Chapter

Glutamate Signaling and NMDA Receptor Dynamics in Healthy Aging and Alzheimer's Disease

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Abstract

This chapter provides a comprehensive overview of glutamate, the primary excitatory neurotransmitter in the central nervous system, and its interaction with N-methyl-D-aspartate receptors (NMDARs), pivotal for synaptic plasticity, neural transmission, and cognitive functions. We highlight the critical role of glutamate signaling in aging and Alzheimer's disease (AD), emphasizing how dysregulated glutamatergic activity contributes to neuronal damage and neurodegeneration through excitotoxicity. A central focus is the pathological overactivation of extrasynaptic NMDARs, which elevates intracellular calcium levels and triggers neurotoxic cascades involving oxidative stress, mitochondrial dysfunction, and apoptosis. Furthermore, hallmark AD pathologies, such as Tau tangles and amyloid-beta (Aβ) plaques, exacerbate glutamate dysregulation, enhancing NMDAR-mediated calcium influx and excitotoxicity. The chapter also explores the role of glutamate transporters in cognitive decline, highlighting age-related impairments in the glutamate-glutamine cycle that reduce extracellular glutamate clearance. Therapeutic strategies targeting glutamate homeostasis and NMDAR signaling may offer novel avenues for mitigating synaptic dysfunction and improving outcomes in AD and age-related cognitive decline. This review aims to lay the foundation for developing targeted interventions to address these neurodegenerative processes.

Keywords: neurodegenerative diseases, Alzheimer's disease, glutamate receptors, cognitive decline, NMDA receptor

1. Introduction

Glutamate is the most abundant free amino acid and the primary excitatory neurotransmitter in the mammalian brain, situated at the intersection of multiple metabolic pathways. It plays a crucial role in fundamental brain processes, including synaptic plasticity, which underlies learning, memory formation, and the development of neural networks. Additionally, glutamate is essential for regulating motor control through its involvement in neuronal circuits within the basal ganglia [1].

However, under pathological conditions, dysregulated glutamate signaling can induce excitotoxicity, contributing to neuronal damage and is implicated in various neurological disorders, including Alzheimer's disease (AD).

1.1 Glutamate synthesis, release, and metabolism

Glutamate is classified as a non-essential amino acid because it is synthesized endogenously within the central nervous system (CNS) through the glutamate-glutamine cycle. Although glutamate has limited direct access from the bloodstream to the brain, neighboring glial cells release glutamine, which is taken up by neuronal presynaptic terminals via excitatory amino acid transporters (EAATs). Within the presynaptic terminals, glutamine is converted to glutamate by the mitochondrial enzyme glutaminase. The synthesized glutamate is then packaged into synaptic vesicles through the action of vesicular glutamate transporters (VGLUTs). Upon the arrival of an action potential, voltage-gated ion channels in the presynaptic membrane open, allowing Na^+ and Ca^{2+} influx, which triggers the release of glutamate into the synaptic cleft. The released glutamate interacts with receptors on the postsynaptic neuron to mediate excitatory neurotransmission, playing a critical role in synaptic communication and neuronal signaling [2]. The influx of Ca^{2+} triggers the fusion of glutamate-containing vesicles with the presynaptic membrane, leading to the release of glutamate into the synaptic cleft. To prevent excitotoxicity and maintain synaptic homeostasis, excitatory amino acid transporters (EAATs) rapidly clear glutamate from the synaptic cleft, transporting it into either glial cells or presynaptic terminals. In glial cells, glutamate is enzymatically converted back into glutamine-by-glutamine synthetase. This glutamine is subsequently shuttled back to neurons, where it is reconverted to glutamate, completing the glutamate-glutamine cycle. The coordinated interaction between neurons and glial cells ensures a continuous and efficient supply of glutamate for neurotransmission while preventing excessive extracellular accumulation [3]. See **Figure 1**.

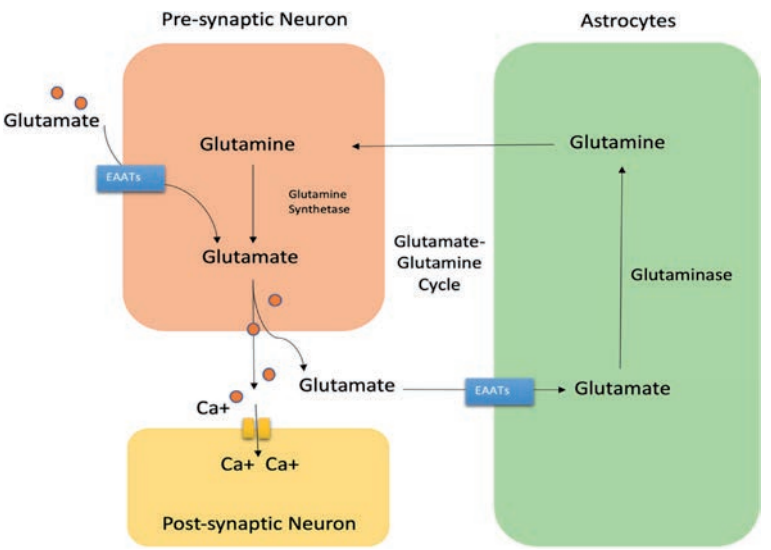

Figure 1.
Simple representation of glutamate-glutamine cycle.

1.2 Glutamate receptors

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate receptors are the three main types of ionotropic glutamate receptors responsible for fast excitatory neurotransmission in the central nervous system (CNS). While they share a similar structural framework, they differ in amino acid composition, subunit assembly, and agonist sensitivity. These receptors are distributed across pre-synaptic, post-synaptic, and extra-synaptic regions, contributing to synaptic transmission and plasticity.

AMPA receptors primarily mediate rapid synaptic responses, while NMDA receptors are involved in slower, calcium-dependent synaptic responses essential for synaptic plasticity. Kainate receptors, formed from distinct genes (GluR5-7, KA-1, and KA-2), are widely distributed throughout the brain and have been implicated in processes such as epileptogenesis and cell death, although their precise physiological roles remain less well understood [4].

In addition to ionotropic receptors, there are eight metabotropic glutamate receptors (mGluR1–8) belonging to the G-protein-coupled receptor family, which modulate neuronal excitability and synaptic transmission over slower timescales. Metabotropic receptors, on the other hand, lack ion channels. Glutamate binds to a metabotropic receptor and activates an intracellular G-protein, which starts signaling cascades that indirectly affect postsynaptic ion channels. In contrast to ionotropic receptors, these receptors have a slower postsynaptic response and can either increase or decrease excitability [5].

Group I mGluRs are located on postsynaptic membranes and are thought to improve responses mediated by ionotropic receptors. On the other hand, group II and III mGluRs, which are mainly found on presynaptic membranes, might act as auto receptors and control glutamate release by means of feedback processes.

This comprehensive distribution and functional diversity highlight the central role of glutamate receptors in both normal CNS function and pathological conditions. (Refer to **Figure 2** and **Table 1**).

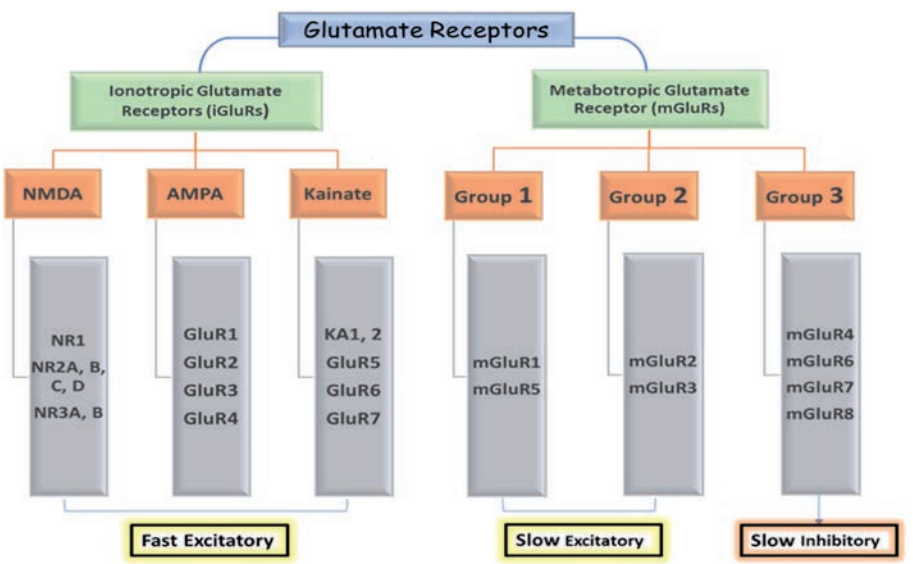

Figure 2.
Classification of glutamate receptors.

Receptor type	Subtypes	Key features	Signaling mechanism
iGluRs	NMDA, AMPA, KA	Fast synaptic transmission, ion flow	Ligand-gated ion channels
mGluRs	mGluR1—mGluR8	Modulation, plasticity, slow effects	G protein-coupled signaling

Table 1.
A comparison table of iGluR/mGluR properties.

1.3 Changes in glutamate levels during aging

With aging, the brain function declines [6], which is associated by a decrease in mitochondrial energy production in the thalamus-cortical neurons, reflected by a reduced rate of the glutamate-glutamine cycle [7]. During physiological aging memory function also tends to decline, due to hypo glutamatergic activities.

In rodents [8, 9] and in humans, not necessarily in all humans, there is a decline of cerebral glutamate levels with the age was observed via proton MR spectroscopy (1H-MRS) especially in the cortical areas [6, 7, 10–12]. Studies were made to quantify glutamine within the cortical region showed subtle results in healthy aging [6, 10].

1.4 Glutamate and neurodegeneration

Glutamate has gained significant interest from neurologists because of its potential role in acute and chronic neurodegenerative disorders. The following three basic underlying mechanisms were suggested:

1. Exogenous dietary glutamate (for instance, MSG compounds) can cause excitotoxicity by stimulating glutamate receptors.

2. In conditions such as cerebral ischemia and brain injury, glutamate released endogenously from neurons contributes to acute neurodegeneration.

3. Excitotoxicity i.e. hyperactivity of glutamatergic receptors can contribute to cell death in neurodegenerative disorders like ALS (Amyotrophic lateral sclerosis), Huntington's disease, Parkinson's disease and Alzheimer's disease [13].

1.5 Glutamate dysfunction in Alzheimer's disease (AD)

The leading cause of pathogenesis of Alzheimer's disease is excitotoxicity of glutamate receptors, especially N-methyl-D-aspartate receptors (NMDARs) [14]. The underlying mechanism of this excitotoxicity is disruption of astrocyte mediated glutamate uptake and excessive release of glutamate in presynaptic terminals induced by beta amyloid plaques [15]. Studies have revealed that the overexcitation, leads to influx of calcium ions, causing neuronal loss and cognitive decline of Alzheimer's disease [16, 17].

This chapter offers a comprehensive review of glutamate, the central nervous system's primary excitatory neurotransmitter and its complex interaction with N-methyl-D-aspartate receptors (NMDARs), critical to synaptic plasticity, neural transmission, and cognitive health. The chapter starts with a description of normal physiological glutamatergic signaling and its significance to healthy brain

health, followed by discussion of how this system gets dysregulated with age and in Alzheimer's disease (AD). A centralized focus is given to the pathological overactivation of extrasynaptic NMDARs, which triggers a cascade of intracellular calcium overloading, oxidative stress, mitochondrial damage, and apoptosis which are major drivers of neuronal loss and cognitive decline. The chapter also borrows from nascent knowledge of how common AD pathologies, i.e., amyloid-beta (Aβ) deposition and tau pathology, lead to glutamate-mediated excitotoxicity. Furthermore, we assess the loss of glutamate transporter function and the impaired glutamate-glutamine cycle, especially in the aging brain, that further aggravate extracellular glutamate accumulation. On this mechanistic foundation, the chapter discusses current and experimental treatment strategies to restore glutamate homeostasis, modulate NMDAR function, and maintain synaptic health. By integrating these lines of evidence, this chapter seeks not only to explain the multifaceted role of glutamatergic dysfunction in AD but also to lay bare its therapeutic potential, paving the way for future intervention into this critical neurotransmitter system.

2. Glutamate transporters dysfunction in Alzheimer's disease

The concentrations of extracellular glutamate are also regulated by glutamate transporters, expressed on neurons and astrocytes. The glutamate transporters play a critical role in preserving synaptic homeostasis, by withdrawing the excess amount of glutamate from the cleft of the synaptic membrane. Glutamate transporter failure is a major cause of excitotoxicity and neuronal injury in neurodegenerative diseases like Alzheimer's [13].

There are two types of glutamate transporters involved in the removal of extra levels of glutamate from synaptic cleft [18]. These EAAT1 and EAAT2T are integral membrane proteins, responsible for clearing excess glutamate from the synaptic cleft into glial cells and neurons [19]. EAAT1 is mostly found in cerebellum and EAAT2 is present on astrocytes in the cerebral cortex and hippocampus to maintain the glutamate level by transporting the excess amount of glutamate in the brain [20].

In AD, the dysregulation of glutamate transporters, specifically EAAT2, results in high extracellular glutamate levels due to decreased astrocytic glutamate uptake and resultant excitotoxicity [21]. Genetic variations of EAAT2 is associated with lower glutamate uptake, contributing to the onset of Alzheimer's disease [22].

2.1 Consequences of impaired glutamate clearance in Alzheimer's disease

The inadequate activities of glutamate transporters i.e. Excitatory Amino Acid Transporters (EAATs) may lead to symptoms of Alzheimer's disease. EAAT1 and EAAT2 transporters maintaining the homeostasis of glutamate levels in the brain [23, 24].

EAAT1 and EAAT2 are predominantly localized on astrocytes, with EAAT1 highly expressed in the cerebellum and EAAT2 in the hippocampus. Their activity prevents excessive glutamate accumulation, thereby avoiding excitotoxicity [25, 26], EAAT2 is not exclusively astrocytic; it has also been detected in neurons, particularly in the hippocampus and retina [27]. Upon glutamate release from presynaptic neurons, a substantial portion diffuses out of the synaptic cleft. Astrocytic EAATs, especially EAAT2, are critical in clearing this excess glutamate, preventing spillover to neighboring synapses and avoiding overactivation of extrasynaptic NMDA receptors. This regulatory mechanism is disrupted in AD.

Amyloid β, a hallmark of AD, has been shown to reduce both EAAT1 and EAAT2 function and expression in rat hippocampal and cortical astrocytes. Human studies have similarly documented decreased expression of these transporters in the hippocampi and cortices of AD patients, correlating with reduced glutamate uptake [27]. While the role of EAAT2 has been relatively well characterized, EAAT1's involvement remains ambiguous. Some studies suggest increased EAAT1 expression in the hippocampus of AD patients, potentially as a compensatory response [26], while others note reduced expression in platelets, indicating systemic glutamate dysregulation [28].

EAAT2 alterations are more consistent: protein levels and function are significantly decreased in the AD frontal cortex despite stable mRNA levels, suggesting post-transcriptional regulation problems [29]. This downregulation is linked with astrocyte dysfunction, increased gliosis, and is associated with, but not fully explained by, amyloid and tau burden [29, 30]. Notably, both astrocytic and neuronal EAAT2 are implicated in memory, with astrocytic deficiency being more strongly tied to AD pathology [31]. Peripheral changes have also been observed, such as reductions in platelet EAAT1 and EAAT3 during aging and AD, indicating potential peripheral biomarkers [28].

Mechanistically, multiple factors link EAAT dysfunction to AD. Neuroinflammation, driven by microglial and astrocyte activation, alters EAAT1/2 expression and impairs synaptic plasticity [32]. Moreover, beta-amyloid disrupts insulin/Akt/EAAT signaling pathways, lowering EAAT protein levels and potentially promoting excitotoxic damage—a process reversible with insulin treatment [33]. Altered EAAT2 is also associated with abnormal expression of the amyloid precursor protein (APP), linking transporter dysfunction with amyloidogenesis [29].

Given that EAAT expression is influenced by neuronal and endothelial signaling, the decline in transporter function in AD may stem from disrupted intercellular communication. Thus, targeting EAAT1 and EAAT2 for therapeutic upregulation holds promise for mitigating glutamate toxicity and slowing disease progression.

In addition, the release of excitotoxicity leads to the generation of reactive microglial cells, which produce cytokines resulting in neuroinflammation [34] and the generation of the neurofibrillary tangles. (Refer to **Table 2** for a brief summary of the role of EAAT1/2 in AD pathology.

2.1.1 Amyloid-beta (Aβ) toxicity

The neuronal death and synaptic dysfunction in Alzheimer's disease is mainly due to abnormal accumulation of amyloid-beta (Aβ) peptides, which are produced by the proteolytic cleavage of amyloid precursor protein (APP) [35]. The primary pathogenic

Protein	Gene	Localization	Alterations in AD
EAAT1	*SLC1A3*	Astrocytes (including Bergmann & Müller glia) Predominant in cerebellum Present in retina [27].	Upregulated in the medial temporal lobe (suggesting compensation) [26] Downregulated in platelets and some brain areas [28].
EAAT2	*SLC1A2*	Astrocytes (and some sparse neurons) Predominant in hippocampus and cortex [27].	Reduced protein levels and function in AD brains [29] Post-transcriptional regulation issues despite stable mRNA levels. Associated with gliosis and abnormal amyloid precursor protein APP dysregulation [30, 31].

Table 2.
Localization and alterations of EAAT 1/2 in AD pathology.

characteristic of AD, insoluble plaques, can be formed by the oligomerization and aggregation of these peptides leading to severe neurotoxicity and synaptic function, especially in soluble forms [36]. They cause synaptic depression and disrupt long-term potentiation (LTP), a neuronal process that underlies learning and memory [37]. Furthermore, Aβ oligomers exacerbate excitotoxicity by interfering with the release of neurotransmitters, especially glutamate [38]. In addition to causing oxidative stress, mitochondrial malfunction, and disruption of intracellular signaling cascades, Aβ toxicity also results in neuronal damage and cell death [39]. Researchers have also suggested that Aβ peptides can stimulate astrocytes and microglia, resulting in neuroinflammatory reactions that worsens neurodegeneration [39]. Postmortem examinations of brains affected by Alzheimer's disease have consistently revealed indications of underlying neuroinflammation. These alterations are indicative of the presence of activated microglia surrounding amyloid plaques and elevated levels of pro-inflammatory cytokines [40]. It is vital to address the underlying processes of Aβ toxicity to explore effective treatment options, which should be aimed at reducing its deleterious effects and stopping the course of Alzheimer's disease.

2.1.2 Tau pathology

Alzheimer's disease cognitive impairment and disease progression are significantly correlated with tau pathology [41]. It is suggested that the underlying mechanism causing neurodegeneration of Alzheimer's disease is abnormal accumulation of hyperphosphorylated Tau proteins.

Tau protein is present in neuronal axons, where it is responsible for intracellular facilitation and stabilization of microtubules. In Alzheimer's disease, the tau proteins become phosphorylated leading to accumulation of neurofibrillary tangles (NFTs) which cause disruption of regular cellular activities like synaptic dysfunction, interference with axonal transport, neuronal damage and cell death [42, 43]. Transgenic animal models have been used in studies to show that overexpression of mutant tau protein recapitulates important characteristics of the pathogenesis of Alzheimer's disease, such as neurodegeneration and synaptic dysfunction [44, 45].

3. The NMDAR paradox

In the central nervous system (CNS), a multitude of excitatory neurotransmission is regulated, via the vesicular discharge of glutamates stimulating ionotropic glutamate receptors (iGluRs) and pre- and postsynaptic G-protein-coupled metabotropic glutamate receptors [46].

N-methyl-d-aspartate receptor (NMDAR) is distinguished from other glutamate receptors, for an increased Ca^{2+} permeability extracellular Mg^{2+} blockade in a voltage dependent manner, as well as the necessity of two co agonists binding to the agonist recognition site i.e. glutamate and glycine (or d-serine), to activate the channel [47].

3.1 Localization of NMDAR

In growing brain circuits, NMDARs placed post synaptically serve as detector, while NMDARs located presynaptic-ally mediate synaptic transmission and activity-dependent synaptic plasticity [48].

The temporal cortex and hippocampus of developing brains exhibit modest expression of the NR1, NR2A, and NR2C subunits of the NMDA receptor, but in

neonates, this expression is distributed across the brain. Although NR2B is hardly noticeable in adults, the NR2B subunit is minimally expressed in the fetal hippocampal and temporal cortex [49]. From weeks 7–21, NR3A levels plummet and rapidly increases post-birth, and decline gradually into adulthood [50], and NR3B levels rise as postnatal development advances, in adulthood, NR3A remains low while NR3B stays high. NR1 expression is low during gestation and escalates until adolescence [51]. Long-term potentiation (LTP) and long-term depression (LTD), two processes underpinning synaptic plasticity, depend on NMDA receptors, which are the principal mediators of calcium signaling in hippocampal neurons [52]. Both NR2A along with NR2B subunits are paramount for inducing of LTD and LTP [53]. See **Figure 3**.

3.2 Synaptic and extra synaptic NMDAR

Extra synaptic NMDARs are the ones that are found outside of the synapse, on the sides of spines or dendrites. They also cluster at sites of contact with nearby structures i.e. axons, axon terminals, or glia [54], while synaptic NMDARs are situated on the postsynaptic membrane of the synapse. When glutamate binds to NMDARs, it causes an unfolding chain of events resulting in the opening of the receptor's ion channel, letting calcium ions (Ca^{2+}) pass through the postsynaptic neurons. In conclusion, Ca^{2+} excess is not the only factor determining neurotoxicity; rather, Ca^{2+} influx through NMDARs positioned beyond the synapse is particularly detrimental to neurons [49]. See **Figure 4**.

Aβ, a protein linked to Alzheimer's disease, initiates extra synaptic NMDA receptors (NMDARs) in neurons, causing astrocytes to release glutamate. The activation of these extra synaptic NMDARs could bring about a drop in miniature excitatory postsynaptic currents (mEPSCs), which are small, spontaneous shifts in the electrical characteristics of neurons at synapses. A drop in mEPSCs may indicate early synaptic damage, contributing to the course of Alzheimer's disease [55].

Synaptic NMDARs are impeded by d-serine degradation, the magnitude of LTP expression is reduced, whereas glycine degradation has no effect on LTP, implying that synaptic NMDARs play an important role in LTP but not extra synaptic. Conversely, both synaptic and extra synaptic NMDARs are necessary for LTD [56].

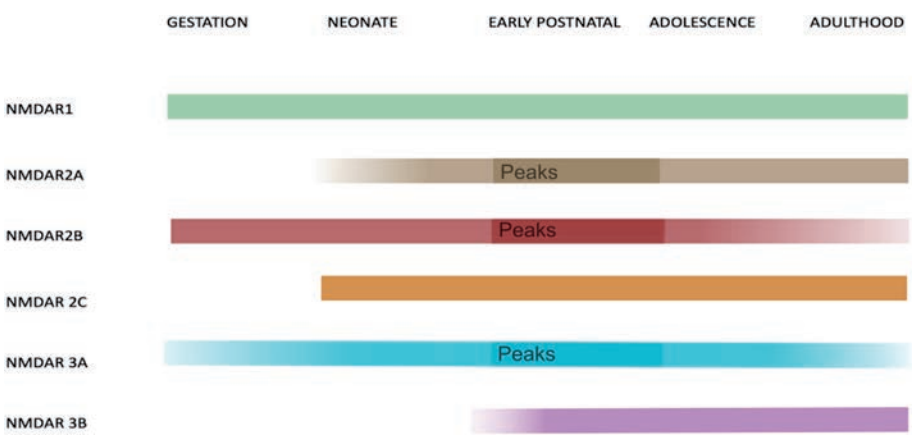

Figure 3.
Developmental timeline of NMDAR receptor subunits.

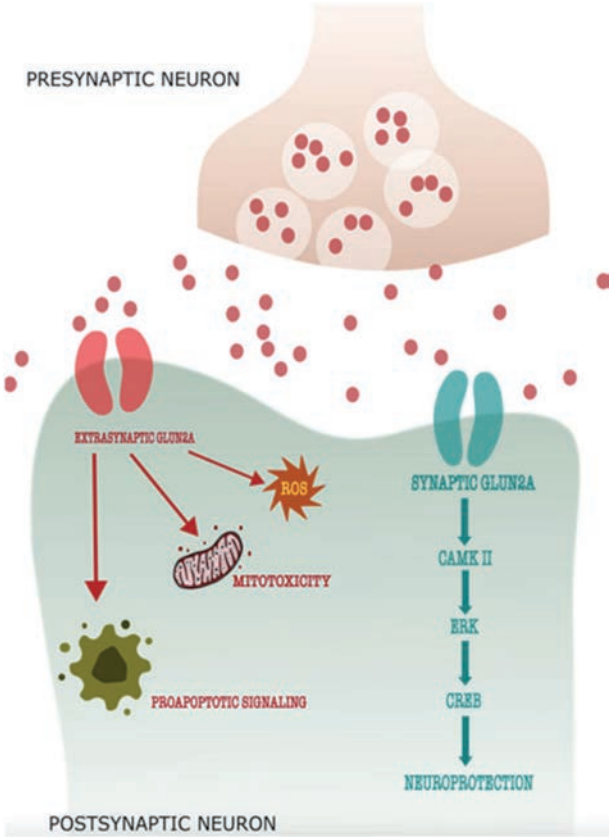

Figure 4.
Postsynaptic changes brought about in a cell by synaptic and extra synaptic receptors.

3.3 Activation of NMDAR

During the resting state, there is a voltage-dependent blockade on NMDA pore by extracellular Mg^{2+}, the block (**Figure 5**) is released upon depolarization of the receptor, hence, the activation is dependent on the membrane potential at the post synaptic end and the frequency of Glutamate being released from the presynaptic terminal, rendering these receptors with a unique potential to simultaneously respond to both presynaptic glutamate release and postsynaptic depolarization with a slow synaptic current, resulting in the ample influx of external Ca^{2+} into the dendritic spine [57, 58]. Consequently, increasing intracellular Ca^{2+} signals the initiation of the cascade of events leading to a multitude of changes in the postsynaptic neuron, resulting in short-term or long-term changes in synaptic strength and excitatory glutamatergic neurotransmission which is critical for survival of neurons and synaptic plasticity [46, 52, 59–62]. The duration and frequency of the activation of synaptic NMDA receptor influences the nature of these changes [63, 64]. Although apparently the synapsis of the NMDAR seems to be directly affected by the glutamate, but the activation through glutamate is only temporary, owing to the continuous presence of extracellular glycine (or d-serine) at a fairly constant concentration [65–67].

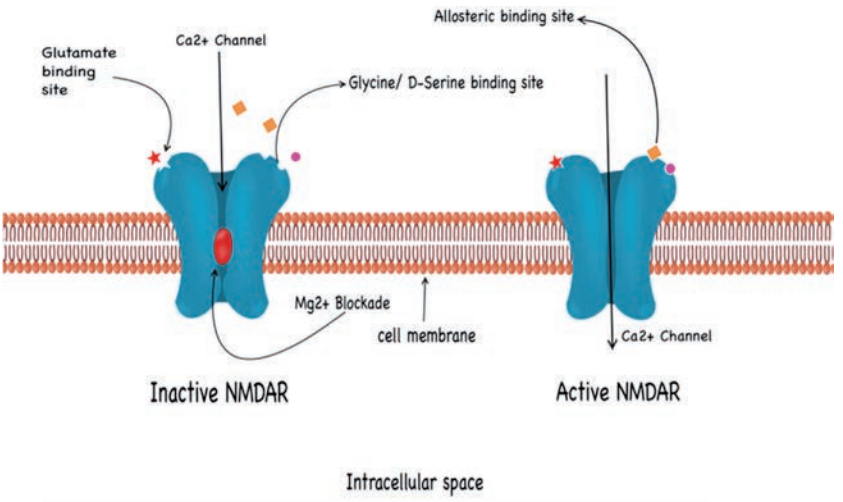

Figure 5.
A comparison of NMDAR in both active and inactive state.

3.4 The tripartite glutamate synapse

The presynaptic terminal, postsynaptic spine, and astrocytic cell engage during glutamate-mediated synaptic transmission. Glutamate is stored in synaptic vesicles by presynaptic glutamate transporters (VGLUTs) [68]. The calcium channels open, allowing calcium to enter, which discharges glutamate into the synapse upon the fusion of the vesicles with the membrane. Once the presynaptic neuron depolarizes glutamate thereafter activates receptors on postsynaptic and presynaptic neurons, as well as on the astrocytes, increasing internal calcium levels in astrocytes results in the release of neurotransmitters that dictate synaptic strength [69].

Glutamate is extracted from the extracellular environment into the astrocytes by excitatory amino acid transporters 1/2 (EAAT1/2) in astrocytes and EAAT2/5 in the presynaptic terminal and stored in vesicles where glutamine synthase turns glutamate into glutamine. The glutamine is transported back to glutamatergic neurons and converted back into glutamate [70]. This glutamate and a co-agonist which can either be glycine or D-serine, binds to the postsynaptic neuron, thereby, depolarizing it, opens the NMDA channels, letting Ca^{2+} influx through the postsynaptic terminal. This can trigger signals which support long-term potentiation (LTP), a process essential for learning and memory [71]. However, the surplus of Ca^{2+} through prolonged stimulation of NMDAR is deleterious to the cell [72].

Glutamate transport systems could shut off excitatory signaling, transport glutamate to extra synaptic receptors, and protect neurons from excitotoxic damage. The sodium-dependent EAATs mediate most of the glutamate transport in the CNS, notably during excitatory transmission. When glutamate release surpasses the capacity of astrocyte clearance systems, or EAAT expression drops, excitotoxicity may occur. Both chronic and acute neurological disorders have been linked to GLT-1/EAAT-2 dysfunction or reduced expression (**Figure 6**) [73].

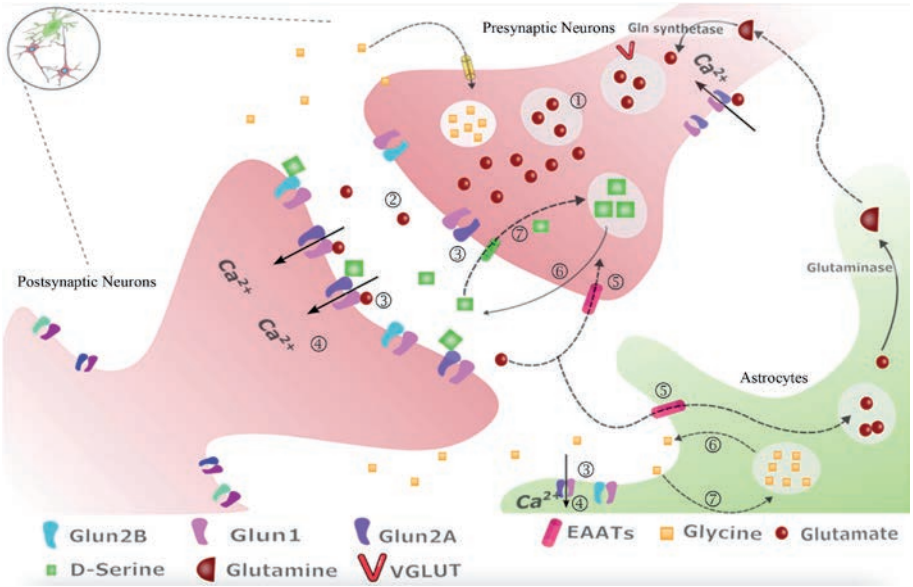

Figure 6.
Overview of the tripartite glutamate synapse. (1) Glutamate is stored in presynaptic vesicles and released into the synaptic cleft. (2) It binds to postsynaptic NMDARs, triggering calcium influx and action potential propagation. (3) Glutamate uptake occurs via EAAT transporters in astrocytes and presynaptic terminals. (4) Glycine and D-serine, released by neurons and astrocytes, modulate receptor activation and are recycled through transporters.

3.4.1 Role of NMDAR in Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder, contributing to cognitive decline and memory loss in almost 40 million people worldwide [74]. AD primarily affects the hippocampus and neocortex—critical regions for cognitive function and memory.

Features of AD

- Synaptic loss
- Deposition of Aβ plaques
- Neurofibrillary tangles (NFTs)
- Hyperphosphorylated tau.

These pathological features contribute to oxidative stress and NMDAR activation, leading to glutamatergic dysfunction and Ca^{2+} dyshomeostasis, both of which play significant roles in AD, particularly in its early stages. Recent studies highlight the involvement of tripartite glutamatergic synapses in AD pathogenesis [75]. The resulting high Ca^{2+} influx and free radical generation further phosphorylate tau, leading to mitochondrial dysfunction, permeability transition pore activation, cytochrome c release, ATP depletion, and ROS formation [49]. Multiple regulatory sites within the tripartite synapse modulate extracellular glutamate levels and are sensitive to

AD-related changes. Interruptions in these synapses contribute to AD pathogenesis through:

1. Overstimulation of NMDARs, contributing to excessive intracellular Ca^{2+} and subsequent cell death [76].

2. Low during gestation Impaired astrocytic glutamate clearance or reduced expression of EAATs, leading to excitotoxicity [73].

3. Dysfunction or downregulation of GLT-1/EAAT-2, which may exacerbate AD [73].

3.5 Pathways and molecular mechanisms involved in the pathology of AD

3.5.1 CREB (cAMP response element binding protein) and synaptic plasticity

CREB is the prototypical signal-regulated transcription factor essential for long-term potentiation (LTP), Within the hippocampus, CREB-mediated gene expression associated with synaptic plasticity, learning and memory, Phosphorylation of CREB at residue ser-133 is particularly important for its transcriptional activity, which is decreased in AD [74].

3.5.2 Activation of CREB

A broad range of signaling processes can trigger the phosphorylation of CREB, which leads to its activation. Some of these processes include an increase in intracellular Ca^{2+} through NMDARs, by growth factors activating receptor tyrosine kinase. This calcium entry through synaptic NMDARs induces CREB phosphorylation and Brain-derived neurotrophic factor (BDNF) expression, while extra synaptic NMDARs shuts-off the CREB pathway [77].

3.5.3 Amyloid-β (Aβ) and CREB

Amyloid-β (Aβ) accumulation in Alzheimer's disease is linked to memory loss, synaptic dysfunction, and a decrease in brain-derived neurotrophic factor (BDNF). Aβ dephosphorylates CREB through inactivation of protein kinase A (PKA) and thus inhibits of long-term potentiation (LTP) generation [78].

3.5.4 Jacob and synaptic plasticity

Jacob is a caldendrin-binding protein in the brain that is localized to the nucleus, it promotes synaptic contact loss while impeding CREB phosphorylation. Elevated NMDAR activity has been shown to aid in Jacob's nuclear accumulation [43]. Cell death or cell survival and synaptic plasticity depend on the level of Jacob phosphorylation. Upon synaptic NMDAR stimulation, phosphorylated Jacob is carried to the nucleus and is believed to be associated with neuroprotection while non-phosphorylated Jacob, on the other hand, has been correlated with decreased CREB activity, dendritic complexity, and synaptic density and is translocated during extra synaptic NMDAR stimulation [79].

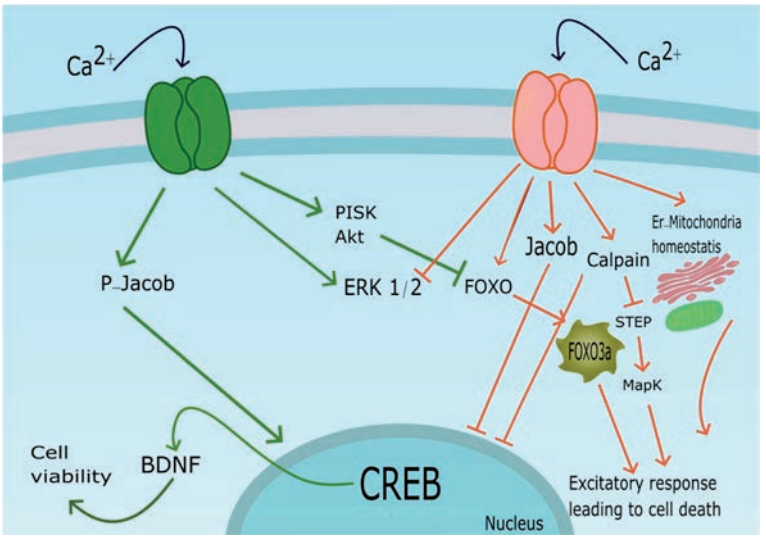

Figure 7.
Synaptic (green) and extrasynaptic (red) NMDAR signaling pathways. Synaptic NMDARs phosphorylate Jacob, activate ERK1/2, and promote CREB activation, enhancing BDNF expression, cell viability, and neuroprotection. Extrasynaptic NMDARs facilitate Jacob nuclear import, FOXO activation, calpain-mediated STEP activation, ER-mitochondrial disruption, and excitotoxicity, leading to cell death.

3.5.5 FoxO3a and ERK signaling

FoxO3a, a fork head transcription factor, influences neuronal function via pathways regulating oxidative stress, autophagy, apoptosis, and mitochondrial activity. FoxO3a modulation affects cognitive decline in AD, stroke, and Parkinson's disease. Increased extrasynaptic NMDAR activity translocate FoxO3a to the nucleus, promoting excitotoxic cell death. Synaptic NMDARs, however, restrict FoxO3a activity through Akt-mediated phosphorylation [71, 80]. Synaptic and extra synaptic NMDARs have opposite effects on the ERK1/2 pathway, which plays a role in neuroprotection mediated by NMDAR. Extra synaptic NMDAR stimulates Calpain, a calcium-dependent protease that is evoked by raised intracellular calcium levels, and a cascade of events lead to the cleavage of striatal enriched tyrosine phosphatase (STEP)61 into STEP33. Unlike STEP61, STEP33 is devoid of a regulatory domain and exhibits continuous activity, which can lead to the dephosphorylation and inactivation of proteins influencing synaptic function. Synaptic NMDAR activation leads to the reduced degeneration of STEP because of STEP61 ubiquitination and degradation, which is associated with ERK1/2 phosphorylation [81].

The ERK1/2 pathway activates CREB which has been linked to NMDAR-mediated neuroprotection. NMDARs play a bi-directional role in ERK regulation based on their localization i.e. synaptic or extra synaptic. Synaptic NMDARs activate ERK, whereas extra synaptic NMDARs deactivate it [82]. Thus, synaptic and extra synaptic NMDARs are mutually antagonistic compared to ERK signaling (**Figure 7**).

4. Therapeutic targets in Alzheimer's disease

The National Institute on Aging identifies two classes of FDA-approved drugs for AD treatment: cholinesterase inhibitors and memantine, an NMDAR antagonist [59].

Memantine reduces tau phosphorylation and prevents neuronal necrosis, impaired axonal transport, DNA damage, and neurite retraction [83]. Trodusquemine mitigates Aβ toxicity [84]. while Neramexane, another NMDAR antagonist, improves memory in animal models [85].

AD disrupts the balance between protective GluN2A-containing synaptic NMDARs and excitotoxic GluN2B-containing extrasynaptic NMDARs. Ifenprodil (a GluN2B antagonist) and D-cycloserine (a co-activator of NMDARs) together showed better protective effects against Aβ toxicity than either alone [86], Enhancing GluN2A activity alone through positive allosteric modulation (e.g., GNE-0723) also improved cognitive function in AD models [47],

These findings suggest that modulating synaptic and extrasynaptic NMDAR activity could be a viable AD treatment strategy. Altering co-agonist levels (glycine and D-serine) may also regulate NMDAR activity [19, 79].

Repetitive transcranial magnetic stimulation (rTMS) has shown promise in AD, Parkinson's, and schizophrenia. Low-frequency rTMS improves NMDAR levels, LTP, and spatial memory in Aβ-induced AD mice, with positive cognitive effects in human trials [56, 87]. Selenium-methionine (Se-Met) restores synaptic integrity by modulating Ca^{2+} influx via NMDARs, leading to improved cognitive function [88].

Table 3 below summarizes aforementioned evidence into Glutamate Modulation, NMDAR subunit targeting and Novel approaches.

Category	Therapy	Mechanism	Effect in AD models/ Humans	Reference
1. Glutamate Modulation	**Memantine** (FDA-approved)	Non-competitive NMDAR antagonist	Reduces tau phosphorylation, neuronal necrosis, axonal transport defects, DNA damage, neurite retraction	[59, 83]
	Neramexane	NMDAR antagonist (memantine derivative)	Improves memory and learning in animal AD models	[85]
	Trodusquemine	Indirect glutamate modulator via Aβ inhibition	Mitigates Aβ toxicity, reducing synaptic damage	[84]
2. NMDAR Subunit Targeting	**Ifenprodil**	Selective GluN2B subunit antagonist (extrasynaptic NMDAR)	Reduces excitotoxicity; enhances Aβ protection when combined with D-cycloserine	[86]
	D-cycloserine	Partial NMDAR co-agonist (at glycine site)	Enhances synaptic NMDAR function; synergistic neuroprotection with Ifenprodil	[86]
	GNE-0723	Positive allosteric modulator of GluN2A-containing NMDARs	Enhances synaptic NMDAR activity; improves cognitive function	[47]
	Glycine / D-serine modulation	Co-agonist level alteration to fine-tune NMDAR activity	May restore NMDAR homeostasis in AD brains	[19, 79, 89]
3. Novel Approaches	**rTMS** (Repetitive Transcranial Magnetic Stimulation)	Non-invasive brain stimulation; enhances NMDAR activity and LTP	Improves spatial memory, synaptic plasticity; positive human trial outcomes	[56, 87]

Category	Therapy	Mechanism	Effect in AD models/ Humans	Reference
	Selenium-methionine (Se-Met)	Regulates Ca^{2+} influx through NMDARs; antioxidant	Restores synaptic integrity; improves cognition in Aβ mouse models	[88]

Table 3.
Summary of therapeutic strategies in AD.

4.1 Biomarker-based monitoring in Alzheimer's disease: Key challenges and emerging approaches

4.1.1 Key challenges

Monitoring treatment efficacy in Alzheimer's disease (AD) using biomarkers remains a formidable challenge, despite significant advancements in their diagnostic utility. Currently established biomarkers—such as amyloid-β and tau; while useful for early and differential diagnosis, fall short in reliably tracking therapeutic response and disease progression, particularly in clinical trials that target amyloid-β pathways [90–94]. This underscores a critical limitation in their scope and sensitivity. Furthermore, a major gap exists in the availability of biomarkers that reflect non-amyloid and non-tau pathologies. Key pathological processes such as neuroinflammation, oxidative stress, lipid metabolism, vascular damage, and impaired protein clearance are underrepresented in current biomarker panels, yet they play essential roles in AD pathogenesis [90, 92–95].

Validation and standardization also pose significant barriers; Although novel biomarkers like neurofilament light (NfL), neurogranin, and YKL-40 show potential, they remain inadequately validated and lack standardized protocols across research centers. This hampers their utility in multi-center trials and clinical translation [92–94]. Additionally, there are practical challenges concerning biomarker accessibility. Cerebrospinal fluid (CSF)-based tests, while reliable, are invasive and less suited for routine clinical monitoring. Although blood-based biomarkers are a promising alternative, they are influenced by patient heterogeneity, blood-brain barrier permeability, and preanalytical variability—factors that complicate consistent measurement [93, 94].

4.1.2 Emerging solutions and approaches

To overcome these limitations, several innovative strategies are under exploration. One promising approach is the use of combination biomarker panels that integrate markers of neurodegeneration, synaptic function, and inflammation. These composite profiles can provide a more nuanced and comprehensive understanding of AD pathology, thus improving the accuracy of treatment monitoring [90, 92, 93, 95]. In parallel, digital and multimodal technologies, such as electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS), are being paired with fluid biomarkers to enable real-time tracking of cognitive changes and therapeutic impact [96]. This reflects a shift toward dynamic and personalized monitoring. Additionally, the integration of systems bioloy, where biomarker data is combined with cognitive assessments, clinical measures, and neuroimaging—holds promise for capturing disease heterogeneity and progression more effectively [92].

While biomarkers have revolutionized the diagnosis of AD, their role in monitoring treatment remains constrained by limited specificity, standardization, and practicality. Addressing these issues requires a multi-pronged strategy: expanding the biomarker repertoire beyond amyloid and tau, validating emerging candidates across diverse populations and centers, and embracing multimodal data integration. Such advances are essential for enabling precision medicine approaches in AD therapy.

5. Conclusion

In summary, glutamate is a foundation of CNS neurotransmission, acting as the main excitatory neurotransmitter that provides synaptic communication and facilitates such important processes as synaptic plasticity, learning, and memory. Glutamate levels are tightly regulated by neurons and glial cells to maintain effective signaling and protect neurons from excitotoxicity. The balance has to be maintained; even minor imbalances will have serious effects on brain health.

Glutamatergic signaling dysregulation has come to be increasingly acknowledged as a core contributor to a variety of neurological and neurodegenerative diseases. In Alzheimer's disease (AD), such disruption is especially marked. Exaggerated activation of glutamate receptors—particularly NMDA receptors—results in prolonged excitotoxicity, propelling neuronal damage and hastening cognitive deterioration. This situation is compounded by dysfunctional glutamate transporters, which are unable to effectively remove surplus extracellular glutamate, further fueling the neurotoxic milieu.

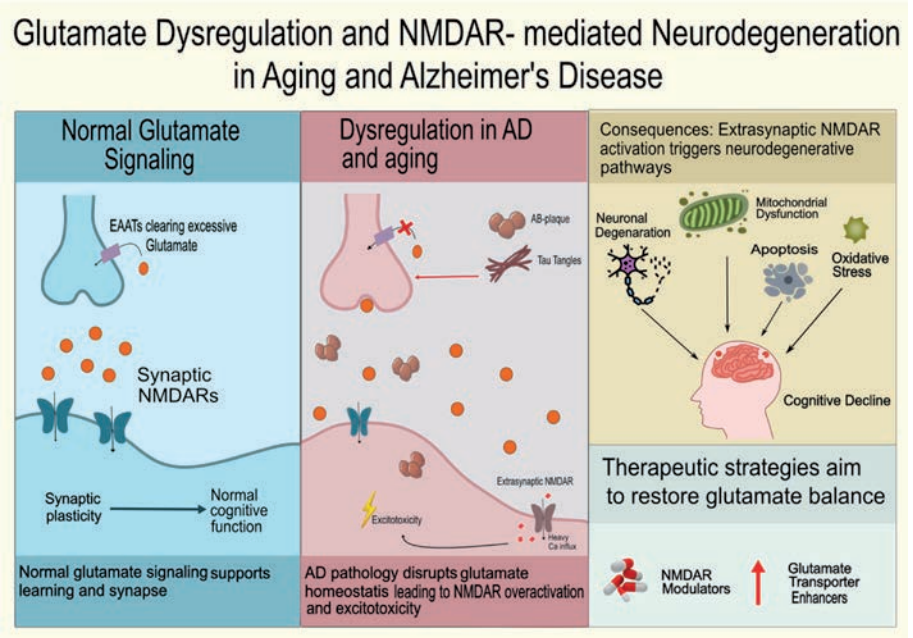

Figure 8.
This figure summarizes how disrupted glutamate clearance in Alzheimer's disease shifts NMDAR activation from synaptic to extrasynaptic sites, driving excitotoxicity and neurodegeneration, and highlights therapeutic approaches to restore glutamate balance.

Despite our great strides, a few knowledge gaps persist. The most important of these are the timing of NMDA receptor–targeted therapies, identification of a consistent biomarker to determine predisposition to excitotoxicity, and the optimal way to combine these interventions with current amyloid-β and tau-based treatments. Resolving these unknowns is important to transform our current understanding into effective, individualized therapeutic regimens.

Directions for the future need to center on the disentanglement of the complex regulation of glutamatergic signaling pathways and pathological derangement in disorders such as AD. Interventions that restore glutamate homeostasis, diminish receptor-mediated toxicity, and enhance synaptic resilience are extremely promising. With future advancements in research, addressing glutamatergic dysfunction may not just be able to slow disease progression but also provide a bridge to maintaining cognition and enhancing outcome for the persons with neurodegenerative disorders (**Figure 8**).

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. Journal of Neural Transmission. 2014;**121**(8):799-817

[2] Albrecht J, Sidoryk-Węgrzynowicz M, Zielińska M, Aschner M. Roles of glutamine in neurotransmission. Neuron Glia Biology. 2010;**6**(4):263-276

[3] Yelamanchi SD, Jayaram S, Thomas JK, Gundimeda S, Khan AA, Singhal A, et al. A pathway map of glutamate metabolism. Journal of Cell Communication and Signaling. 2015;**10**(1):69-75

[4] Willard SS, Koochekpour S. Glutamate, glutamate receptors, and downstream signaling pathways. International Journal of Biological Sciences. 2013;**9**(9):948-959

[5] Vandenberg RJ, Ryan RM. Mechanisms of glutamate transport. Physiological Reviews. 2013;**93**(4):1621-1657

[6] Schubert F, Gallinat J, Seifert F, Rinneberg H. Glutamate concentrations in human brain using single voxel proton magnetic resonance spectroscopy at 3 tesla. NeuroImage. 2004;**21**:1762-1771

[7] Boumezbeur F, Mason GF, de Graaf RA, al et. Altered brain mitochondrial metabolism in healthy aging as assessed by in vivo magnetic resonance spectroscopy. Journal of Cerebral Blood Flow and Metabolism. 2010;**30**(1):211-221

[8] Segovia G, Porras A, Del Arco A, Mora F. Glutamatergic neurotransmission in aging: A critical perspective. Mechanisms of Ageing and Development. 2001;**122**:1-29

[9] Zhang X, Liu H, Wu J, Zhang X, Liu M, Wang Y. Metabonomic alterations in hippocampus, temporal and prefrontal cortex with age in rats. Neurochemistry International. 2009;**54**:481-487

[10] Kaiser L, Schuff N, Cashdollar N, Weiner M. Age-related glutamate and glutamine concentration changes in normal human brain: 1H MR spectroscopy study at 4 T. Neurobiology of Aging. 2005;**26**:665-672

[11] Zahr N, Mayer D, Pfefferbaum A, Sullivan E. Low striatal glutamate levels underlie cognitive decline in the elderly: Evidence from in vivo molecular spectroscopy. Cerebral Cortex. 2008;**18**:2241-2250

[12] Chang L, Jiang C, Ernst T, al et. Effects of age and sex on brain glutamate and other metabolites. Magnetic Resonance Imaging. 2009;**27**:142-145

[13] Conway M. Alzheimer's disease: Targeting the glutamatergic system. Biogerontology. 2020;**13**:257-274

[14] Zhong W, Wu A, Berglund K, Gu X, Jiang M, Talati J, et al. Pathogenesis of sporadic Alzheimer's disease by deficiency of NMDA receptor subunit GluN3A. Alzheimer's & Dementia. 2021;**18**:222-239

[15] Yu SP, Jiang M, Shim S, Pourkhodadad S, Wei L. Extrasynaptic NMDA receptors in acute and chronic excitotoxicity: Implications for preventive treatments of ischemic stroke and late-onset alzheimer's disease. Molecular Neurodegeneration. 2023;**18**:43

[16] Ortiz-Sanz C, Balantzategi U, Quintela-López T, Ruiz A, Luchena C, Zuazo-Ibarra J, et al. Amyloid β /

PKC-dependent alterations in NMDA receptor composition are detected in early stages of Alzheimer's disease. Cell Death & Disease. 2022;**13**(3):1-12

[17] Dejakaisaya H, Kwan P, Jones N. Astrocyte and glutamate involvement in the pathogenesis of epilepsy in Alzheimer's disease. Epilepsia. 2021;**62**(7):1485-1493

[18] Zhang ZH et al. Selenium restores synaptic deficits by modulating NMDA receptors and Selenoprotein K in an Alzheimer's disease model. Antioxidants & Redox Signaling. 2021;**35**(11):863-884

[19] Bell K, Ducatenzeiler A, Ribeiro-da-Silva A, Duff K, Bennett D, Claudio CA. The amyloid pathology progresses in a neurotransmitter-specific manner. Neurobiology of Aging. 2006;**27**:1644-1657

[20] Ferrarese C, Begni B, Canevari C, Zoia C, Piolti R, Frigo M, et al. Glutamate uptake is decreased in platelets from Alzheimer's disease patients. Annals of Neurology. 2000;**47**:641-643

[21] Rodriguez-Lopez A, Torres-Paniagua A, Acero G, Díaz G, Gevorkian G. Increased TSPO expression, pyroglutamate-modified amyloid beta (AβN3(pE)) accumulation and transient clustering of microglia in the thalamus of Tg-SwDI mice. Journal of Neuroimmunology. 2023;**382**:578150-578150

[22] Walsh D, Selkoe D. Amyloid β-protein and beyond: The path forward in Alzheimer's disease. Current Opinion in Neurobiology. 2020;**61**:116-124

[23] Lee V, Goedert M, Trojanowski J. Neurodegenerative tauopathies. Annual Review of Neuroscience. 2001;**24**:1121-1159

[24] Dabir DV, Robinson MB, Swanson E, Zhang B, Trojanowski JQ, Lee VM, et al. Impaired glutamate transport in a mouse model of tau pathology in astrocytes. The Journal of Neuroscience. 2006;**26**:644-654

[25] Parkin GM, Udawela M, Gibbons A, Dean B. Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders. WJP. 2018;**8**(2):51-63

[26] Wood OWG, Yeung JHY, Palpagama TH, Turner C, Waldvogel HJ, Faull RLM, et al. Upregulated excitatory amino acid transporter 1 (EAAT1) expression in the human medial temporal lobe in Alzheimer's disease. Neuroscience. 2025;**566**:87-96

[27] Todd AC, Hardingham GE. The regulation of astrocytic glutamate transporters in health and neurodegenerative diseases. IJMS. 2020;**21**(24):9607

[28] Zoia C, Cogliati T, Tagliabue E, Cavaletti G, Sala G, Galimberti G, et al. Glutamate transporters in platelets: EAAT1 decrease in aging and in Alzheimer's disease. Neurobiology of Aging. 2004;**25**(2):149-157

[29] Li S, Mallory M, Alford M, Tanaka S, Masliah E. Glutamate transporter alterations in Alzheimer disease are possibly associated with abnormal APP expression. Journal of Neuropathology and Experimental Neurology. 1997;**56**(8):901-911

[30] Simpson JE, Ince PG, Lace G, Forster G, Shaw PJ, Matthews F, et al. Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain. Neurobiology of Aging. 2010;**31**(4):578-590

[31] Liu SY, Ma YL, Hsu WL, Lee E. P1-206: Pias1 Ser-503 phosphorylation-mediated Elk-1 Sumoylation promotes neuronal survival in APP/PS1 mice. Alzheimer's & Dementia. 2019;**15**(7S_Part_6):315-316. DOI: 10.1016/j.jalz.2019.06.761

[32] Li SJ, Ma MH, Li JM, Lu XY, Lu CB, Zhou SF, et al. CNTN1 aggravates neuroinflammation and triggers cognitive deficits in male mice by boosting crosstalk between microglia and astrocytes. Aging and Disease. 2023;**14**(5):1853

[33] Han X, Yang L, Du H, Sun Q, Wang X, Cong L, et al. Insulin attenuates beta-amyloid-associated insulin/Akt/EAAT signaling perturbations in human astrocytes. Cellular and Molecular Neurobiology. 2016;**36**(6):851-864

[34] Thai D. Excitatory amino acid transporter EAAT-2 in tangle-bearing neurons in Alzheimer's disease. Brain Pathology. 2002;**12**:405-411

[35] Tamagno E, Guglielmotto M, Vasciaveo V, Tabaton M. Oxidative stress and Beta amyloid in Alzheimer's disease. Which comes first: The chicken or the egg? Antioxidants. 2021;**10**(9):1479

[36] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim S, et al. The amyloid-β pathway in Alzheimer's disease. Molecular Psychiatry. 2021;**26**(10):5481-5503

[37] Bruni A, Bernardi L, Gabelli C. From beta amyloid to altered proteostasis in Alzheimer's disease. Ageing Research Reviews. 2020;**64**:101126

[38] Srivastava A, Das B, Yao A, Yan R. Metabotropic glutamate receptors in Alzheimer's disease synaptic dysfunction: Therapeutic opportunities and Hope for the future. Journal of Alzheimer's Disease. 2020;**78**(4):1345-1361

[39] Onyango I, Jauregui G, Čarná M, Bennett J, Stokin G. Neuroinflammation in Alzheimer's disease. Biomedicine. 2021;**9**(5):524

[40] Liu Y, Si Z, Zou C, Mei X, Li X, Luo H, et al. Targeting neuroinflammation in Alzheimer's disease: From mechanisms to clinical applications. Neural Regeneration Research. 2023;**18**(4):708

[41] Jellinger K. Neuropathological assessment of the Alzheimer spectrum. Journal of Neural Transmission. 2020;**127**(9):1229-1256

[42] Goedert M et al. Tau protein and frontotemporal dementias. In: Frontotemporal Dementias. Cham, Switzerland: Springer; 2021

[43] Muralidar S, Ambi S, Sekaran S, Thirumalai D, Palaniappan B. Role of tau protein in Alzheimer's disease: The prime pathological player. International Journal of Biological Macromolecules. 2020;**163**:1599-1617

[44] Qu L, Sha S, Xing X, Wang T, Li Y, Zhang R, et al. DNA vaccines targeting amyloid-β oligomer ameliorate cognitive deficits of aged APP/PS1/tau triple-transgenic mouse models of Alzheimer's disease. Neural Regeneration Research. 2022;**17**(10):2305

[45] Hashem J, Hu M, Zhang J, Gao F, Chen C, Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. Journal of Neuroinflammation. 2022;**19**(1):206

[46] Traynelis SF et al. Glutamate receptor ion channels: Structure,

regulation, and function. Pharmacological Reviews. 2010;**62**(3):405-496

[47] Hanson JE et al. GluN2A NMDA receptor enhancement improves brain oscillations, synchrony, and cognitive functions in Dravet syndrome and Alzheimer's disease models. Cell Reports. 2020;**30**(2):381-396.e4

[48] Duguid IC. Presynaptic NMDA receptors: Are they dendritic receptors in disguise? Brain Research Bulletin. 2013;**93**:4-9

[49] Zhang Y et al. Dysfunction of NMDA receptors in Alzheimer's disease. Neurological Sciences. 2016;**37**:1039-1047

[50] Takai H et al. Distribution of N-methyl-d-aspartate receptors (NMDARs) in the developing rat brain. Experimental and Molecular Pathology. 2003;**75**(1):89-94

[51] Henson MA et al. Developmental regulation of the NMDA receptor subunits, NR3A and NR1, in human prefrontal cortex. Cerebral Cortex. 2008;**18**(11):2560-2573

[52] Lau CG et al. Regulation of NMDA receptor Ca^{2+} signalling and synaptic plasticity. Biochemical Society Transactions. 2009;**37**(6):1369-1374

[53] Müller T et al. Both NR2A and NR2B subunits of the NMDA receptor are critical for long-term potentiation and long-term depression in the lateral amygdala of horizontal slices of adult mice. Learning & Memory. 2009;**16**(6):395-405

[54] Parsons MP, Raymond LA. Extrasynaptic NMDA receptor involvement in central nervous system disorders. Neuron. 2014;**82**(2):279-293

[55] Talantova M et al. Correction to supporting information for Talantova et al., aβ induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss. Proceedings of the National Academy of Sciences. 2015;**112**(28):3751-3752

[56] Papouin T et al. Synaptic and extrasynaptic NMDA receptors are gated by different endogenous coagonists. Cell. 2012;**150**(3):633-646

[57] Bourne HR, Nicoll R. Molecular machines integrate coincident synaptic signals. Cell. 1993;**72**:65-75

[58] Nevian T, Sakmann B. Single spine Ca^{2+} signals evoked by coincident EPSPs and backpropagating action potentials in spiny stellate cells of layer 4 in the juvenile rat somatosensory barrel cortex. The Journal of Neuroscience. 2004;**24**(7):1689-1699

[59] Hetman M, Kharebava G. Survival signaling pathways activated by NMDA receptors. Current Topics in Medicinal Chemistry. 2006;**6**:787-799

[60] Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nature Reviews Neuroscience. 2009;**10**(9):647-658

[61] Higley MJ, Sabatini BL. Calcium signaling in dendritic spines. Cold Spring Harbor Perspectives in Biology. 2012;**4**(4):a005686-a005686

[62] Volianskis A et al. Long-term potentiation and the role of N -methyl- d -aspartate receptors. Brain Research. 2015;**1621**:5-16

[63] Wang R, Reddy P. Role of glutamate and NMDA receptors in Alzheimer's disease. Journal of Alzheimer's Disease. 2017;**57**(4):1041-1048

[64] Citri A, Malenka RC. Synaptic plasticity: Multiple forms, functions, and mechanisms. Neuropsychopharmacology. 2008;**33**(1):18-41

[65] Granger AJ, Raymond RA. Expression mechanisms underlying long-term potentiation: A postsynaptic view, 10 years on. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014;**369**(1633):20130136

[66] Wolosker H. NMDA receptor regulation by D-serine: New findings and perspectives. Molecular Neurobiology. 2007;**36**(2):152-164

[67] Oliet SHR, Mothet JP. Regulation of N-methyl-d-aspartate receptors by astrocytic d-serine. Neuroscience. 2009;**158**(1):275-283

[68] Mothet JP et al. Time and space profiling of NMDA receptor co-agonist functions. Journal of Neurochemistry. 2015;**135**(2):210-225

[69] Südhof TC. The synaptic vesicle cycle. Annual Review of Neuroscience. 2004;**27**(1):509-547

[70] Rudy CC et al. The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. Aging and Disease. 2015;**6**(2):131

[71] Pal MM. Glutamate: The master neurotransmitter and its implications in chronic stress and mood disorders. Frontiers in Human Neuroscience. 2021;**15**:722323

[72] Henneberger C et al. Long-term potentiation depends on release of d-serine from astrocytes. Nature. 2010;**463**(7278):232-236

[73] Ferreira IL et al. Amyloid Beta peptide 1-42 disturbs intracellular calcium homeostasis through activation of GluN2B-containing N-methyl-d-aspartate receptors in cortical cultures. Cell Calcium. 2012;**51**(2):95-106

[74] Soni N et al. GLT-1 transporter: An effective pharmacological target for various neurological disorders. Pharmacology Biochemistry and Behavior. 2014;**127**:70-81

[75] Mota SI et al. Dysfunctional synapse in Alzheimer's disease—A focus on NMDA receptors. Neuropharmacology. 2014;**76**:16-26

[76] Kamat PK et al. Okadaic acid-induced tau phosphorylation in rat brain: Role of NMDA receptor. Neuroscience. 2013;**238**:97-113

[77] Alberini CM. Transcription factors in long-term memory and synaptic plasticity. Physiological Reviews. 2009;**89**(1):121-145

[78] Du H et al. Cyclophilin D deficiency rescues aβ-impaired PKA/CREB signaling and alleviates synaptic degeneration. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014;**1842**(12):2517-2527

[79] Dieterich DC et al. Caldendrin–Jacob: A protein liaison that couples NMDA receptor signalling to the nucleus. PLoS Biology. 2008;**6**(2):e34

[80] Qin W et al. Regulation of forkhead transcription factor FoxO3a contributes to calorie restriction-induced prevention of Alzheimer's disease-type amyloid neuropathology and spatial memory deterioration. Annals of the New York Academy of Sciences. 2008;**1147**(1):335-347

[81] Dick O, Bading H. Synaptic activity and nuclear calcium signaling protect hippocampal neurons from death signal-associated nuclear translocation

of FoxO3a induced by extrasynaptic N-methyl-d-aspartate receptors. Journal of Biological Chemistry. 2010;**285**(25):19354-19361

[82] Xu J et al. Extrasynaptic NMDA receptors couple preferentially to excitotoxicity via calpain-mediated cleavage of STEP. The Journal of Neuroscience. 2009;**29**(29):9330-9343

[83] Siddiqui AJ et al. Targeting NMDA receptor in Alzheimer's disease: Identifying novel inhibitors using computational approaches. Frontiers in Pharmacology. 2023;**14**:1208968

[84] Song M, Rauw G, Baker G, Kar S. Memantine protects rat cortical cultured neurons against beta-amyloid-induced toxicity by attenuating tau phosphorylation. European Journal of Neuroscience. 2008;**28**(10):1989-2002

[85] Zhang L et al. Tyrosine phosphatase PTP1B impairs presynaptic NMDA receptor-mediated plasticity in a mouse model of Alzheimer's disease. Neurobiology of Disease. 2021;**156**:105402

[86] Huang Y et al. Modulating the balance of synaptic and extrasynaptic NMDA receptors shows positive effects against amyloid-β-induced neurotoxicity. Journal of Alzheimer's Disease. 2017;**57**(3):885-897

[87] Tan T. Others. Low-frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) reverses Aβ1-42-mediated memory deficits in rats. Experimental Gerontology. 2013;**48**(8):786-794

[88] Anderkova L, Rektorova I. Cognitive effects of repetitive transcranial magnetic stimulation in patients with neurodegenerative diseases—Clinician's perspective. Journal of the Neurological Sciences. 2014;**339**(1-2):15-25

[89] Meunier C et al. Contribution of astroglial Cx43 hemichannels to the modulation of glutamatergic currents by D-serine in the mouse prefrontal cortex. The Journal of Neuroscience. 2017;**37**(37):9064-9075

[90] Park SA, Han SM, Kim CE. New fluid biomarkers tracking non-amyloid-β and non-tau pathology in Alzheimer's disease. Experimental & Molecular Medicine. 2020;**52**(4):556-568

[91] Pascoal TA, Aguzzoli CS, Lussier FZ, Crivelli L, Suemoto CK, Fortea J, et al. Insights into the use of biomarkers in clinical trials in Alzheimer's disease. eBioMedicine. 2024;**108**:105322

[92] Tarawneh R. Biomarkers: Our path towards a cure for Alzheimer disease. Biomarker Insights. 2020;**15**:117727192097636

[93] Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J, et al. Current state of Alzheimer's fluid biomarkers. Acta Neuropathologica. 2018;**136**(6):821-853

[94] Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, et al. The future of blood-based biomarkers for Alzheimer's disease. Alzheimer's & Dementia. 2014;**10**(1):115-131

[95] Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease—Preparing for a new era of disease-modifying therapies. Molecular Psychiatry. 2021;**26**(1):296-308

[96] Zhang Y, Zhang Y, Jiang Z, Xu M, Qing K. The effect of EEG and fNIRS in the digital assessment and digital therapy of Alzheimer's disease: A systematic review. Frontiers in Neuroscience. 2023;**17**:1269359