Review

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Synaptic Plasticity and Cognitive Enhancement: Bridging Neuropathological Cognitive Disorders to Emerging Neuropharmacological Strategies

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Synaptic plasticity refers to the fundamental process through which synaptic connections become stronger or weaker in response to experience, thereby forming the basis of learning and memory. Disruption of this process is increasingly regarded as a common underlying mechanism of several cognitive and neuropsychiatric disorders, including Alzheimer's disease, major depressive disorder, schizophrenia, and cognitive aging. This review focuses on synaptic plasticity as a unifying framework that connects neuropathological cognitive disorders to emerging neuropharmacological strategies, with particular attention to clinical translation and precision medicine approaches. The review has three interrelated aims: (i) to clarify the molecular mechanisms that regulate synaptic plasticity, (ii) to investigate how these mechanisms become dysregulated in cognitive disorders, and (iii) to evaluate emerging pharmacological strategies targeting synaptic plasticity for cognitive enhancement. Among the areas receiving special attention are glutamatergic and GABAergic neurotransmission, neurotrophic signaling pathways such as brain-derived neurotrophic factor (BDNF), intracellular cascades including mechanistic target of rapamycin (mTOR) and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), and epigenetic regulators. With respect to their effects on long-term potentiation, synaptogenesis, and neural circuit function, novel therapeutic agents, including ampakines, N-methyl-D-aspartate (NMDA) receptor modulators, and allosteric gamma-aminobutyric acid (GABA) receptor modulators, are also assessed in this review. In both healthy individuals and disease populations, the review further considers the cognitive and neuroplastic effects of nootropics, psychedelics, and other neuromodulatory compounds. As key enablers of translational progress, the review highlights recent advances in brain-penetrant and target-selective agents, as well as improvements in drug delivery systems and biomarker development. This review aims to provide a comprehensive framework for developing safer, more effective, and more precise interventions for cognitive impairment by integrating neurobiological mechanisms, neuropathological insights, and therapeutic innovation.

Keywords: synaptic plasticity; Alzheimer's disease; cognitive enhancement; neuropathology; neuropharmacology; long-term potentiation; neurotrophic signaling; nootropics

Introduction

Fundamental to daily life and overall well-being are cognitive functions such as learning, memory, attention, and executive processes. Characterized by a progressive decline in memory, dementia is a common neurological disorder, of which Alzheimer's disease (AD) represents the most prevalent form worldwide [1]. From a neuropathological standpoint, the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles is a defining feature of AD [2]. These pathological features have strongly influenced recent therapeutic approaches. In 2021, the Food and Drug Administration (FDA) granted accelerated approval to the monoclonal antibody aducanumab (Aduhelm) on the basis of its ability to reduce amyloid-beta plaques. However, the decision remained highly controversial because of the limited evidence supporting clinical cognitive benefit, the conflicting efficacy findings reported in the Phase III trials, and the subsequent discontinuation of its development and commercialization in 2024. More recently, based on Phase III evidence demonstrating a modest reduction in the rate of cognitive decline, lecanemab (Leqembi) received traditional FDA approval in 2023. Donanemab (Kisunla) was subsequently approved in 2024 after also demonstrating delayed clinical progression in patients with early symptomatic AD [3]. As the first disease-modifying therapies for AD to demonstrate modification of the cognitive trajectory, these second-generation anti-amyloid antibodies represent an important therapeutic advance; nevertheless, their clinical benefits remain modest, and their use is associated with the risk of amyloid-related imaging abnormalities. Despite these developments, symptomatic treatment options for AD remain limited to four medications: three acetylcholinesterase (AChE) inhibitors

(galantamine, rivastigmine, and donepezil) and the N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). However, these drugs offer only symptomatic relief and provide no protection against neuronal loss or the progression of cognitive decline. Within this context, the development of therapeutic approaches capable of modifying the underlying disease pathophysiology and slowing or halting disease progression is of critical importance [4]. Synaptic plasticity describes the capacity of neurons in the brain to modify the efficacy and structural organization of synaptic transmission in response to different stimuli. It forms part of the broader concept of neuronal plasticity, which also includes functional plasticity, associated with the electrical properties of neurons, and structural plasticity, linked to axonal organization and neurogenesis [5]. Owing to the brain's inherent ability to transform transient experiences into lasting memory traces and adapt neurotransmission, its architecture remains in a continuous state of change, with neural connections being constantly remodeled [6]. This persistent remodeling also involves synaptic pruning, a physiological process through which synapses are eliminated during postnatal development and throughout adulthood to improve the efficiency of neuronal networks [7]. Within the mammalian central nervous system (CNS), dendritic spines function as postsynaptic sites of excitatory synapses. Extending from dendritic shafts, these structures exhibit dynamic changes in their number, size, and morphology in response to hormonal fluctuations, developmental stages, and alterations in afferent input [8]. Such dendritic spine plasticity is associated with either enhancement or reduction of synaptic transmission strength. These forms of synaptic modification, known as long-term potentiation (LTP) and long-term depression (LTD), are regarded as cellular correlates of learning and memory [9]. Long-term neuronal synaptic plasticity is a broad term referring to persistent, experience-dependent changes in the efficacy of synaptic transmission and includes both potentiation and long-term depression. Synapses in the brain can undergo plastic changes in response to various stimulation protocols, such as theta-burst stimulation, high-frequency bursts, and chemical induction [10]. In recent years, growing evidence has emphasized the critical contribution of disrupted synaptic plasticity to the development of several neurological and psychiatric disorders, including AD, schizophrenia, major depressive disorder, and age-related cognitive decline [11]. Consequently, the modulation of synaptic plasticity has emerged as a promising therapeutic approach for improving cognitive function and potentially reversing or alleviating cognitive deficits [12].

Recent advancements in molecular neuroscience, neuropathology, and neuropharmacology have identified numerous targets involved in the regulation of synaptic plasticity [13]. These targets encompass glutamatergic and GABAergic neurotransmission, neurotrophic factors such as brain-derived neurotrophic factor (BDNF), intracellular signaling pathways involving mechanistic target of rapamycin (mTOR), cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), and mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK), as well as epigenetic modulators. Novel pharmacological compounds that act on these mechanisms, including ampakines, NMDA receptor modulators, psychedelics, and nootropics [14], are currently being investigated for their potential to enhance cognitive function. This review presents a comprehensive analysis of synaptic plasticity as a unifying mechanistic framework that connects neuropathological cognitive disorders, including AD, major depressive disorder, schizophrenia, and cognitive aging, with emerging neuropharmacological strategies. It explores the molecular mechanisms underlying synaptic plasticity, the manner in which these mechanisms become dysregulated in cognitive disorders, and the evidence supporting pharmacological interventions designed to restore or enhance synaptic function. Moreover, the review assesses current translational challenges and future directions in precision medicine, with the aim of identifying safer and more effective strategies for cognitive enhancement.

Molecular Basis of Synaptic Plasticity

Synaptic plasticity refers to the capacity of synaptic connections between neurons to undergo activity-dependent changes in their strength, structure, and efficacy. This dynamic process provides the cellular basis for learning, memory consolidation, and cognitive adaptability [15]. It encompasses complex interactions among neurotransmitters, receptors, and intracellular signaling pathways at the molecular level. Following neurotransmitter release from the presynaptic neuron, these molecules bind to postsynaptic receptors and induce an influx of calcium ions (Ca^{2+}). The resulting Ca^{2+} entry activates several kinases, including calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC), which phosphorylate existing receptors and facilitate the insertion of additional receptors into the postsynaptic membrane [16]. At the same time, changes in gene expression promote the synthesis of new proteins that further alter synaptic structure and function. LTP and LTD represent two extensively studied forms of synaptic plasticity involving distinct molecular pathways that strengthen and weaken synaptic connections, respectively [17]. Together, these molecular mechanisms support the dynamic organization of neural circuits and their capacity to adapt to environmental stimuli and experiences.

Long-Term Potentiation and Long-Term Depression

LTP and LTD represent the two most extensively characterized forms of synaptic plasticity. LTP involves a persistent enhancement of synaptic strength following high-frequency stimulation, whereas LTD involves a sustained reduction in synaptic efficacy, commonly triggered by low-

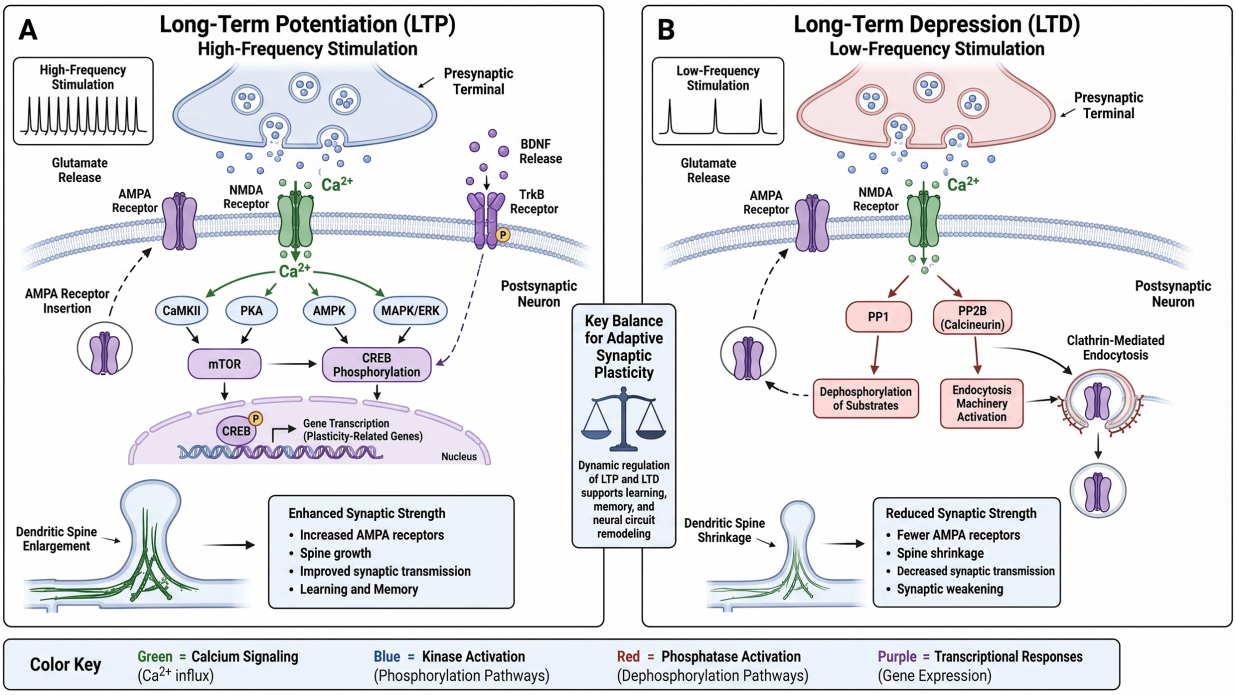

Fig. 1. Molecular mechanisms of synaptic plasticity. (A) Long-term Potentiation (LTP): High-frequency stimulation induces glutamate release and NMDA receptor-mediated Ca^{2+} influx, thereby activating the CaMKII, PKA, AMPK, and MAPK/ERK signaling cascades. These kinase-mediated pathways facilitate AMPA receptor insertion into the postsynaptic membrane, enhance BDNF release, and stimulate mTOR- and CREB-dependent transcription, ultimately resulting in dendritic spine enlargement and increased synaptic transmission strength. (B) Long-term Depression (LTD): Low-frequency stimulation produces a more modest Ca^{2+} influx that preferentially activates phosphatases such as protein phosphatase 1 (PP1) and calcineurin (PP2B). This signaling promotes AMPA receptor internalization through clathrin-mediated endocytosis, resulting in dendritic spine shrinkage and synaptic weakening. The balance between LTP and LTD is essential for adaptive remodeling of neural circuits. Color Key: green, calcium signaling; blue, kinase activation; red, phosphatase activation; purple, transcriptional responses. The figure was created using BioRender (https://www.biorender.com/). NMDA, N-methyl-D-aspartate; CaMKII, calmodulin-dependent protein kinase II; PKA, protein kinase A; AMPK, adenosine Monophosphate-activated Protein Kinase; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; mTOR, mechanistic target of rapamycin; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; LTP, long-term potentiation.

frequency stimulation. Both processes are essential for refining synaptic networks during learning and memory formation [18,19], as illustrated in Fig. 1.

At glutamatergic synapses, LTP is mainly driven by the activation of NMDA receptors, which function as calcium-permeable coincidence detectors [20]. Ca^{2+} entry through these receptors activates downstream signaling pathways involving CaMKII, protein kinase A (PKA), MAPKs, and CREB, ultimately promoting gene transcription and synaptic remodeling [21]. In contrast, LTD is commonly triggered by a moderate influx of Ca^{2+} that preferentially activates protein phosphatases, including PP1 and calcineurin. This activation promotes the dephosphorylation of synaptic proteins and the internalization of AMPA receptors, thereby reducing synaptic transmission [22].

Neurotransmitter Systems

Multiple neurotransmitter systems contribute to the regulation of synaptic plasticity.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system and plays an essential role in the induction of LTP and LTD, two major cellular models of synaptic plasticity. Its actions are mediated by ionotropic receptors, particularly AMPA receptors, which support rapid excitatory neurotransmission, and NMDA receptors. NMDA receptors exhibit a distinctive voltage dependence and allow Ca^{2+} entry, enabling them to function as critical coincidence detectors. When sufficient postsynaptic depolarization occurs, their activation produces a Ca^{2+} influx that triggers biochemical cascades underlying either LTP or LTD, depending on the spatiotemporal pattern and intensity of the signal. In addition, metabotropic

glutamate receptors (mGluRs) regulate synaptic plasticity through G protein-coupled signaling pathways by modulating second messenger systems, intrinsic excitability, and receptor trafficking, thereby contributing to multiple forms of plasticity, including mGluR-LTD [23,24].

Gamma-Aminobutyric Acid (GABA)

GABA acts as the main inhibitory neurotransmitter. Although often indirect, its contribution to synaptic plasticity remains essential for maintaining excitatory-inhibitory (E-I) balance. Neuronal firing thresholds, network oscillations, and the precise temporal coordination required for Hebbian plasticity mechanisms, including NMDA receptor-dependent LTP, are modulated by GABAergic inhibition [25]. Moreover, GABAergic signaling can exhibit its own forms of plasticity, including inhibitory LTP and LTD, which dynamically modify the strength and timing of inhibition and thereby affect circuit excitability and information processing during critical developmental periods and learning [26,27].

Neuromodulators (Acetylcholine, Dopamine, Serotonin, Norepinephrine)

These neurotransmitters are typically released in a diffuse pattern from subcortical nuclei and exert a substantial influence on synaptic plasticity through changes in neuronal and network states, rather than by supporting rapid point-to-point transmission [28].

Acetylcholine (ACh): Originating from the basal forebrain, cholinergic pathways have a central role in supporting attention, arousal, and cortical plasticity. Primarily through muscarinic receptors (mAChRs), ACh facilitates LTP in cortical and hippocampal regions, while these receptors regulate intracellular signaling, intrinsic excitability, and attentional filtering, all of which are essential for learning [29,30].

Dopamine (DA): Dopaminergic activity, particularly in the ventral tegmental area (VTA) and substantia nigra, is vital for reward learning, reinforcement, and motivation. DA release functions as an instructional signal that affects plasticity, particularly LTP, in target areas including the prefrontal cortex, striatum, and hippocampus, mainly through D1/D5 receptors and cAMP/PKA signaling pathways, thereby strengthening rewarded behaviors and associations [31,32,33].

Serotonin (5-HT): Originating from the raphe nuclei, serotonergic pathways influence mood, emotion, and cognitive flexibility. Through multiple receptor subtypes, including 5-HT1A and 5-HT4, 5-HT modulates LTP and LTD in the hippocampus, cortex, and amygdala, thereby affecting learning, memory consolidation, and emotional processing [34,35].

Norepinephrine (NE): Arising from the locus coeruleus, noradrenergic input promotes arousal, attention, vigilance, and memory consolidation. Particularly during significant events, NE release facilitates LTP in regions including the hippocampus and amygdala through β-adrenergic receptors and cAMP signaling, thereby supporting the encoding of emotionally salient or novel experiences [36].

The interaction between the rapid ionotropic effects of glutamate and GABA, establishing the fundamental framework for synaptic excitation and inhibition, and the slower modulatory effects of acetylcholine, dopamine, serotonin, and norepinephrine, which regulate and shape plasticity based on behavioral state and salience, creates the intricate neurochemical environment necessary for adaptive synaptic changes that underlie cognition and behavior.

Neurotrophic Factors

Neurotrophic factors are essential signaling molecules that play a vital role in supporting neuronal survival, development, and the activity-dependent modification of synaptic strength, which is fundamental to learning and memory, known as synaptic plasticity. By linking neuronal activity to lasting structural and functional modifications at synapses, they function as key mediators [37].

BDNF

BDNF is the most extensively studied neurotrophic factor associated with synaptic plasticity. Particularly abundant in the hippocampus, cortex, and amygdala, it is widely expressed in the brain and plays a crucial role in learning and memory [38]. Through interaction with its high-affinity receptor, Tropomyosin receptor kinase B (TrkB), BDNF initiates several intracellular signaling pathways, including MAPK/ERK, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), and phospholipase C gamma (PLCγ). These pathways: (1) enhance synaptic transmission by promoting the surface expression and phosphorylation of AMPA and NMDA receptors, increasing presynaptic glutamate release, and modulating voltage-gated ion channels [39]. (2) Promote Structural Plasticity: Stimulate actin polymerization, dendritic spine formation, growth, and stabilization through Rho GTPase regulation (e.g., Rac1 and Cdc42) [13,40]. (3) Regulate Gene Expression: Activate transcription factors, such as CREB, leading to the expression of genes related to plasticity (e.g., *Arc* and *c-Fos*) necessary for long-term synaptic modifications [41]. (4) Modulation of LTP and LTD: BDNF is crucial for the induction and maintenance of LTP, particularly in the hippocampus. Its release is often activity-dependent (e.g., via high-frequency stimulation). Conversely, BDNF can also facilitate certain forms of LTD under specific conditions, underscoring its bidirectional role [42,43]. (5) Activity-Dependent Secretion: BDNF is frequently stored in dense-core vesicles and released from dendrites and/or axons in response to neuronal activity (especially Ca^{2+} influx), allowing it to act locally or retrogradely at synapses and stimulating its own release to mediate synaptic plasticity [44].

Other Neurotrophins (NT-3, NT-4/5)

Through NT-3–TrkC signaling, neurotrophin-3 (NT-3) and its high-affinity receptor TrkC play an essential role in neuronal differentiation, axonal growth, synapse development, and plasticity within the nervous system. By interacting with the presynaptic protein tyrosine phosphatase σ (PTPσ), postsynaptic TrkC acts as a synaptogenic cell adhesion molecule. Distinct domains within the extracellular region of TrkC serve as binding sites for NT-3 and PTPσ. The binding of PTPσ to cell-surface-expressed TrkC is enhanced by NT-3, which also increases the presynapse-inducing activity of TrkC in rat hippocampal neurons. Although NT-3 is primarily associated with development, it also influences synaptic plasticity in the adult brain, affecting LTP in the hippocampus and cortex, regulating GABAergic inhibition, and promoting synapse formation [45,46]. Neurotrophin-4/5 (NT-4/5): Although both BDNF and NT-4/5 bind to and activate TrkB receptors, they regulate different neuronal functions. The exact molecular mechanism through which BDNF and NT-4/5 activate TrkB and produce distinct outcomes remains unclear. BDNF and NT4 lead to different endocytic sorting of TrkB receptors, resulting in diverse biological functions. Although its role may overlap with or partially compensate for BDNF in certain circuits, NT4/5 supports synaptic plasticity, neuronal survival, and dendritic growth [47].

Glial Cell Line-Derived Neurotrophic Factors (GDNF) Family

The GDNF family comprises four closely related proteins: GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN), in addition to a newly identified protein, growth/differentiation factor 15 (GDF15). The primary receptor facilitating the transmission of GDNF family of ligands (GFLs) signals within neurons is the receptor tyrosine kinase known as rearranged during transfection (RET). GFLs do not directly bind to RET; rather, they interact with the co-receptor GDNF family receptor alpha (GFRα) or GDNF family receptor α-like (GFRAL). While crucial for the survival of dopaminergic and motor neurons, GDNF also plays a significant role in modulating synaptic plasticity, particularly within dopaminergic synapses of the striatum, thereby affecting reward learning and motor control [48].

The p75 Neurotrophin Receptor (p75NTR)

This low-affinity receptor binds to all neurotrophins, including both pro- and mature forms, and modulates Trk signaling. Depending on the context and co-receptors, p75NTR signaling can promote neuronal survival, growth, or apoptosis. In the context of synaptic plasticity, p75NTR regulates dendritic spine morphology, affects NMDA receptors function, and modulates hippocampal LTP and LTD. Moreover, it limits the density of excitatory synapses [49]. Neurotrophic factors serve as a bridge between the rapid electrical/chemical signaling at synapses and the slower, more enduring structural and functional adaptations: (1) Brief episodes of synaptic activity, including those that occur during learning, are converted by these mediators into persistent alterations in synaptic protein synthesis, receptor trafficking, and spine morphology. (2) They help stabilize the synaptic changes that underlie long-term memory. (3) Particularly involving BDNF, dysregulation of neurotrophic factor signaling is strongly linked to cognitive decline associated with aging, neurodegenerative diseases such as AD, and neuropsychiatric disorders including depression and schizophrenia [50].

Molecular Basis of Synaptic Plasticity and Intracellular Signaling Pathways

During synaptic plasticity, intracellular signaling pathways serve as essential biochemical systems that transform transient synaptic activity into lasting changes in synaptic strength. As molecular intermediaries, these pathways connect neurotransmitter release with the resulting functional or structural modifications at synapses. The principal roles of intracellular signaling pathways include: (1) Signal Detection and Amplification: Initial events, including neurotransmitter binding, membrane depolarization, and Ca^{2+} influx, are detected by these pathways, which amplify such weak signals into robust cellular responses [51]. (2) Integration of Multiple Signals: These pathways integrate inputs from various receptors (NMDA, AMPA, mGluR, TrkB), voltage-gated channels, and neuromodulators (dopamine and acetylcholine) to determine the direction (LTP vs. LTD) and magnitude of plasticity [52]. (3) Transduction to Effectors: They transmit signals to specific effector molecules within the postsynaptic neuron (and occasionally presynaptically) that directly modify synaptic functions [53]. (4) Temporal Control: These pathways manage the sequence of events, ranging from rapid post-translational modifications (minutes) to slower gene transcription and protein synthesis (hours to days), thereby facilitating different phases of plasticity (early vs. late LTP/LTD) [18]. (5) Spatial Localization: Through scaffolding proteins and localized translation, they direct signaling events toward specific synapses (synapse specificity), thereby permitting the independent modification of individual synapses [54,55]. (6) Regulation of Effector Mechanisms: These pathways directly govern the key mechanisms underlying plasticity, including: (i) Receptor Trafficking: Phosphorylation-dependent insertion/removal of AMPA receptors. (ii) Ion Channel Modulation: Altering channel conductance or kinetics. (iii) Cytoskeletal Rearrangements: Modifying spine shape and size. (iv) Gene Transcription & Protein Synthesis: Initiating new protein synthesis for long-term maintenance [56]. The major intracellular signaling pathways involved in synaptic plasticity include the following:

Calcium (Ca^{2+}) Signaling

Calcium serves as a fundamental regulator. During postsynaptic depolarization, Ca^{2+} influx occurs primarily through NMDA receptors or voltage-gated calcium channels (VGCCs) and is essential for initiating various forms of LTP and LTD. Through interaction with sensors such as calmodulin (CaM), Ca^{2+} ions subsequently activate downstream pathways, including CaMKII and calcineurin. The resulting form of plasticity is determined by the amplitude, source, and spatiotemporal properties of the calcium signal (e.g., a high and rapid Ca^{2+} influx induces LTP, whereas a low and prolonged influx leads to LTD) [57,58].

Ca^{2+}/Calmodulin-Dependent Protein Kinase II (CaMKII)

This enzyme serves as a pivotal mediator in the induction of LTP and is frequently referred to as the "memory molecule". It is activated upon the binding of Ca^{2+}/CaM. Autophosphorylation at T286/287 occurs independently of Ca^{2+}, establishing a molecular memory trace. CaMKII phosphorylates AMPA receptors (specifically the GluA1 subunit), thereby enhancing conductance and facilitating their insertion into the synapse. Moreover, it phosphorylates scaffolding proteins such as PSD-95, thereby stabilizing receptors and other signaling molecules and enhancing signal transmission [21,59,60].

Protein Kinase A (PKA) Pathway

cAMP functions as a crucial secondary messenger in both pre- and postsynaptic plasticity across diverse neuronal types. This mechanism is fundamental for late-phase long-term potentiation (L-LTP), linking short-term events to enduring modifications. Neuromodulators, such as dopamine via D1 receptors, regulate this process. The principal cAMP-dependent signaling pathway associated with synaptic plasticity is mediated through the activation of the PKA molecular cascade. PKA is activated by cAMP, which is synthesized by adenylyl cyclase in response to Gs-coupled receptors such as β-adrenergic or D1 receptors. It phosphorylates the inhibitory subunits of PKC, thereby alleviating inhibition, and CREB, thus initiating transcription, as well as AMPA receptors (GluA1) to facilitate trafficking. Consequently, several downstream potential synaptic PKA target proteins have been implicated in cAMP-dependent synaptic plasticity, including synapsin, rabphilin, synaptotagmin-12, RIM1a, tomosyn, and P/Q-type calcium channels. Through changes in synaptic release probability and calcium channel clustering, modulation of the expression of some of these proteins produces both short- and long-term alterations in synaptic efficacy [61].

PKC Pathway

The PKC pathway is instrumental in both the initiation and maintenance of LTP, particularly in specific brain regions such as the amygdala. This pathway can be activated by calcium ions (Ca^{2+}), diacylglycerol (DAG), or PKA. PKC phosphorylates a variety of substrates, including AMPA receptors, neurogranin, and MARCKS, thereby modulating receptor activity and cytoskeletal architecture [62,63].

Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) Pathway

The MAPK/ERK pathway is critical for synaptic tagging and capture during late-phase LTP (L-LTP). It processes signals from growth factors such as BDNF and its receptor TrkB, NMDA receptors, and Ca^{2+}. Activation occurs via the Ras/Raf cascades, leading to the phosphorylation of transcription factors such as CREB and Elk-1, which initiate gene expression. Moreover, it phosphorylates Ribosomal S6 kinase (RSK), thereby influencing the translation machinery, including synaptic proteins, which affects local function and plasticity [63].

CREB

CREB is a pivotal transcription factor involved in long-term synaptic plasticity and memory consolidation. It integrates signals from PKA, calcium/calmodulin-dependent protein kinase IV (CaMKIV), and MAPK. Upon phosphorylation, CREB binds to cAMP response elements (CRE) in DNA, facilitating the transcription of genes related to plasticity, such as *Arc*, *BDNF*, *C/EBP*, and receptor/channel subunits. The expression of genes associated with synaptic plasticity is regulated through CREB-mediated transcription [64].

mTOR Signaling

The mTOR signaling pathway is an important regulator of activity-dependent protein synthesis at synapses, essential for both L-LTP and LTD. It is activated by growth factors such as BDNF/TrkB, Ca^{2+}, and other pathways. mTOR phosphorylates key translation initiation factors like 4E-BP and S6K1, promoting cap-dependent translation of synaptic proteins both locally and in the soma [65,66].

Small GTPases (Ras, Rap, Rho, Rac, Cdc42)

These molecules are integral to the regulation of cytoskeletal dynamics, receptor trafficking, and the morphological changes of spines during synaptic plasticity. They operate as molecular switches, activated by guanine nucleotide Exchange Factors (GEFs) in response to Ca^{2+} receptor stimulation. Their influence extends to actin polymerization and depolymerization (Rho GTPases) and MAPK signaling pathways (Ras/Rap) [67].

Nitric Oxide (NO) and Retrograde Signaling

Nitric oxide plays a pivotal role in augmenting presynaptic activity during specific forms of LTP, such as cerebellar LTP. The influx of Ca^{2+} into the postsynaptic neuron activates neuronal nitric oxide synthase (nNOS), leading to

the diffusion of NO back to the presynaptic terminal. At this site, soluble guanylyl cyclase (sGC) is activated, leading to elevated cGMP levels, which then activate protein kinase G (PKG) and promote neurotransmitter release [68]. Consequently, intracellular signaling pathways constitute dynamic, interconnected networks that detect synaptic activity and plasticity, determine the appropriate response (either potentiation or depression), and execute the biochemical and structural modifications underlying synaptic plasticity. These pathways translate transient electrical and chemical signals into enduring changes in synaptic strength, forming the cellular basis of learning and memory. Disruptions in these pathways are associated with various neurological and psychiatric disorders [69].

Structural Remodeling

Structural remodeling is essential for synaptic plasticity, the process by which synapses are either strengthened or weakened in response to neural activity. This remodeling encompasses changes in the shape and organization of synaptic components, including dendritic spines, axon terminals, and the postsynaptic density. For example, during LTP, existing dendritic spines may enlarge, and new spines may form, thereby increasing the surface area available for synaptic transmission [70]. Conversely, LTD can lead to the shrinkage or elimination of spines. These structural changes are driven by various molecular mechanisms, including the reorganization of the actin cytoskeleton, protein synthesis, and the trafficking of neurotransmitter receptors. The actin cytoskeleton, modulated by signaling molecules such as Rho GTPases, supports these morphological transformations. The dynamic nature of structural remodeling facilitates the formation of new neural circuits and the modification of existing ones, contributing to learning, memory formation, and adaptive behaviors in response to environmental stimuli [71]. By providing a comprehensive understanding of these molecular mechanisms, a foundation is established for identifying pharmacological targets capable of enhancing or restoring synaptic plasticity in cognitive disorders.

Neuropathological Mechanisms and Synaptic Plasticity Dysregulation in Cognitive Disorders

The regulation of synaptic plasticity remains essential for preserving cognitive functions across an individual's lifespan [2]. A broad range of neurological and psychiatric disorders characterized by cognitive impairments has been linked to disturbances in the complex molecular and cellular mechanisms that regulate synaptic plasticity. By understanding the dysregulation of synaptic plasticity, critical insights into disease pathogenesis can be obtained, while the development of targeted therapeutic interventions can also be facilitated [13].

Overview of Common Neuropathological Mechanisms and Synaptic Plasticity Dysregulation in Cognitive Disorders

Rather than resulting from a single cause, synaptic dysfunction generally develops through several overlapping processes. Across neurodegenerative, neuropsychiatric, and vascular-metabolic disorders, synapses lose stability, efficiency, and adaptive capacity, and this functional decline often correlates more closely with cognitive deterioration than neuronal death itself [72,73,74,75,76,77,78].

Disruption of the balance between excitation and inhibition is one of the most important contributors. For example, when glutamatergic signaling is disrupted through NMDA receptor hypofunction or altered AMPA receptor trafficking, long-term potentiation becomes impaired, while synapses shift toward maladaptive forms of weakening [79,80]. At the same time, when GABAergic inhibition is reduced, neural circuits become less precise and increasingly unstable, which explains why this imbalance is frequently discussed in conditions such as schizophrenia and AD [26,81].

A further key factor is the reduction in neurotrophic support. With decreased BDNF signaling and impaired TrkB activity, maintaining dendritic spine stability and properly remodeling synapses in response to activity become more difficult [39,40]. Because they regulate receptor trafficking, protein synthesis, and structural plasticity, downstream signaling pathways such as ERK/MAPK, CREB-related transcription, and PI3K/AKT/mTOR are also important; when these pathways are disrupted, synapses lose much of their capacity to transform transient activity into lasting change [41,65,70].

Synapses are also placed under substantial pressure by mitochondrial dysfunction, oxidative stress, and calcium imbalance. By reducing the energy available for neurotransmission, these disturbances disrupt vesicle cycling and increase synaptic vulnerability to excitotoxic damage. By reinforcing other pathological processes, particularly inflammation, they also make synaptic injury part of a broader self-amplifying cycle [72,82,83].

Neuroinflammation is now seen as a central driver of synaptic decline [84,85]. Overactivated microglia and astrocytes can alter receptor signaling, reduce trophic support, and promote excessive pruning through complement-related pathways, all of which weaken synaptic structure and plasticity [86]. For this reason, inflammatory signaling is increasingly regarded as a major contributor to synaptic loss across a range of cognitive disorders [87,88,89].

Synaptic function can also be indirectly impaired by systemic conditions such as diabetes and hypertension. By compromising vascular health, elevating oxidative stress, disrupting blood-brain barrier integrity, and maintaining low-grade inflammation, these disorders reduce cerebral perfusion and metabolic support, thereby progressively making synapses more vulnerable over time [76,77].

Taken together, these disturbances constitute an interconnected framework rather than acting as isolated mechanisms. Neurotransmitter imbalance, loss of trophic support, defects in intracellular signaling, mitochondrial stress, and inflammation interact with and reinforce one another, progressively impairing synaptic connectivity and cognitive performance.

Alzheimer's Disease

In AD, early synaptic loss within the hippocampus and neocortex is well documented and represents the principal structural correlate of the cognitive decline associated with AD. Both animal models and clinical studies have demonstrated the important role of synaptic dysfunction in the pathophysiology of AD. Postmortem analyses of brain tissue have also revealed dendritic damage, characterized by pronounced spine loss and a decrease in synapse numbers [90]. Furthermore, key elements in AD pathophysiology, such as amyloid-beta (Aβ) and tau, have been implicated in promoting synaptic dysfunction [89,91], affecting both pre- and postsynaptic components. Numerous studies have demonstrated that Aβ oligomers and fibrils are detrimental to synapses, leading to alterations in spine morphology and density, reducing levels of proteins essential for neurotransmission [92,93]. The accumulation of Aβ monomers/oligomers disrupts synaptic communication between neurons, contributing to neurodegeneration [94]. The accumulation of Aβ oligomers and tau pathology directly interferes with LTP and enhances LTD by disrupting NMDA and AMPA receptor function, impairing calcium homeostasis, and altering synaptic receptor trafficking. Moreover, synaptic dysfunction is further aggravated by Aβ-induced oxidative stress, neuroinflammation, and impaired neurotrophic support, particularly through reduced BDNF signaling [95,96,97,98]. The axonal transport of synapse-related proteins is also affected by tau dysfunction, while phospho-tau accumulation has been detected in synaptic fractions obtained from the brains of patients with AD [2,91]. Pathogenic tau disrupts presynaptic functions, including synaptic vesicle mobility and release rate, thereby reducing neurotransmission in fly and rat neurons [99]. Moreover, tau tangles within neurons obstruct the transport of essential molecules necessary for normal neuronal function and health [79]. Vanderlinden et al. [100] demonstrated *in vivo* that synaptic loss occurred two years after tau accumulation. Indeed, all components of the amyloid cascade are synaptic elements at both pre- and postsynaptic sites. Lundgren et al. [101] found that ADAM10 and BACE1 are highly concentrated in synaptic vesicles in the brain of rodents and humans, playing a crucial role in regulating functional membrane proteins at the synapse. Moreover, some components of γ-secretase, like presenilins, are found in synaptic organelles [102]. Under normal circumstances, microglia are crucial in managing neuronal activity and synaptic plasticity. In AD, these cells have been noticed to mediate early synapse elimination, negatively affecting learning and memory functions [87,88]. Significant disruptions in neural circuit function can arise from abnormal synaptic changes, impacting behavior and cognition. Initially, synaptic dysfunction may be reversible; however, it can progress to a stage where synapse loss becomes irreversible. This dysfunction or synaptic loss frequently precedes memory impairments in AD, potentially leading to neurodegeneration [103]. Numerous studies have documented alterations in synaptic proteins and plasticity during the early stages of AD in both human and mouse brains. The memory and cognitive deficits observed in the prodromal and mild cognitive impairment (MCI) stages of AD are likely associated with synaptic dysfunction, although the precise molecular and cellular mechanisms underlying this dysfunction remain incompletely understood [104,105,106,107,108]. Fig. 2 illustrates the differences in synaptic signaling pathways in AD due to amyloidopathy compared to synaptic plasticity.

Cognitive Aging

Normal aging is associated with a gradual yet discernible decline in synaptic plasticity and cognitive functions. This decline is influenced by age-related reductions in neurotransmitter levels, compromised neurotrophic support, increased oxidative stress, and disrupted calcium signaling, all of which contribute to diminished LTP and heightened susceptibility to LTD. These changes render the aging brain more vulnerable to neurodegenerative processes and cognitive decline [109].

Major Depressive Disorder

In the context of major depressive disorder (MDD), synaptic atrophy and reduced synaptic connectivity, particularly in the prefrontal cortex and hippocampus, are significant contributors to the cognitive deficits frequently observed in patients. Chronic stress, a major precipitant of depression, leads to dendritic spine loss, impairs neurogenesis, and disrupts the BDNF-TrkB signaling pathway, which is crucial for synaptic maintenance. Recent studies suggest that rapid-acting antidepressants such as ketamine may exert their effects by restoring synaptic plasticity through NMDA receptor antagonism, activation of mTOR signaling, and enhanced synaptogenesis [110]. Fig. 3 illustrates synaptic signaling pathways in major depressive disorder. Under stress-induced pathological conditions, chronic stress and elevated cortisol reduce BDNF expression, impair glutamatergic transmission, and promote neuroinflammation, which together contribute to dendritic spine atrophy. In contrast, therapeutic restoration occurs through agents such as ketamine and esketamine, which produce rapid antidepressant effects via NMDA receptor antagonism and downstream mTOR activation, thereby promoting BDNF release and synaptogenesis. Selective serotonin reuptake inhibitors further support recovery by enhancing serotonin-CREB signaling.

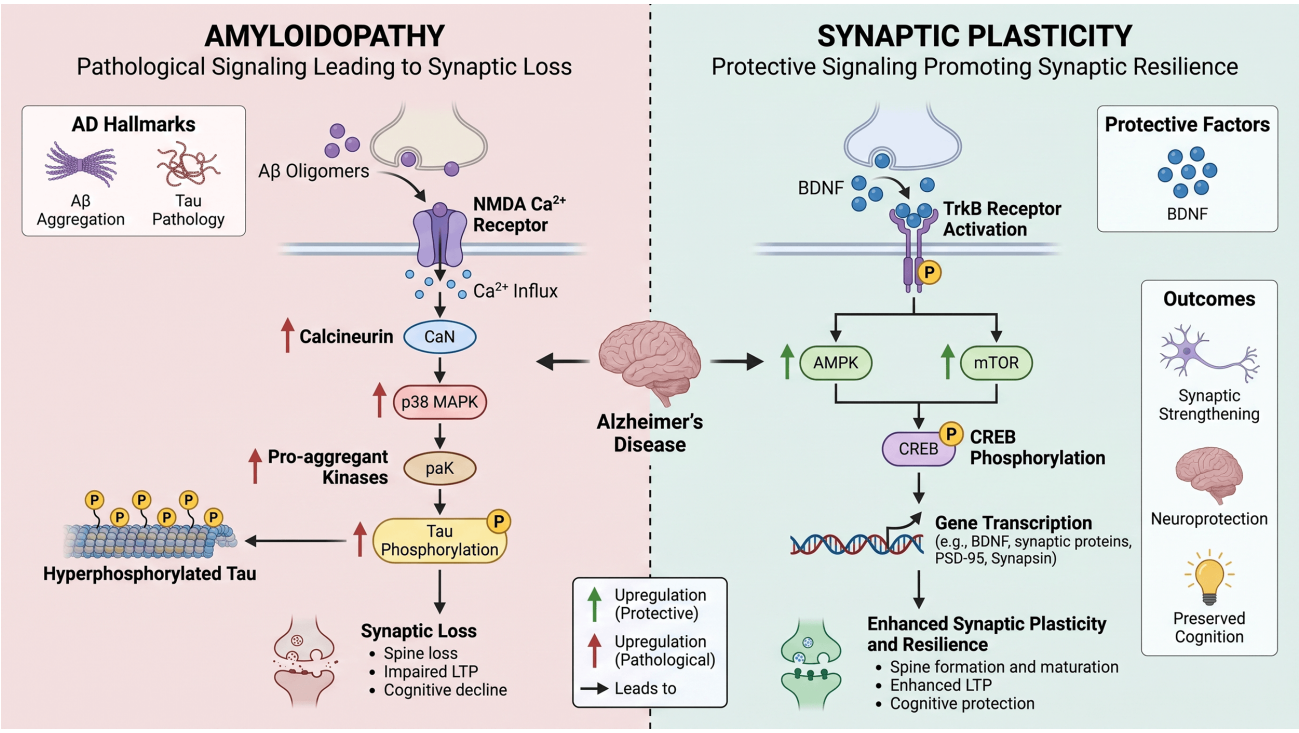

Fig. 2. Altered synaptic signaling pathways in Alzheimer's disease: amyloidopathy versus synaptic plasticity. This figure contrasts pathological and protective synaptic signaling pathways in Alzheimer's disease. The left panel, Amyloidopathy, shows how Aβ oligomers interact with NMDA receptors, leading to Ca^{2+} influx and activation of calcineurin (CaN) and p38 MAPK. These downstream events promote tau phosphorylation via proline-directed kinases, contributing to synaptic loss, impaired long-term potentiation (LTP), and cognitive decline. The right panel, Synaptic Plasticity, depicts BDNF-mediated signaling through TrkB receptors, which activates AMPK, mTOR, and CREB-dependent transcription. This pathway supports dendritic spine formation, enhances synaptic resilience, and promotes neuroprotection. Together, the figure highlights the molecular distinction between neurodegenerative and neuroprotective signaling in Alzheimer's disease. Upward arrows (↑) indicate increased activity, activation, or upregulation of the indicated signaling components or processes. The figure was created using BioRender (https://www.biorender.com/).

Schizophrenia

Profound cognitive deficits characterize schizophrenia, including impairments in working memory, executive function, and attention, and these deficits are strongly associated with functional outcomes. Rather than being considered secondary symptoms, these cognitive impairments are increasingly recognized as core features of the disorder [78]. At the synaptic level, alterations in glutamatergic neurotransmission are associated with schizophrenia, particularly NMDA receptor hypofunction, which disrupts long-term potentiation and synaptic connectivity within the prefrontal cortex and hippocampus [80]. Reduced dendritic spine density in cortical pyramidal neurons has been reported in some studies, indicating a loss of synaptic connections. Impaired gamma oscillations and disruption of excitatory-inhibitory balance result from dysfunction of parvalbumin-positive GABAergic interneurons, which provide perisomatic inhibition to pyramidal cells [111,112,113]. Moreover, altered dopaminergic signaling, particularly hyperdopaminergic activity in the striatum and hypodopaminergic function in the prefrontal cortex, contributes to cognitive and negative symptoms [114]. Emerging evidence also implicates dysregulation of BDNF-TrkB signaling and aberrant synaptic pruning mediated by complement cascade activation, particularly through increased *C4* expression, which may drive excessive elimination of synapses during critical developmental periods [115]. These converging mechanisms highlight synaptic dysfunction as a central pathophysiological feature of schizophrenia and underscore the potential of synaptic plasticity-modulating agents as novel therapeutic strategies. Fig. 4 summarizes the synaptic alterations in signaling pathways and synaptic plasticity in Schizophrenia.

Neuropharmacological Molecular Targets For Modulating Synaptic Plasticity

Overview

Multiple molecular and cellular targets for pharmacological intervention arise from the complex nature of synaptic plasticity. Through modulation of neurotransmitter systems, intracellular signaling pathways, neurotrophic sup-

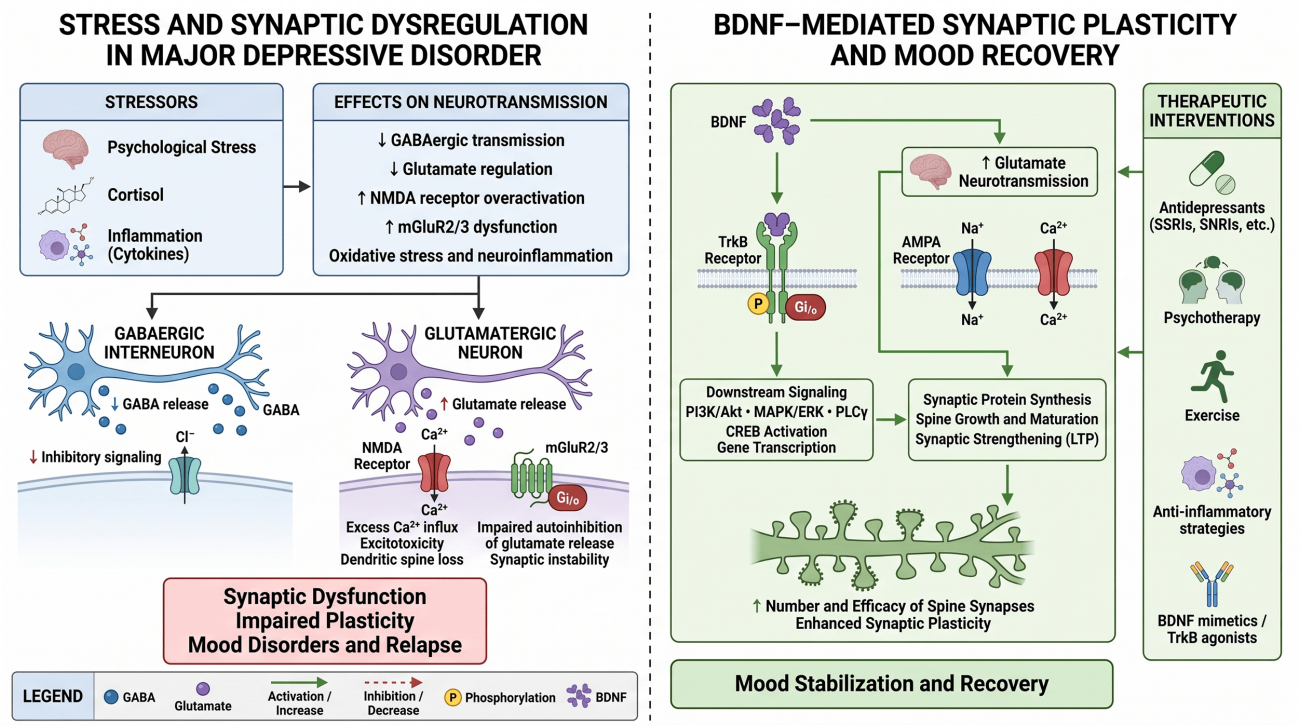

Fig. 3. Synaptic signaling pathways in mood regulation and synaptic plasticity in major depressive disorder. This figure illustrates the balance between stress-induced synaptic dysregulation and BDNF-mediated synaptic recovery in major depressive disorder. In the left panel, stressors including elevated cortisol and inflammation are shown to disrupt GABAergic and glutamatergic neurotransmission, resulting in NMDA receptor overactivation, mGluR2/3 dysfunction, oxidative stress, neuroinflammation, synaptic instability, and mood disturbance. In the right panel, the protective effects of BDNF signaling are illustrated, whereby enhanced glutamatergic transmission together with activation of AMPA and TrkB receptors stimulates downstream PI3K/Akt, MAPK/ERK, and PLCγ pathways, promotes CREB-dependent transcription, and supports synaptic protein synthesis, spine maturation, and long-term potentiation. Therapeutic interventions, including antidepressants, psychotherapy, exercise, anti-inflammatory strategies, and BDNF/TrkB-targeted approaches, may restore synaptic plasticity and support mood stabilization and recovery. The upward arrows (↑) indicate an increase, while the downward arrows (↓) indicate a decrease. The figure was created using BioRender (https://www.biorender.com/). PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; PLCγ, phospholipase C gamma.

port, and epigenetic regulation, restoration of synaptic function and improvement of cognitive performance may be achieved [116,117].

A growing body of research has identified several key targets that can modulate synaptic plasticity through distinct but interconnected mechanisms. These include the glutamatergic system, particularly NMDA and AMPA receptors [118]; the GABAergic system [119]; the cholinergic system [28]; neurotrophic factors such as BDNF and TrkB [120]; intracellular signaling cascades including mTOR, CREB, and MAPK; and epigenetic regulators such as Histone Deacetylase (HDAC)s and DNMTs [121,122]. Among the representative pharmacological agents are ketamine, memantine, and ampakines for glutamatergic modulation; neurosteroids targeting GABAergic signaling; acetylcholinesterase inhibitors for cholinergic enhancement; neurotrophic mimetics; and inhibitors of HDAC and DNMT activity. Fig. 5 summarizes these target classes.

Glutamatergic System

Through NMDA and AMPA receptors, the glutamatergic system plays a central role in LTP and LTD, both of which are fundamental to memory and cognition. The regulation of synaptic transmission and synaptic plasticity depends on the coordinated activity of glutamate receptors. Disruption of these receptors can contribute to neurological disorders, including epilepsy, intellectual disability, and neurodegenerative diseases, making modulation of glutamate receptor activity a valuable therapeutic approach [123]. Moreover, ketamine, an NMDA receptor antagonist, has demonstrated rapid antidepressant effects at sub-anesthetic doses, with these effects attributed to mTOR pathway activation and enhanced synaptogenesis [124]. By positively modulating AMPA receptors, ampakines have shown potential in preclinical models to enhance memory and attention through improved synaptic transmission [125]. Particularly for mGluR5, modulators of mGluRs are being investigated for their roles in Fragile

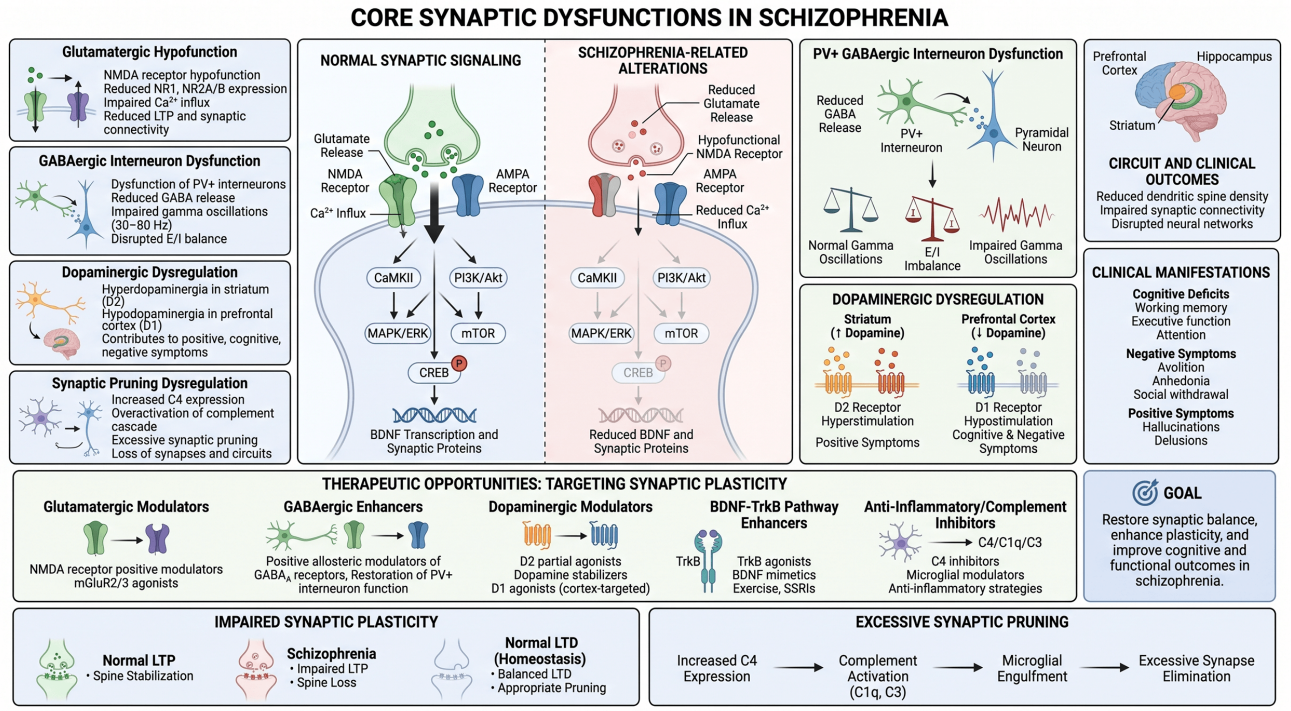

Fig. 4. Synaptic signaling pathways and synaptic plasticity in schizophrenia. This schematic illustrates major molecular and cellular mechanisms underlying synaptic dysfunction in schizophrenia. The figure highlights glutamatergic hypofunction resulting from reduced NMDA receptor activity, dysfunction of parvalbumin-positive (PV+) GABAergic interneurons leading to impaired gamma oscillations and excitatory–inhibitory imbalance, region-specific dopaminergic dysregulation characterized by hyperdopaminergia in the striatum and hypodopaminergia in the prefrontal cortex, and excessive complement-mediated synaptic pruning associated with increased *C4* expression and microglial activation. These abnormalities impair intracellular signaling pathways, including CaMKII, PI3K/Akt, MAPK/ERK, mTOR, and CREB, reduce BDNF-dependent synaptic protein expression, and disrupt long-term potentiation, resulting in dendritic spine loss, impaired synaptic plasticity, and cognitive dysfunction. The lower panel summarizes emerging therapeutic strategies targeting glutamatergic, GABAergic, dopaminergic, BDNF–TrkB, and complement-mediated pathways to restore synaptic plasticity and improve cognitive and functional outcomes in schizophrenia. The figure was created using BioRender (https://www.biorender.com/).

X syndrome and schizophrenia, indicating their potential for broader cognitive applications [126].

GABAergic System

Maintaining the balance between excitation and inhibition depends substantially on the GABAergic inhibitory system, which is essential for normal synaptic function. When GABAergic signaling is disrupted, reduced plasticity may occur in association with several cognitive disorders. GABA-A Receptor Modulators: By specifically targeting extrasynaptic GABA-A receptors, certain compounds may reduce tonic inhibition and improve cognitive flexibility without inducing sedation [119]. Cognitive functions may also be improved by GABA-B receptor antagonists through reduction of the excessive inhibitory tone that restricts synaptic plasticity [127]. Neurosteroids, including allopregnanolone and brexanolone, act as positive modulators of GABAergic transmission and are currently being investigated for their neuroprotective and cognitive-enhancing effects. By increasing inhibitory tone, these substances help restore the excitatory-inhibitory balance required for optimal synaptic plasticity [128].

Cholinergic and Monoaminergic Systems

A pivotal role in cognitive functions such as attention, learning, and memory is played by the cholinergic system, particularly through nicotinic and muscarinic receptors. Sustaining attention, working memory, and learning processes depends on effective cholinergic neurotransmission. In patients with AD, acetylcholinesterase inhibitors have long been used to prolong the availability of acetylcholine within synapses [129]. More targeted approaches have focused on nicotinic acetylcholine receptors (nAChRs), particularly α7 nAChR agonists such as encenicline, which have shown potential for improving cognitive function in disorders including schizophrenia and AD, although clinical trial outcomes have been inconsistent [130]. Furthermore, monoaminergic systems, encompassing dopamine, serotonin, and norepinephrine, influence synaptic plasticity through complex interactions with glutamatergic and

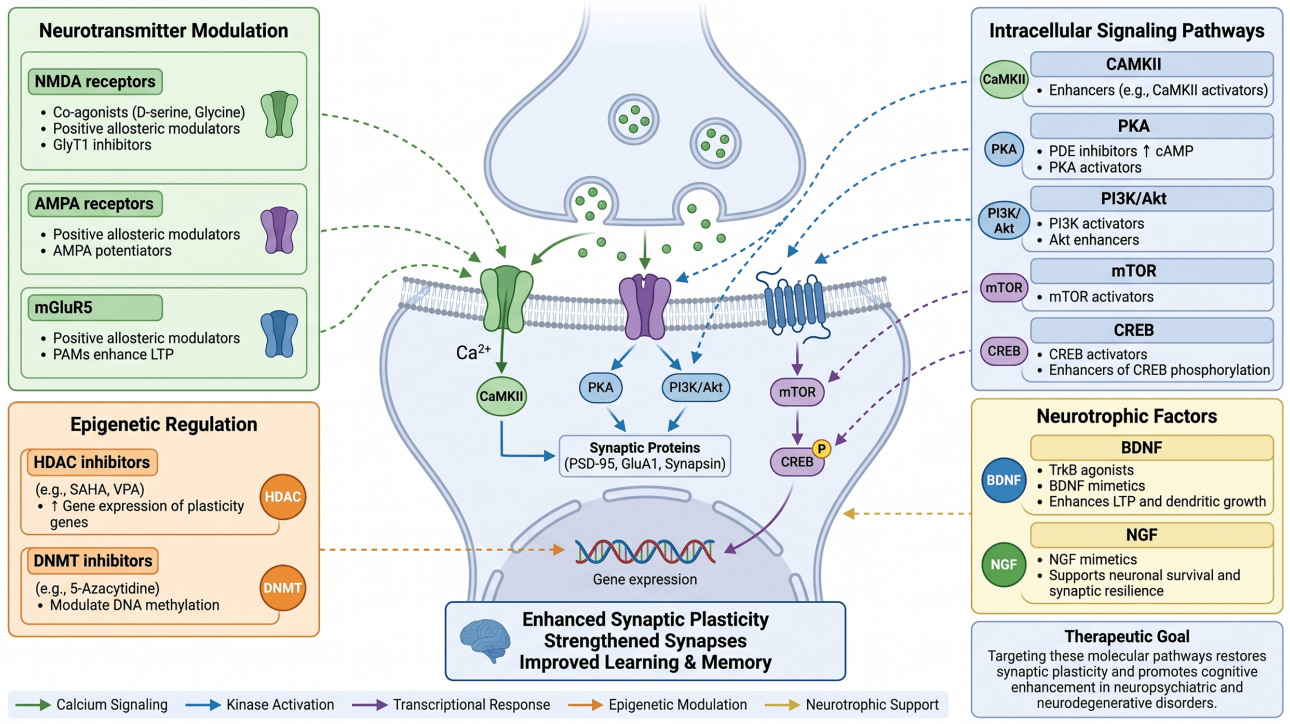

Fig. 5. Neuropharmacological molecular targets of synaptic plasticity for cognitive enhancement. This schematic illustrates the principal molecular targets involved in the regulation of synaptic plasticity and cognitive function. The figure highlights four interconnected therapeutic domains: neurotransmitter modulation, including NMDA, AMPA, and mGluR5 receptors; intracellular signaling pathways, including CaMKII, PKA, PI3K/Akt, mTOR, and CREB; epigenetic regulation through HDAC and DNMT inhibitors; and neurotrophic factors such as BDNF and NGF. These pathways converge to promote synaptic protein synthesis, dendritic spine formation, and long-term potentiation, thereby enhancing synaptic plasticity, learning, and memory. Collectively, these mechanisms represent promising neuropharmacological targets for the treatment of cognitive impairment in neurodegenerative, neuropsychiatric, and aging-related disorders. The figure was created using BioRender (https://www.biorender.com/). HDAC, Histone Deacetylase.

GABAergic networks, rendering them significant targets for the treatment of cognitive and mood disorders [131].

Neurotrophic Factors (BDNF and NGF)

The maintenance and adaptation of synapses depend critically on neurotrophic factors, particularly BDNF. By activating TrkB receptors, small-molecule TrkB agonists reproduce the synaptogenic actions of BDNF and show potential for targeting synaptic deficits associated with neurodegenerative and psychiatric disorders. Considered promising candidates for cognitive improvement, BDNF mimetics either increase endogenous BDNF production or reproduce its downstream signaling pathways, as exemplified by 7,8-dihydroxyflavone. Furthermore, nerve growth factor (NGF)-based therapies are being investigated, particularly for their potential role in supporting the cholinergic system during aging and neurodegenerative processes [50,120,132].

Neuropharmacological Molecular Targets and Intracellular Signaling Pathways

Multiple intracellular pathways are integral to the long-term maintenance of synaptic plasticity. Among these, the most significant intracellular signaling pathways influencing synaptic plasticity include: (1) The Trk-PI3K-AKT signaling pathway, wherein Tropomyosin-associated kinase B (TrkB) serves as the high-affinity receptor for BDNF. TrkB signaling enhances LTP, whereas p75NTR signaling supports LTD. Neuronal regulation is associated with the balance between these two receptor-ligand binding forms [133]. Following BDNF binding to TrkB, receptor dimerization occurs, leading to TrkB activation and the initiation of cellular signaling, which subsequently activates the downstream phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. Maintaining a normal signaling cascade, enhancing synaptic plasticity, and promoting neuronal protection critically depend on this activation [120]. Within the nervous system, the PI3K/AKT pathway plays a vital role by preventing neuronal apoptosis and promoting neuronal growth. Following TrkB activation, the PI3K regulatory subunit, designated as p110, binds to

phosphorylated tyrosine, thereby promoting the recruitment of PI3K to the plasma membrane. In proximity to phosphoinositol (PI) at the cell membrane, the catalytic subunit p85 facilitates its phosphorylation. As a downstream component of PI3K, AKT contains a pleckstrin homology (PH) domain that facilitates binding to these phosphorylated molecules [134]. Once bound, AKT translocates from the cytoplasm to the plasma membrane, inducing a conformational change that alleviates the inhibition of its catalytic active site by the pH domain, thereby activating AKT kinase activity. This activation reduces cellular apoptosis while promoting cell growth and differentiation. The PI3K-AKT pathway influences the physiological functions of neuronal cells through reciprocal regulation with BDNF, diminishing apoptosis and enhancing cell survival by inducing trophic factors. This presents promising opportunities for the clinical application of endogenous neural stem cells (NSCs) [91,135]. (2) The mTOR pathway is integral to the regulation of various cellular processes, including metabolism, catabolism, immune responses, autophagy, survival, proliferation, and migration, thereby maintaining cellular homeostasis. This signaling pathway comprises two distinct multi-subunit complexes, mTOR complex 1 and 2 (mTORC1/2). Several key proteins, including AKT, protein kinase C, insulin growth factor receptor (IGF-1R), and Unc-51-like autophagy-activating kinases, are phosphorylated through mTOR activity. The mTOR pathway plays an essential role in regulating translation, lipid and nucleotide synthesis, lysosome formation, nutrient sensing, and growth factor signaling. Through activation of mTOR signaling, the synthesis of synaptic proteins and the growth of dendritic spines are facilitated [136]. Agents that modulate the mTOR, such as ketamine and rapalogues, demonstrate potential as rapid-onset antidepressants and for their cognitive effects [137]. (3) CREB pathway: CREB is predominantly activated through phosphorylation, particularly at the serine 133 site. Several kinases, including protein kinase A, ERK, and calcium/calmodulin-dependent protein kinases (CaMKs), are capable of phosphorylating CREB [138]. Augmenting CREB activity can lead to the upregulation of genes associated with neuronal plasticity, such as BDNF, which is believed to facilitate the formation of new synaptic connections [139]. Various pharmacological classes that enhance CREB activity have been investigated for their potential to improve learning and memory. These include antidepressants (e.g., amitriptyline and fluoxetine), substances of abuse (e.g., cocaine and morphine) that activate CREB in the nucleus accumbens, a brain region linked to reward. This activation is thought to contribute to both the rewarding effects of these substances and the development of tolerance and withdrawal symptoms [140], as well as certain antipsychotics (e.g., haloperidol). The mechanisms frequently involve increased CREB phosphorylation, a critical step in its activation [141]. (4) ERK/MAPK pathway: The ERK/MAPK pathway constitutes a critical signaling cascade integral to various cellular functions, including cell growth, differentiation, and survival, and is essential for memory consolidation. While many pharmacological agents target this pathway to inhibit its activity, some can also enhance it, either directly or indirectly. Pharmacological activators of the ERK/MAPK pathway may improve long-term cognitive outcomes [142]. Examples of drugs that can enhance the ERK/MAPK pathway include BRAF inhibitors such as dabrafenib and encorafenib, which are primarily used to inhibit the mutated BRAF protein in cancers but can also paradoxically activate the ERK/MAPK pathway in cells with wild-type BRAF [143,144]. Modafinil, another cognitive enhancer, also activates ERK/MAPK signaling in the prefrontal cortex, potentially contributing to its wakefulness-promoting and cognitive-enhancing effects [145]. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, commonly used as antidepressants, may enhance ERK/MAPK signaling, which could be involved in their antidepressant effects [146].

Emerging Neuropharmacological Agents

With advancing understanding of the mechanisms underlying synaptic plasticity, an expanding range of neuropharmacological agents is being developed to improve cognitive function. These agents target a broad spectrum of pathways, extending from conventional neurotransmitter systems to emerging molecular regulators of synaptic structure and function, as outlined in Table 1 (Ref. [118,121,122,124,125,126,129,130,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163]). This section examines key emerging compounds that demonstrate substantial therapeutic potential.

Ampakines and NMDA Receptor Modulators

Ampakines

Ampakines constitute a class of positive allosteric modulators of AMPA receptors that strengthen excitatory synaptic transmission and support the induction of LTP [164]. Cognitive-enhancing effects have been reported for compounds such as CX516, CX717, and LY451395 in preclinical models and early clinical trials. Through enhancement of AMPA receptor-mediated currents, ampakines indirectly increase the expression of BDNF and neurotrophic signaling, thereby contributing to synaptic stabilization [118]. Edonerpic maleate, a novel small compound, binds to collapsin response mediator protein 2 (CRMP2) and may enhance synaptic plasticity by promoting the delivery of synaptic AMPA receptors, resulting in accelerated recovery from brain damage in rodents during rehabilitative training. The therapeutic potential of this compound will be further evaluated in future preclinical and clinical studies [165].

Table 1. Summary of neuropharmacological agents targeting synaptic plasticity.

Agent/Class/Trial ID	Primary target(s)	Mechanism of action	Therapeutic indications	Clinical status	Ref.
Ampakines: CX516: NCT00001662 for Alzheimer's disease CX717: NCT03375021 for Adult ADHD LY451395: NCT00051909 Alzheimer's disease	AMPA receptors	Potentiate excitatory transmission and facilitate LTP	Cognitive impairment associated with Alzheimer's disease and ADHD (investigational)	Investigational, early-phase and Phase II trials complete, no approved agent	[118,125,149,150]
mGluR5 modulators: CDPPB: Preclinical investigation for schizophrenia Basimglurant: NCT02433093 for major depressive disorder	Metabotropic glutamate receptor 5	Modulate glutamate signaling and improve synaptic function	Fragile X syndrome, Major Depressive Disorder, Schizophrenia (investigational)	Basimglurant completed Phase II trials; CDPPB remains preclinical	[126,151,152]
NMDA receptor modulators: D-cycloserine: NCT00408031 for Depression Esketamine: NCT01640080 for Depression Memantine: NCT00040261 for Depression, NCT00857649 for Alzheimer's disease, and NCT02258828 for Posttraumatic stress disorder (PTSD).	NMDA receptors (partial agonists/antagonists)	Enhance synaptic plasticity, promote rapid antidepressant effects	Depression, Posttraumatic stress disorder (PTSD), schizophrenia	Esketamine: approved for treatment-resistant depression; Memantine: approved for moderate-to-severe Alzheimer's disease; D-cycloserine: investigational	[118,147,153,154]
Neurosteroids: Pregnenolone: NCT03645096 for Depression Allopregnanolone: NCT04838301 for Neurodegeneration, NCT06238700 for Depression and Anxiety Ganaxolone: NCT01339689 for Anxiety and Posttraumatic stress disorder (PTSD). Brexanolone: Approved	GABA-A receptors, NMDA receptors	Modulate inhibitory/excitatory balance, neuroprotective effects	Depression, Anxiety, Neurodegeneration	Approved Brexanolone; others in trials	[148,155]
Acetylcholinesterase inhibitors: Donepezil: NCT02580305 for Dementia Rivastigmine: NCT00099216 for Vascular dementia Galantamine: NCT00679627 for Dementia	Acetylcholinesterase enzyme	Prolong acetylcholine activity, improve attention and memory	AD, Dementia	Approved	[129]
Nicotinic receptor agonists: EVP-6124: NCT02004392 for Cognitive disorders	Nicotinic α7 receptors	Enhance cholinergic neurotransmission and cognitive processing	Schizophrenia, Cognitive disorders	Phase II/III trials	[130,156,157]

Table 1. Continued.

Agent/Class/Trial ID	Primary target(s)	Mechanism of action	Therapeutic indications	Clinical status	Ref.
mTOR modulators: (ketamine and rapalogues derivatives, indirect pathways)	mTOR signaling pathway	Promote protein synthesis and synaptic remodeling	Depression, Cognitive impairment	Experimental/Preclinical	[124]
TrkB and Akt activators: (BDNF, NSI-189 Phosphate)	Stimulation of neurogenesis of hippocampus-derived neural stem cells	Activation of the TrkB and Akt pathways	Major depressive disorder	Preclinical	[158,159,160]
BDNF mimetics: (7,8-DHF, LM22A-4)	TrkB receptors	Promote neurotrophic signaling and synaptogenesis	Neurodegenerative diseases	Preclinical	[161]
HDAC inhibitors	Histone deacetylases	Epigenetic modulation of synaptic gene expression	Cognitive disorders, Mood disorders	Preclinical	[121,122,162]
DNMT inhibitors	DNA methyltransferases	Demethylation of synaptic plasticity genes	Cognitive enhancement (experimental)	Preclinical	[163]

NMDA Receptor Modulators

The aim is to optimize glutamatergic transmission while avoiding the induction of excitotoxicity. As a partial NMDA receptor agonist, D-cycloserine has shown potential for improving learning and the extinction of fear memory. At sub-anesthetic doses, rapid antidepressant effects are produced by ketamine and esketamine, mainly through NMDA receptor antagonism and subsequent activation of mTOR signaling, which promotes synaptogenesis. Although these synaptogenic mechanisms may contribute to cognitive recovery in depression-related cognitive deficits, the direct cognitive-enhancing effects of ketamine in healthy individuals or non-depressed populations remain uncertain. Transient cognitive impairment, including deficits in working memory and executive function, can occur following acute ketamine administration, while its primary established clinical indication remains treatment-resistant depression rather than independent cognitive enhancement [147,166]. In AD, glutamatergic excitotoxicity can be induced by amyloid-beta (Aβ), which enhances glutamate release and/or inhibits glutamate reuptake through NMDA channels in neurons and hybridomas, thereby increasing Ca^{2+} entry into neurons and producing intracellular toxic effects. Such overstimulation has been proposed as one of the etiopathogenic mechanisms underlying neurodegeneration in AD [167,168]. This toxic effect is targeted by memantine, a moderate-affinity open-channel non-competitive blocker of NMDA receptors [169]. However, concerns regarding a possible lack of efficacy, particularly because it remains uncertain whether protection against neurotoxicity can be achieved without adversely affecting cognition, together with conflicting preclinical findings on the effects of memantine on synaptic plasticity, indicate that further investigation is required. In this regard, animal studies have produced inconsistent results [170]. These receptors play a crucial role in LTP, raising the question of whether memantine, currently used to treat AD, helps or hinders NMDA receptor-dependent brain plasticity. Some studies suggest that memantine can correct LTP issues caused by soluble Aβ in the dentate gyrus without impairing memory or cognitive skills. However, at higher doses, it can disrupt synaptic plasticity and behavior, possibly due to excessive NMDA receptor blockade [171].

Modulators of mGluRs

Several innovative therapeutic strategies are being developed to modulate mGluR, with a particular emphasis on the glutamatergic system [172]. As members of the G-protein-coupled receptor (GPCR) superfamily, mGluRs activate G-protein complexes to transduce extracellular signals into intracellular responses. These receptors are classified into three groups (group I, group II, and group III) based on factors such as biomechanics, topology, pharmacology, and sequence homology. Current therapeutic efforts are primarily directed towards mGluR group II, specifically subtypes 2 and 3 (mGluR2/3). Activation of mGluR2/3 at presynaptic sites inhibits adenylate cyclase (AC) through coupling with the Gi/o component of the heterotrimeric G-protein, leading to a reduction in cAMP levels. This reduction subsequently inhibits calcium channels, thereby decreasing glutamatergic neuronal excitability and reducing glutamate release [173]. Agonists targeting these receptors, such as LY354740 [174], LY379268 [175], and LY404039 [176], have been synthesized. However, substantial clinical setbacks have affected the mGluR2/3 agonist program for schizophrenia. LY2140023 (pomaglumetad methionil), an orally administered prodrug of LY404039, failed to show efficacy across multiple Phase III clinical trials in schizophrenia, including the HBBI and HBBK studies, with no significant improvement in either positive or negative symptoms relative to placebo [177]. Similarly, AZD8529, another mGluR2/3 PAM developed by AstraZeneca, failed to show efficacy in a Phase IIb trial for schizophrenia [178]. Following these negative outcomes, research attention has shifted away from direct mGluR2/3 agonism toward alternative approaches, including positive allosteric modulators (PAMs) and other glutamatergic targets. Compared with traditional agonists, PAMs may provide greater receptor selectivity and tolerability and can regulate receptor activity for longer periods because they bind outside the receptor's active site, thereby reducing the likelihood of receptor desensitization [179].

GABA Receptor Modulators

An alternative strategy for restoring the balance required for optimal plasticity involves targeting the inhibitory GABAergic system. By enhancing phasic inhibition without producing excessive sedation, selective GABA A receptor modulators may improve cognitive flexibility. Neurosteroids, including brexanolone, which is approved for postpartum depression, interact with GABA A receptors and have shown neuroprotective and pro-plasticity properties [81]. As a novel anticonvulsant medication, ganaxolone has emerged for the treatment of refractory status epilepticus [148].

Nootropics and Cognitive Enhancers

A diverse range of substances, known as nootropics or smart drugs, aim to enhance cognitive abilities. Racetams, including piracetam, levetiracetam, and aniracetam, improve synaptic plasticity by influencing AMPA receptors and membrane fluidity [180]. Modafinil and armodafinil, initially developed for narcolepsy, exhibit cognitive enhancement effects by modulating the dopaminergic, glutamatergic, and adrenergic systems [181]. L-theanine, caffeine, and adaptogens have also been studied for their mild cognitive benefits, particularly in healthy individuals [182].

Psychoplastogens (Psychedelics and Neuromodulatory Compounds)

A new class of compounds known as psychoplastogens, which includes psychedelics such as psilocybin, LSD, and ayahuasca-derived DMT, has garnered significant interest due to their rapid and enduring effects on synaptogenesis and neuroplasticity. Recent studies have renewed interest in utilizing psychedelics to enhance synaptic plasticity and address mood and cognitive disorders. These substances promote synaptic plasticity through various mechanisms, resulting in rapid dendritic spine growth and improved synaptic connectivity, a phenomenon referred to as psychoplastogenic effects [183]. These compounds primarily function through 5-HT2A receptor agonism, enhancing structural plasticity in cortical neurons [184]. They are currently undergoing clinical investigation for the treatment of treatment-resistant depression, posttraumatic stress disorder (PTSD), cognitive impairment, and substance use disorders [185]. Psychedelic-assisted therapy may offer a novel approach that combines pharmacological plasticity enhancement with psychological interventions to facilitate enduring cognitive and emotional changes [183].

Epigenetic and Transcriptional Modulators

The critical contribution of epigenetic mechanisms to synaptic plasticity has been increasingly emphasized, as these mechanisms regulate the gene expression required for persistent synaptic modifications. By promoting chromatin relaxation and gene transcription, Histone Deacetylase (HDAC) inhibitors, including vorinostat and sodium butyrate, enhance the expression of plasticity-related genes and improve cognitive functions [186]. DNA Methyltransferase (DNMT) inhibitors, which modulate DNA methylation patterns, have the potential to correct aberrant gene silencing linked to cognitive deficits [187]. Non-coding RNAs, including microRNAs and long non-coding RNAs, are increasingly recognized as regulators of synaptic gene networks and as potential therapeutic targets [188]. The complexity of synaptic plasticity regulation is reflected in the diversity of these pharmacological targets. Through modulation of different pharmacological targets, synaptic plasticity may provide a promising strategy for addressing cognitive impairments across a range of neurological and psychiatric disorders. Although encouraging findings have been reported for many of these agents in preclinical models and early-phase trials, concerns remain regarding their long-term safety, specificity, and interindividual variability in treatment response [189]. To fully realize the therapeutic potential of targeting synaptic plasticity, continued research on combination therapies, biomarker-guided interventions, and personalized medical approaches remains essential. The following section examines how these targets are being developed into novel neuropharmacological agents currently under preclinical and clinical evaluation.

Novel Drug Delivery Systems and Brain-Targeted Therapies

Greater precision and efficacy in pharmacological treatments have been achieved through advances in drug delivery technologies. More efficient delivery of neuroactive compounds to targeted brain regions is facilitated by nanoparticle-based carriers, liposomes, and blood-brain barrier-penetrating peptides. Through the delivery of neurotrophic factors or synaptic regulators, gene therapy provides the potential for long-term modulation of plasticity [190].

For rapid and noninvasive targeting of the brain, intranasal delivery systems are currently being investigated, particularly for neuropeptides and small molecules. Neuropharmacology continues to progress rapidly, with numerous agents showing potential in both preclinical studies and early-phase clinical trials. Nevertheless, before these approaches can be widely implemented, several challenges need to be resolved, including concerns regarding safety, long-term efficacy, and the tailoring of treatments to individual patients [191]. The following section reviews the current status of clinical translation and addresses ongoing trials and future directions.

Clinical Translation and Therapeutic Potential

Although substantial progress has been made in clarifying the molecular mechanisms that underlie synaptic plasticity, the translation of these findings into effective clinical interventions continues to pose considerable challenges. Some promising compounds have advanced into clinical trials, providing potential novel therapeutic options for cognitive impairments associated with different neurological and psychiatric disorders.

Cognitive Enhancement in Neurodegenerative Disorders

In AD, existing treatments such as acetylcholinesterase inhibitors (donepezil and rivastigmine) and NMDA receptor antagonists (memantine) provide limited symptomatic relief and do not halt disease progression [192]. Emerging therapies targeting synaptic plasticity aim to intervene at earlier stages of the disease. Therapies based on BDNF, including TrkB agonists and neurotrophin mimetics, have been developed to enhance synaptic resilience [161]. Potential improvements in cognitive function have been observed with ampakines and NMDA receptor modulators in preliminary trials, although additional validation is still needed to confirm their long-term efficacy and safety [125]. By reducing the harmful effects of protein aggregates on synaptic functions, anti-amyloid and anti-tau immunotherapies may indirectly contribute to the support of synaptic plasticity [193]. In Parkinson's disease, compounds designed to enhance glutamatergic and dopaminergic synaptic transmission are

currently being investigated for both motor and cognitive symptoms, together with the neuroprotective potential of glial cell line-derived neurotrophic factor (GDNF) [194].

Psychiatric Disorders: Schizophrenia, Depression, and PTSD

Current antipsychotic medications inadequately address cognitive deficits in schizophrenia. Agents targeting synaptic plasticity offer new therapeutic avenues. Metabotropic glutamate receptor (mGluR) modulators, NMDA receptor co-agonists (such as glycine and D-serine), and GABAergic modulators have been explored to enhance prefrontal cortical plasticity. The combination of cognitive remediation therapies with plasticity-enhancing agents may yield synergistic improvements in outcomes [195]. In MDD, rapid-acting treatments such as ketamine have revolutionized treatment paradigms by demonstrating swift and sustained antidepressant effects through synaptogenic mechanisms. Significant benefits in treatment-resistant depression have been demonstrated in clinical trials of esketamine nasal spray, highlighting the therapeutic importance of mTOR activation and synaptic remodeling [153]. For PTSD and depression, emerging research on psychedelics indicates that these substances may promote lasting improvements in cognition and emotional regulation through synaptic rewiring, particularly when used in combination with psychotherapeutic support [196].

Cognitive Enhancement in Aging and Healthy Individuals

Increasing attention is being directed toward strategies that preserve cognitive functions during natural aging beyond conventional disease-modifying treatments. The combined effects of nutraceuticals, nootropics, and lifestyle interventions, including physical activity and cognitive exercises, on synaptic health are currently being investigated. Preliminary research is also assessing whether safe and well-tolerated compounds, such as L-theanine, omega-3 fatty acids, and polyphenols, can enhance neuroplasticity. Although the ethical implications of cognitive enhancement in healthy individuals remain under debate, its regulated use is being cautiously explored for professionals who require sustained high levels of cognitive performance [180].

Future Directions and Challenges

Recent progress in understanding the mechanisms of synaptic plasticity has opened opportunities for potential cognitive improvement across neurological, psychiatric, and age-related cognitive disorders. Despite this progress, significant challenges remain in translating these insights into treatments that are universally effective, safe, and sustainable. The major challenges include: (1) Individual differences: Individual responses to synaptic modulators are shaped by genetic, epigenetic, and environmental factors, emphasizing the need for personalized medical strategies. (2) Long-term safety: Risks associated with prolonged modulation of synaptic plasticity include excitotoxicity, maladaptive plasticity, and symptoms resembling psychosis. (3) Biomarker development: Reliable biomarkers are urgently required to monitor treatment effects and predict clinical outcomes. (4) Ethical considerations: Significant ethical and regulatory concerns regarding fairness, coercion, and unintended consequences arise from the use of cognitive enhancers by individuals without medical conditions. As shown in Table 2 (Ref. [5,197,198,199,200]), several critical areas will shape future research and clinical applications.

Precision Medicine and Personalized Approaches

Individual variability in synaptic plasticity regulation, influenced by genetics, epigenetics, the environment, and comorbid conditions, necessitates personalized medical approaches, including genetic screening (e.g., polymorphisms in BDNF, NMDA receptors, or catechol-O-methyltransferase (COMT)) to guide optimal pharmacological interventions [201]. The development of biomarkers is essential for identifying individuals most likely to benefit, tracking treatment responses, and reducing side effects. Through advanced neuroimaging techniques, such as functional MRI and PET scans targeting synaptic markers, synaptic function can be assessed *in vivo* in real time [202,203].

Combination Therapies

Because synaptic plasticity is regulated through complex and interconnected pathways, combination therapies may offer greater benefits than single-agent approaches: (1) Adaptive plasticity may be synergistically enhanced by combining pharmacological agents with behavioral interventions, including cognitive training, psychotherapy, and physical exercise. (2) Multiple aspects of synaptic dysfunction could be addressed simultaneously by targeting several pharmacological pathways, including glutamatergic, GABAergic, and neurotrophic systems [5,197,204].

Long-Term Safety and Ethical Considerations

Although many emerging therapies have shown rapid efficacy, uncertainty remains regarding their long-term safety. Maladaptive plasticity, aberrant learning, and psychiatric destabilization, including psychosis and addiction, are potential risks associated with prolonged enhancement of synaptic plasticity [5]. In healthy individuals, ethical concerns surrounding non-therapeutic cognitive enhancement involve issues of fairness, equity, access, and unintended social consequences. To ensure patient safety, regulatory frameworks must maintain a balance between innovation and rigorous oversight [197,198].

Table 2. Challenges in clinical translation of synaptic plasticity modulators.

Challenge	Description	Proposed solutions	Ref.
Variability in patient response	Genetic, epigenetic, environmental differences	Personalized medicine, biomarkers	[197,198]
Long-term safety	Risk of maladaptive plasticity	Longitudinal studies, careful dosing	[5]
Biomarker development	Lack of real-time synaptic plasticity markers	Imaging, electrophysiology, fluid biomarkers	[199,200]
Ethical concerns	Fair access, misuse for enhancement	Regulation, public policy development	[197,198]

Expanding Research on Novel Mechanisms

Several emerging areas are expected to drive further progress in therapies focused on synaptic plasticity. These areas include: (1) Epigenetic modulators, including HDAC inhibitors and non-coding RNAs, which offer novel approaches for modulating gene expression patterns linked to plasticity [121,122]. (2) The interactions between the microbiome and the brain are increasingly recognized as influential on synaptic function, thereby presenting new targets for intervention [205]. (3) Modulating the immune system could provide innovative strategies, given the significant role of neuroinflammation in synaptic dysfunction across various cognitive disorders [206,207].

Emerging Technologies for Drug Discovery and Monitoring

Technological advancements are expected to accelerate both drug discovery and therapy monitoring. Artificial intelligence (AI) and machine learning hold the potential to enhance target identification, drug screening, and personalized treatment planning [208]. Organoid models and induced pluripotent stem cells (iPSCs) offer human-relevant preclinical models for investigating synaptic dysfunction [209,210]. Closed-loop neuromodulation devices, such as responsive neurostimulation and transcranial stimulation, may enable real-time dynamic modulation of plasticity [211].

Toward a Unified Framework of Cognitive Enhancement

Ultimately, the successful translation of synaptic plasticity research requires a comprehensive framework that integrates (1) neuropathology, (2) molecular pharmacology, (3) neurocircuitry modulation, (4) cognitive-behavioral science, (5) individual patient profiles, and (6) ethical and societal considerations. As convergence among these fields increases, the development of safe, effective, and targeted neuropharmacological strategies for cognitive enhancement becomes progressively more feasible. Through continued interdisciplinary collaboration, scientific rigor, and ethical vigilance, targeting synaptic plasticity holds substantial potential to transform the treatment of cognitive impairment and strengthen cognitive resilience.

Conclusions

A central mechanism underlying learning, memory, adaptive cognition, and resilience across health and disease is synaptic plasticity. A broad range of therapeutic targets has been revealed through advances in understanding the molecular and cellular basis of synaptic remodeling, including glutamatergic and GABAergic signaling, neurotrophic pathways, intracellular cascades, and epigenetic regulators. Promising avenues for restoring synaptic function in neurodegenerative, psychiatric, and age-related cognitive disorders are offered by emerging neuropharmacological strategies, together with psychoplastogens, neuromodulatory approaches, and adjunct behavioral interventions.

However, the translation of these findings into effective clinical therapies continues to present significant challenges. The need for precision medicine approaches, biomarker-guided treatment selection, and careful longitudinal evaluation is emphasized by the complexity of synaptic networks, variability in individual patient responses, and the potential for long-term maladaptive effects. In addition, cognitive enhancement in healthy individuals raises ethical concerns that require thoughtful regulation to ensure responsible and equitable use. Future advances will depend on interdisciplinary collaboration across neuroscience, pharmacology, psychology, bioethics, and regulatory science to establish safe, targeted, and durable interventions.

In summary, substantial promise for improving cognitive outcomes and reshaping the treatment of cognitive impairment is offered by synaptic plasticity-based neuropharmacology. Through rigorous mechanistic research, translational innovation, and ethical oversight, these approaches may ultimately contribute to both enhanced therapeutic efficacy and a broader understanding of brain adaptability.

Availability of Data and Materials

Not applicable.

Author Contributions

SMA is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this work, the author used Paperpal AI (version 2024, Cactus Communications Services Pte. Ltd., Mumbai, India) for language polishing and grammar correction. After its use, the author thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

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