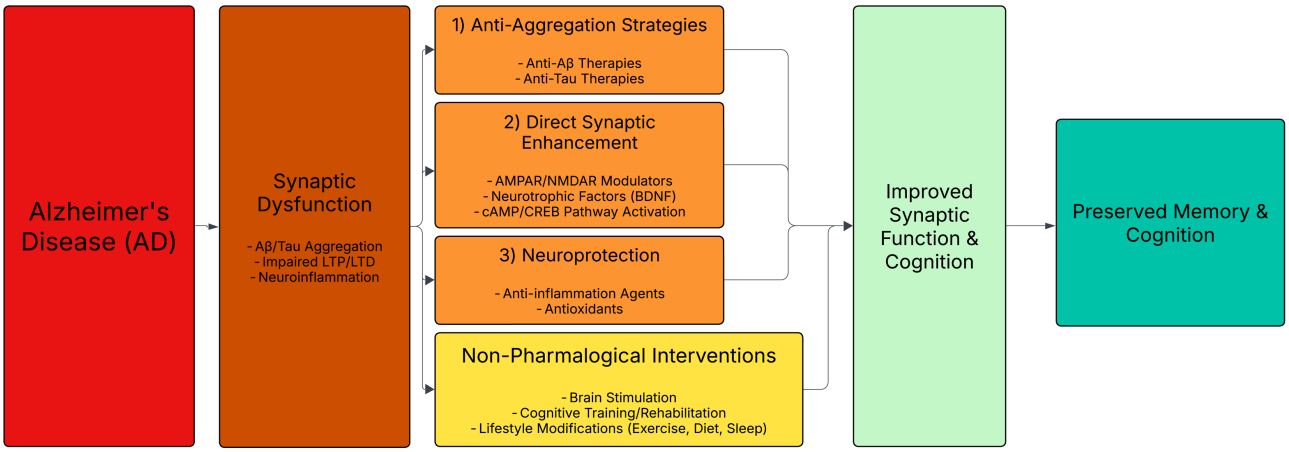

Figure 6. Flow chart illustrating therapeutic approaches targeting synaptic dysfunction in Alzheimer's disease (AD). Synaptic dysfunction, driven by Aβ and tau aggregation, impaired LTP/LTD, and neuroinflammation, can be addressed through multiple strategies. These include anti-aggregation of proteins, direct enhancement of synaptic plasticity via receptor modulators or neurotrophic factors, and reduction of inflammation and oxidative stress. Non-pharmacological interventions, such as brain stimulation, cognitive training, and lifestyle modifications, complement pharmacological strategies. Together, these approaches aim to restore synaptic plasticity and ultimately preserve memory and cognition [25].

Inflammation is another major factor. Cytokines like IL-1β and TNF-α, when chronically elevated, have been linked to weaker LTP and memory decline. MRI evidence of hippocampal shrinkage in patients with Alzheimer's is often tied to ongoing inflammation. Treatments that lower inflammatory signals or block their

release may help create a healthier environment where synapses can strengthen normally again [15]-[17]. **Figure 6** highlights these anti-inflammatory and neuroprotective strategies as key pathways for restoring synaptic function and preventing further degeneration.

Finally, computational modeling gives us a way to test how these interventions might work at the network level. The Hebbian learning rule, which states that "neurons that fire together wire together", shows how small changes in synaptic weights shift the balance between strengthening (LTP) and weakening (LTD). By plugging in experimental data—like how NMDA currents are reduced or how tau disrupts transport—models can predict whether a certain drug could push the system back toward normal plasticity. When combined with MRI markers that show which brain areas are shrinking or failing, these models can guide where treatments might have the most impact [5] [20]-[22] [24].

Taken together, pharmacological and anti-inflammatory strategies target the molecular impairments highlighted in our mechanistic slide (amyloid-β, tau, cytokines), while computational modeling links these interventions to network-level outcomes captured by Hebbian equations. MRI evidence then grounds these findings in human pathology, providing both a validation tool and a translational endpoint.

A promising future direction is the development of combination therapies that target amyloid-β, tau, and inflammation simultaneously, rather than treating each pathway in isolation. Single-target clinical trials have often failed to produce meaningful improvements in cognitive outcomes, likely because synaptic dysfunction in Alzheimer's arises from the interplay of multiple molecular disruptions. The purpose of our literature review is to bring together three major approaches researchers have taken in the past-MRI imaging, cytokine-mediated inflammation, and amyloid-β/tau pathology—and integrate them into a unified perspective. By combining these lines of research, we aim to provide insights that could guide more comprehensive and effective strategies for studying Alzheimer's disease [8] [11] [14]-[17] [26].

Synaptic plasticity represents the critical interface where molecular pathology in AD translates into cognitive decline. Evidence across amyloid-β accumulation, tau hyperphosphorylation and neuroinflammation demonstrates that each pathway converges on the disruption of long-term potentiation, long-term depression, and spike-timing-dependent plasticity [3] [4] [12]. Human imaging and biomarkers studies confirm that these synaptic impairments manifest as measurable atrophy and inflammatory signature, while computational models provide a framework to link cellular mechanisms to network-level dysfunction [16] [18] [20] [22]. By integrating molecular, imaging, and modeling approaches, this review emphasizes that AD cannot be understood through a single lens; only a combined strategy can capture its complexity [14] [26]. Moving forward, multimodal research pipelines that align synaptic biomarkers with structural imaging and predictive computational tools will be essential for designing effective combination therapies [5] [9]

[11]. Ultimately, restoring synaptic plasticity may not only slow the progression of AD but also preserve the very neural adaptability that underlies memory and self-identity [3] [21].

This study explored how problems in synaptic plasticity may lead to memory loss in AD. It showed that changes like amyloid-β buildup, tau damage, and inflammation weaken communication between neurons. The computational model demonstrated that lowering the learning rate can mimic weaker neural connections and slower learning. Together, these results suggest that combining biological research with computer modeling can help explain how brain networks break down and guide new ways to restore healthy synaptic function in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix. Figure and Model Generation Notes

The computational modeling component of this study was designed to simulate synaptic strengthening based on Hebbian learning principles. A simplified neural network consisting of three input neurons and two output neurons was implemented to model synaptic weight changes during repeated coactivation. Synaptic weights were initialized randomly and updated according to the Hebbian learning rule after each training epoch to simulate experience-dependent plasticity. The model was developed and tested using Python with numerical computations using NumPy and visualization conducted in Matplotlib. Learning-rate variations were systematically applied to observe differences in convergence behavior and synaptic stability.

AI-Assisted Writing and Editing

The original manuscript was written first and then AI tools, including ChatGPT (OpenAI GPT-5), were used to assist in the drafting and refinement of the manuscript. The AI tool supported tasks such as grammatical editing. All generated content was critically reviewed, revised, and verified to ensure factual accuracy and conceptual integrity.

Figure Design and Visualization

All figures were created using BioRender, Python-based visualization tools, and Lucid Chart. BioRender was used to create schematic representations of biological and computational processes (e.g., **Figure 1**, **Figure 2**, & **Figure 4**), Python was employed to generate simulation outputs, and Lucid Chart was used for flow charts.