

Wenjing Shi<sup>1,2</sup>  
Jie Bai<sup>2,\*</sup> 

# Glutamatergic Dysregulation in Depression, Schizophrenia, and Addiction: Mechanisms and Therapeutic Strategies

<sup>1</sup>Faculty of Life Science and Technology, Kunming University of Science and Technology, 650500 Kunming, Yunnan, China

<sup>2</sup>Medical School, Kunming University of Science and Technology, 650500 Kunming, Yunnan, China

## Abstract

Glutamate, the principal excitatory neurotransmitter in the brain, plays a central role in neurotransmission, synaptic plasticity, and cognitive function. Dysregulation of glutamatergic signaling is implicated in depression, schizophrenia (SCZ), and addiction. N-methyl-D-aspartate receptor/ $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (NMDAR/AMPA) abnormalities and neuroinflammation disrupt synaptic plasticity in depression. NMDARs hypofunction and cortical excitation-inhibition imbalance are involved in SCZ. Therapeutic strategies targeting the glutamate system, including receptor modulation, glial function restoration, and inflammation control, offer promising avenues for treatment. However, their successful clinical application will require overcoming key obstacles such as disease heterogeneity, the lack of reliable biomarkers for these diseases, and stage-specific pathophysiological differences.

## Keywords

glutamate; depression; schizophrenia; addiction

Submitted: 30 April 2026 Revised: 7 July 2026 Accepted: 11 July 2026 Online First: 23 September 2026

\*Corresponding author details: Jie Bai, Medical School, Kunming University of Science and Technology, 650500 Kunming, Yunnan, China. Email: [jiebai662001@126.com](mailto:jiebai662001@126.com)

## Introduction

The glutamatergic system is one of the primary excitatory neurotransmitter systems in mammals; it plays a role in signal transmission within the brain and supports more complex brain functions such as cognitive processing [1,2]. Glutamate transmission participates in synaptic signaling and neural network activity, serving a crucial role in numerous fundamental biological processes such as neural development, cognition, and behavioral regulation [1,3]. A growing body of evidence suggests that imbalances in glutamate homeostasis are closely linked to the pathophysiological processes underlying various psychiatric and neurodegenerative disorders. This not only highlights the significant theoretical value of the glutamate system in elucidating disease mechanisms but also underscores its importance as a potential therapeutic target.

In recent years, the role of glutamatergic system dysfunction in various mental disorders has attracted increasing attention [4]. Research indicates that conditions such as depression, schizophrenia (SCZ), and addiction are all associated with abnormalities in glutamate receptor function [5]. In summary, alterations in glutamate receptor expression and abnormalities in glutamate transport can trigger excitotoxicity in neural circuits, leading to impairments in emotional, cognitive, and behavioral functions [6]. Particularly in the field of depression, fast-acting antidepressants modulate glutamate receptors and produce significant therapeutic effects; these findings highlight glutamate as a potential therapeutic target for affective disorders [7].

Elucidating the molecular mechanisms underlying glutamatergic dysregulation in these diseases could provide a crucial basis for potential therapeutic strategies targeting the glutamatergic system. This review summarizes the physiological functions of glutamate, explores how glutamatergic dysregulation contributes to the pathogenesis of

depression, SCZ, and addiction, and summarizes emerging therapeutic approaches targeting the glutamatergic system for these disorders. While numerous reviews have examined glutamatergic dysfunction in individual disorders, the present review distinguishes itself by providing a comparative analysis across depression, SCZ, and addiction. Specifically, we focus on synthesizing evidence for shared versus disorder-specific mechanisms of glutamatergic dysregulation (e.g., receptor subunit composition, glial transporter dysfunction, or cross-talk with neuroinflammation). Furthermore, we critically evaluate emerging therapeutic strategies that target the glutamatergic system, with an emphasis on translational challenges and opportunities that are often overlooked in disorder-focused reviews.

## Physiological Role and Regulatory Mechanisms of Glutamate

Glutamatergic signaling is tightly regulated by receptor activation, transporters, and neuron-glial interactions; therefore, it is essential for maintaining synaptic stability and the excitability of neural circuits [8]. It is crucial for the transmission of excitatory signals between neurons, enabling fast communication that is essential for a wide range of brain functions such as sensory processing, motor control, and higher cognitive processes [9]. In particular, glutamate's role in synaptic plasticity underlies learning and memory, making it central to adaptive neural changes [10]. In the nervous system, glutamate exerts its effects mainly through ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) [11]. Ionotropic receptors such as N-methyl-D-aspartate receptors (NMDARs),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), and kainate receptors play a crucial role in fast synaptic transmission and neuronal depolarization [12]. In contrast, mGluRs (e.g., mGluR1/2/3) are involved in the regulation of neurotransmitter release and synaptic long-term plasticity [13].

Glutamate function is not limited to receptor activation; it is also tightly regulated by glutamate transporters. Glutamate transporter proteins, particularly glial glutamate transporter 1/excitatory amino acid transporter 2 (GLT-1/EAAT2), are primarily expressed in astrocytes, where they play a critical role in clearing excess glutamate from the synaptic cleft, preventing excitotoxicity due to overactivation of glutamate receptors [14,15]. The cystine/glutamate antiporter (system Xc<sup>-</sup>) represents a non-redundant heterodimeric antiporter assembled via a disulfide bond between its unique light-chain component solute carrier family 7 member 11 (xCT) and the shared heavy-

chain subunit solute carrier family 3 member 2 (4F2hc, CD98) [16]. In astrocytes, System Xc<sup>-</sup> serves as a major non-vesicular glutamate exporter, critically influencing glutamate homeostasis and excitotoxic thresholds [17]. Dysfunction in system Xc<sup>-</sup> has been implicated in several psychiatric disorders, including addiction disorders and SCZ, reflecting its role in glutamate regulation [18].

## Glutamatergic Mechanisms and Therapeutic Strategies in Depression

### *Glutamate System Alterations in Depression*

In this review, depression refers to the broad spectrum of depressive conditions, while major depressive disorder (MDD) specifically denotes clinically diagnosed MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Recent work points to the fact that glutamatergic dysfunction plays a central role in the pathophysiology of depression. Traditional theories focused on monoaminergic systems (serotonin, dopamine, and norepinephrine) as the primary mechanisms underlying depression [19,20]. NMDARs mediate synaptic plasticity and excitatory neurotransmission, and their dysfunction is closely linked to multiple psychiatric illnesses, including depression [21,22]. SiNiSan (SNS) alleviates depression-like behaviors in the adolescent mouse model by downregulating NMDAR expression and modulating the activities of serotonergic/ $\gamma$ -aminobutyric acid (GABAergic) neurons in the dorsal raphe nucleus (DRN) [23]. Subsequent studies have confirmed that blocking NMDAR at rest can inactivate eukaryotic elongation factor 2 kinase (eEF2K) and inhibit the translation of brain-derived neurotrophic factor (BDNF), thereby producing rapid-acting behavioral antidepressant effects [24,25]. Another study showed that knocking down the glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2B (NR2B) in GABAergic interneurons specifically reversed antidepressant-like behaviors [26].

The mGluRs have become increasingly important in the pathophysiology and treatment of MDD, particularly because they regulate glutamatergic transmission, synaptic plasticity, and stress-related circuit remodeling in a more modulatory manner than iGluRs [27,28]. Among the eight receptor subtypes, mGluR5 has emerged as the most intensively studied target in depression. Recent evidence indicates that mGluR5 is not only involved in chronic stress-related maladaptation, but may also participate in rapid antidepressant signaling [29]. Notably, a study demonstrated that enhancement of endogenous mGluR5 signaling was sufficient to induce rapid antidepressant-like behavioral ef-

fects and synaptic potentiation. At the same time, while pharmacological blockade of mGluR5 prevented ketamine-like responses, suggesting a functional convergence between mGluR5-dependent signaling and rapid antidepressant plasticity pathways [30]. Mechanistically, this effect was linked to calcineurin activation, eukaryotic elongation factor 2 (eEF2) dephosphorylation, and increased BDNF expression [31]. In parallel, dysregulated mGluR5 signaling may contribute to impaired neuroplasticity in depression and mGluR5-directed ligands remain promising candidates for next-generation antidepressant development.

#### *Relationship Between the Glutamate System and Neuroinflammation in Depression*

Neuroinflammation has been shown to contribute significantly to the pathophysiology of depression, and it is thought to exacerbate glutamatergic dysfunction. Inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and C-reactive protein (CRP) can increase glutamate release in the prefrontal cortex (PFC) and hippocampus, further disturbing glutamate signaling and contributing to excitotoxicity [32,33]. Clinical evidence indicates that peripheral blood IL-6 levels are elevated in depressed patients [34], while preclinical studies show that increased TNF- $\alpha$  mediates astrocyte activation via receptor binding, exacerbating depression-like behaviors in chronic unpredictable mild stress (CUMS) mice [35,36]. Astrocytes are vital for maintaining glutamate homeostasis, and their dysfunction has been implicated in the pathophysiology of depression. Among these, astrocytic glutamate transporters (such as GLT-1/EAAT2) are responsible for clearing excess glutamate from the synapse, preventing excitotoxicity [15]. In depression, reduced expression and function of these transporters lead to glutamate spillover and neuronal hyperexcitability.

Astrocytic dysfunction results in impaired glutamate uptake and altered glutamate recycling, exacerbating the glutamate imbalance in depression [37,38]. The connection between neuroinflammation and glutamate dysfunction also highlights the importance of inflammation-related glutamatergic dysregulation in depression [39]. Beyond this, these inflammatory processes contribute to the synaptic loss and neuroplasticity deficits observed in depressive states [40]. These results indicate that glutamatergic dysfunction, neuroinflammation, and neuroplasticity impairments form a complex interplay that exacerbates the symptoms of depression. Understanding the molecular underpinnings of these interactions is central to developing more effective therapeutic interventions for depression.

#### *Glutamate-Mediated Molecular Mechanisms and Therapeutic Strategies in Depression*

Given the above mechanisms, targeting the glutamatergic system has become a major approach for antidepressant discovery in both preclinical studies and clinical applications. Ketamine and its S-enantiomer, esketamine, exemplify rapid-acting antidepressants. Mechanistic research demonstrates that ketamine exerts its effects primarily via noncompetitive antagonism of NMDARs, transiently increasing synaptic glutamate release, which in turn potentiates AMPAR-mediated signaling and activates BDNF-tropomyosin receptor kinase B (TrkB)-mammalian target of rapamycin (mTOR)-dependent synaptogenesis and synaptic plasticity restoration. This cascade accounts for the fast antidepressant action seen within hours [21,41,42]. Clinically, intranasal esketamine has been approved by the Food and Drug Administration (FDA) for treatment-resistant depression. It shows fast efficacy, including in patients unresponsive to conventional antidepressants, although its use necessitates careful monitoring due to potential dissociation, sedation, hypertensive responses, and abuse liability [43,44]. Besides esketamine, the dextromethorphan-bupropion combination has emerged as another glutamatergic-targeted therapy. Dextromethorphan functions as a noncompetitive NMDAR antagonist and sigma-1 receptor agonist, while bupropion inhibits cytochrome P450 2D6 (CYP2D6) to increase dextromethorphan bioavailability, thereby enhancing its antidepressant efficacy [45,46].

Group II mGluR2/3 continue to show a more complex translational profile. Preclinical studies have consistently suggested that mGluR2/3 antagonists or negative allosteric modulators can produce antidepressant-like effects resembling those of ketamine, likely through disinhibition of cortical glutamate transmission and recruitment of downstream AMPA-BDNF signaling [47,48]. However, clinical translation has been less encouraging: a randomized placebo-controlled trial found that the mGluR2/3 negative allosteric modulator decoglurant did not significantly improve symptoms in partially refractory MDD [49]. Beyond groups I and II, group III receptors, especially mGluR7, are receiving increasing attention because of their role in presynaptic regulation of stress reactivity, affective behavior, and emotional learning, although current evidence remains largely preclinical [50]. A series of studies have tested glutamatergic agents in preclinical models and clinical trials for depression, with relevant research progress summarized in Table 1 (Ref. [51–58]).

**Table 1. Studies using glutamatergic agents in preclinical models and clinical trials of depression.**

| Drug                           | Target   | Mechanism of action                             | Principal effect                                                                                                                                                                                                                                     | Development stage | Study subjects                   | References                                             |
|--------------------------------|----------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------|--------------------------------------------------------|
| Ketamine                       | NMDAR    | Noncompetitive antagonism                       | In patients with depression, it produces a rapid antidepressant effect. Preclinical studies suggest that this effect is associated with subsequent AMPAR activation, upregulation of mTOR/BDNF signaling, and enhanced synaptic plasticity.          | Clinical study    | Patients with depression         | Berman <i>et al.</i> [51], Kang <i>et al.</i> [52]     |
| Dextromethorphan/<br>Bupropion | NMDAR    | Noncompetitive NMDAR antagonist                 | In a Phase III randomized, double-blind trial, it demonstrated rapid improvement of depressive symptoms in patients with MDD, with a signal of efficacy emerging as early as week 1 and superior efficacy compared with placebo at week 6.           | Clinical study    | Patients with MDD                | Iosifescu <i>et al.</i> [53]                           |
| Basimglurant                   | mGluR5   | Negative allosteric modulator                   | In a large randomized clinical trial, the primary endpoint did not significantly differ from placebo.                                                                                                                                                | Clinical study    | Patients with MDD                | Quiroz <i>et al.</i> [54]                              |
| Rapastinel (GLYX-13)           | NMDAR    | Positive modulation/partial agonist-like effect | Rapid antidepressant effects lasting ~1 week after a single dose; enhances LTP and increases dendritic spine density in mPFC and hippocampus. However, Phase III trials failed to demonstrate efficacy, leading to discontinued development for MDD. | Clinical study    | Patients with MDD; rodent models | Donello <i>et al.</i> [55], Moskal <i>et al.</i> [56], |
| MGS0039LY341495                | mGluR2/3 | Antagonizes                                     | It exhibits antidepressant-like effects in animal models, and these effects are dependent on AMPAR activation within the mPFC                                                                                                                        | Preclinical study | Rodent models                    | Pałucha-Poniewiera <i>et al.</i> [57]                  |
| MPEP                           | mGluR5   | Antagonizes                                     | It exhibits antidepressant-like effects in multiple rodent models of depression and serves as a classic tool compound for investigating mGluR5-mediated mechanisms                                                                                   | Preclinical study | Rodent models                    | Tatarczyńska <i>et al.</i> [58]                        |

AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; LTP, long-term potentiation; MDD, major depressive disorder; mGluR, metabotropic glutamate receptor; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NMDAR, N-methyl-D-aspartate receptor; MPEP, 2-methyl-6-(phenylethynyl) pyridine. Rapastinel (GLYX-13): an amidated tetrapeptide (Thr-Pro-Pro-Thr-NH<sub>2</sub>) that acts as a glycine site partial agonist and positive allosteric modulator (PAM) of NMDARs.

Together, glutamate-mediated molecular mechanisms associated with depression primarily encompass NMDAR/AMPA dysregulation, aberrant BDNF signaling, impaired astrocytic glutamate homeostasis, and inflammation-associated metabolic pathway disturbances, and the latest literature supports the view that mGluRs are central modulators of depression-relevant synaptic and circuit plasticity, with mGluR5 representing the most promising near-term target, yet the main challenge in this field is translating strong preclinical results into biomarker-driven, subtype-selective therapies for clinically heterogeneous depressive disorders. Such mechanistic insights help to understand depression and offer a rational framework for designing novel, fast-acting antidepressants.

## Glutamatergic Mechanisms and Therapeutic Strategies in SCZ

### *Glutamatergic Mechanisms in SCZ*

SCZ presents with three main symptom categories: positive symptoms such as hallucinations and delusions, negative symptoms like apathy and social withdrawal, and deficits in cognitive function [59]. Growing evidence suggests that glutamatergic dysfunction is central to SCZ pathophysiology. Although the dopamine hypothesis remains highly influential, it does not fully account for the broad clinical spectrum of the disorder, especially negative symptoms and cognitive impairment [60,61]. Conversely, the glutamatergic model offers a more comprehensive account of deficits across psychosis, blunted affect, avolition, and impaired higher cognitive function [62] (Fig. 1).

Among the various glutamate-related hypotheses, NMDAR hypofunction continues to be the most strongly supported. Pharmacological studies have yielded particularly strong evidence: administration of noncompetitive NMDAR antagonists such as phencyclidine (PCP) and ketamine can induce a syndrome in healthy individuals that resembles multiple domains of SCZ, including positive symptoms, negative symptoms, and cognitive deficits [63,64]. These findings strongly back the notion that NMDAR dysfunction is mechanistically relevant rather than merely secondary to chronic illness or medication exposure. Notably, NMDAR hypofunction should not be taken as a consistent reduction in glutamatergic neurotransmission throughout the brain. A more refined model proposes that reduced NMDAR signaling on parvalbumin-positive GABAergic interneurons weakens inhibitory control over cortical pyramidal neurons, which disinhibits glutamatergic neurons and promotes an increase in glutamate release, resulting in the glutamate-induced excitotoxicity [65,66].

The mGluRs have become increasingly important to SCZ, because they regulate glutamate signaling, synaptic plasticity, and neural circuit stability [67]. In this context, mGluRs are important because they can modulate both glutamate transmission and inhibitory control in the cortex. Among different subtypes, mGluR1 and mGluR5 are mainly linked to postsynaptic mechanisms. mGluR1 has been reported to enhance somatostatin interneuron activity in the PFC, suggesting a role in restoring excitation/inhibition balance and improving SCZ-related cognitive deficits [68]. Astrocytic mGluR5 links synaptic activity to mitochondrial energy production, and its dysregulation may contribute to cognitive and neurodevelopmental disorders [69,70]. In addition to its role in cognitive functions, mGluR5 also modulates dopaminergic signaling in the striatum and PFC, which may contribute to the hyperdopaminergic states associated with positive symptoms of SCZ [71,72]. Conversely, mGluR2 and mGluR3 are more intimately linked to presynaptic and modulatory regulation. These receptors can reduce excessive glutamate release and stabilize cortical and thalamocortical activity [73,74]. Following presynaptic activation, mGluR2/3, which are coupled with the G inhibitory/o protein (Gi/o) subunit of the heterotrimeric G-protein, inhibit adenylate cyclase (AC). This inhibition reduces cyclic adenosine monophosphate (cAMP) levels, which in turn suppresses Ca<sup>2+</sup> channel activity, leading to a decrease in the excitability of glutamatergic neurons and consequently attenuating glutamate release [13,75]. Of these, mGluR3 is particularly notable, as the mGluR3 gene has been linked to SCZ risk and cognition-related phenotypes in multiple studies [76,77]. Experimental work also suggests that activation of mGluR3 may rescue synaptic and behavioral abnormalities relevant to SCZ [77].

In 22q11 deletion syndrome (22q11DS), a major genetic risk factor for SCZ, mitochondrial dysfunction is thought to play an important role [78]. In 22q11DS, several deleted genes code for mitochondrial proteins, establishing a connection between mitochondrial dysfunction and the development of SCZ [79]. During the early stages of brain development, astrocytic mGluR5 stimulates mitochondrial biogenesis through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), a process critical for astrocyte maturation, synaptic support, and the establishment of functional circuits. Disruptions in astrocyte maturation, especially in the late-developing PFC, may contribute to the cognitive deficits seen in SCZ [69,80]. Neurons derived from induced pluripotent stem cells (iPSCs) of 22q11DS patients show a compensatory increase in mitochondrial activity even in the absence of SCZ. In contrast, neurons from SCZ patients exhibit decreased adeno-

sine triphosphate (ATP) production. Activation of PGC-1 $\alpha$  restores mitochondrial function, underscoring its protective role [81].

Glutamatergic signaling is critically dependent on astrocytic regulation of extracellular glutamate levels. Astrocytes remove synaptically released glutamate primarily through EAAT1 and EAAT2, thus maintaining synaptic precision and preventing excessive extrasynaptic receptor activation [82]. Compromised astrocytic uptake may therefore contribute to glutamate spillover, altered synaptic integration, and maladaptive plasticity. Previous studies have suggested cell-specific abnormalities in glutamate transporter systems in SCZ [83,84], and recent studies have expanded this view by showing broader disruption of neuron-astrocyte transcriptional programs in the disorder [80]. Rather, glutamatergic dysfunction in SCZ should increasingly be framed within a neuron-glia systems framework.

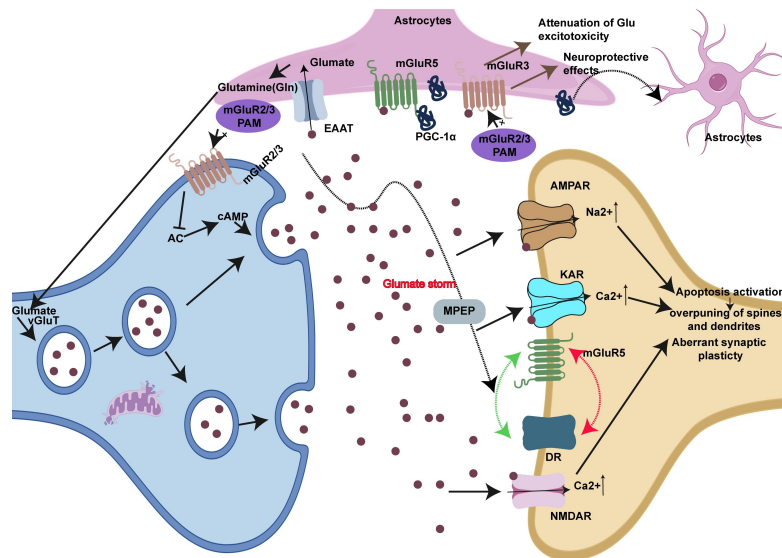
Another layer of complexity comes from neuroimmune regulation of glutamatergic signaling. The kynurenine pathway, which converts tryptophan into diverse neuroactive molecules, provides a critical link between inflammation and glutamatergic transmission [85]. Importantly, kynurenic acid (KYNA) acts as an endogenous antagonist at NMDARs and  $\alpha$ -7 nicotinic acetylcholine receptors, while quinolinic acid (QUIN) can promote excitotoxic glutamatergic activity [86–88]. Meta-analytic data indicate that kynurenine pathway abnormalities are present in SCZ and may differ between central and peripheral compartments [89]. These alterations may be particularly relevant to cognitive impairment and treatment resistance [90]. By regulating NMDAR tone and cholinergic-glutamatergic crosstalk, kynurenine metabolites can shape information processing, attentional control, and synaptic plasticity [87]. This has sparked growing interest in neuroinflammation as a critical mediator of glutamatergic heterogeneity across SCZ subtypes. Thus, glutamatergic interventions have been explored not only as alternative antipsychotic strategies, but also as adjunctive approaches targeting symptom domains that are poorly addressed by current standard treatments. Fig. 1 summarizes the glutamatergic mechanisms in SCZ.

#### *Therapeutic Strategies Targeting the Glutamatergic System in SCZ*

Translational approaches have targeted enhancement of NMDAR signaling via the glycine modulatory site [91]. Agents investigated for this purpose include D-serine, glycine, D-cycloserine, D-alanine, and sarcosine [92]. By increasing co-agonist occupancy at NMDARs, these com-

pounds may partially restore receptor function and improve cortical synaptic plasticity [93]. While early studies yielded promising signals, especially for negative symptoms and cognition, the overall evidence base remains inconsistent [92,94]. Among these compounds, D-serine has continued to attract particular interest due to its endogenous physiological role at the co-agonist site of NMDARs. However, whether D-serine acts as a gliotransmitter or a neuronal cotransmitter remains debated [95]. Yet, its clinical development has been constrained by uncertainty regarding dose-response relationships, interindividual metabolic differences, and the absence of validated biomarkers for treatment selection [96]. Thus, despite strong mechanistic appeal, co-agonist-based NMDAR enhancement has not yet produced a broadly effective clinical intervention. Multiple studies have investigated glutamatergic agents in preclinical models and clinical trials of SCZ, and related research progress is summarized in Table 2 (Ref. [98,108–113]).

Inhibition of glycine transporter 1 (GlyT1) is another approach designed to increase synaptic glycine concentrations and thereby potentiate NMDAR function indirectly [97]. This approach has been deemed particularly attractive for cognitive impairment in SCZ. Among candidate agents, icleperitin (BI 425809) progressed furthest in clinical development [98]. In 6-month Phase III trials, icleperitin failed to reach its primary and key secondary endpoints, with no significant improvement in cognition or functional outcomes versus placebo [99]. The experience with GlyT1 inhibitors highlights a key takeaway: mechanism-based interventions need to be combined with appropriate patient stratification and well-chosen cognitive endpoints to deliver tangible results. Sarcosine is another proven selective GlyT1 inhibitor [100]. D-amino acid oxidase (DAAO), the enzyme responsible for D-serine degradation. By reducing D-serine catabolism, DAAO inhibitors may increase endogenous co-agonist availability for NMDARs. This approach has regained attention in recent years, particularly through compounds such as sodium benzoate and TAK-831 (luvadaxistat) [101,102]. A meta-analysis of randomized controlled trials reported that DAAO inhibitors were associated with improvements in Positive and Negative Syndrome Scale (PANSS) total score, positive symptoms, negative symptoms, and general psychopathology, with additional signals for cognitive benefit [102]. Yet, the evidence remains preliminary. Trial numbers are limited, sample sizes are modest, and the apparent benefit may not generalize across compounds. For example, recent phase 2 data with luvadaxistat did not establish clear efficacy in patients with persistent negative symptoms [103]. Therefore, DAAO inhibition represents a promising yet incompletely validated therapeutic strategy.



**Fig. 1. The glutamate hypothesis of SCZ and modulation through the glutamate receptors.** The core deficit is hypothesized to be NMDAR hypofunction, particularly on GABAergic interneurons. This leads to a state of cortical disinhibition, resulting in an imbalanced E/I ratio within key neural circuits. Aberrant synaptic plasticity and dendritic overpruning may occur as secondary consequences of E/I imbalance. Astrocytes clear synaptic glutamate via EAATs, convert it to glutamine, and recycle it back to presynaptic neurons via vGluT for glutamate resynthesis. In SCZ, mGluR2/3 positive allosteric modulators (PAMs) mitigate glutamatergic dysregulation and promote neuroprotection. Aberrant astrocytic mGluR5 signaling impairs PGC-1 $\alpha$ -mediated mitochondrial biogenesis, disrupting astrocyte maturation and glutamate homeostasis. Neuronal mGluR5 downregulation further reduces NMDAR activity, while mGluR5 antagonists (e.g., MPEP) may restore cognitive function and normalize glutamatergic signaling. NMDAR, N-methyl-D-aspartate receptor; AMPAR,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; EAAT, excitatory amino acid transporter; vGluT, vesicular glutamate transporter; mGluRs, metabotropic glutamate receptors; mGluR2/3, metabotropic glutamate receptor 2/3; mGluR5, metabotropic glutamate receptor 5; mGluR3, metabotropic glutamate receptor 3; PAM, positive allosteric modulator; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; MPEP, 2-methyl-6-(phenylethynyl) pyridine; KAR, kainate receptor; DR, dopamine receptor.

Astrocytic mGluR5 represents a promising therapeutic target across a range of neurological and psychiatric disorders. 2-methyl-6-(phenylethynyl) pyridine (MPEP), have shown potential to reduce synaptic dysfunction, excitotoxicity, and neuroinflammation [104]. A mechanistically distinct glutamatergic strategy aims to reduce excessive presynaptic glutamate release through stimulation of mGluR2/3. This approach was initially attractive because it offered a means of modulating cortical hyperexcitability without directly stimulating iGluRs [105]. The best-characterized example, pomgulated methionil (LY2140023), generated substantial enthusiasm as a possible nondopaminergic antipsychotic. Nonetheless, later-stage studies did not confirm consistent clinical efficacy, and its development was discontinued [106,107].

Glutamatergic dysfunction is now widely regarded as a major component of SCZ pathophysiology. The most robust evidence implicates NMDARs hypofunction, cortical E/I imbalance, circuit-level dysregulation linking glutamatergic and dopaminergic systems, astrocytic impair-

ment in glutamate homeostasis, and neuroimmune modulation through the kynurenine pathway. While therapeutic strategies targeting these mechanisms have not yet yielded a broadly effective alternative to conventional antipsychotic medications, they have markedly advanced our understanding of the disorder and established critical avenues for the future development of novel treatments. The key question is not whether glutamatergic dysfunction is involved in SCZ, but how this pathway can be translated into clinically effective and personalized therapies. The most promising path forward lies in precision-guided, biomarker-informed glutamatergic therapeutics, particularly for negative symptoms and cognitive impairment that remain inadequately addressed by dopamine-centered treatment approaches.

## Glutamatergic Mechanisms and Therapeutic Strategies in Drug Addiction

### Glutamate-Related Molecular Mechanisms and Drug Addiction

**Table 2. Studies using glutamatergic agents in preclinical models and clinical trials of SCZ.**

| Drug                        | Target                                              | Mechanism of action                      | Principal effect                                                                                                                                                                                                     | Development stage | Study subjects                                | References                      |
|-----------------------------|-----------------------------------------------------|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------------|---------------------------------|
| Glycine                     | NMDAR glycine co-agonist site                       | Co-agonism/Enhancement of NMDAR function | In several early-phase studies, improvements were observed in negative symptoms and certain cognitive or overall symptom domains; however, when combined with clozapine, the effect was either diminished or absent. | Clinical study    | Patients with SCZ (early-phase studies)       | Javitt <i>et al.</i> [108]      |
| D-serine                    | Glycine co-agonist site of the NMDAR                | Co-agonist                               | When added to antipsychotic therapy, some studies have demonstrated improvements in positive, negative, and cognitive symptoms.                                                                                      | Clinical study    | Patients with SCZ (adjunct to antipsychotics) | Tsai <i>et al.</i> [109]        |
| Sarcosine (N-methylglycine) | GlyT1 inhibition indirectly enhances NMDAR function | GlyT1 inhibitor                          | In small-scale studies, it has been shown to improve negative and overall symptoms.                                                                                                                                  | Clinical study    | Patients with SCZ                             | Lane <i>et al.</i> [110]        |
| BI 425809 (iclepertin)      | GlyT1 inhibition indirectly enhances NMDAR function | GlyT1 inhibitor                          | It primarily targets cognitive impairment; Phase II studies have shown a signal of cognitive improvement.                                                                                                            | Clinical study    | Patients with SCZ                             | Rosenbrock <i>et al.</i> [98]   |
| LY404039                    | mGluR2/3                                            | Agonist                                  | It exhibits antipsychotic-like effects in animal models induced by phencyclidine (PCP) or amphetamine.                                                                                                               | Preclinical study | Rodent models                                 | Rorick-Kehn <i>et al.</i> [111] |
| CDPPB                       | mGluR5                                              | PAM                                      | It ameliorates MK-801-induced recognition memory deficits, an effect associated with increased phosphorylation of GluR1 and CREB in the PFC and hippocampus.                                                         | Preclinical study | Rodent models                                 | Uslaner <i>et al.</i> [112]     |
| BMS-955829                  | mGluR5                                              | PAM                                      | In rodents, it preserves improvements in set-shifting and novel object recognition, supporting its potential for cognitive enhancement.                                                                              | Preclinical study | Rodent models                                 | Yang <i>et al.</i> [113]        |

CREB, cAMP response element-binding protein; GluR1, glutamate receptor 1 (subtype of AMPA receptor); GlyT1, glycine transporter type 1; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; PAM, positive allosteric modulator; PCP, phencyclidine; SCZ, schizophrenia; CDPPB, 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide; PFC, prefrontal cortex. BI 425809 (iclepertin): an investigational GlyT1 inhibitor for cognitive impairment in SCZ; LY404039: a selective mGluR2/3 agonist (also known as pomaglumetad methionil); MK-801: dizocilpine, a noncompetitive NMDAR antagonist used to induce SCZ-like deficits in animal models.

Addiction is a psychiatric disorder characterized by compulsive substance use, accompanied by intense drug craving that promotes persistent drug-seeking and drug-taking behaviors [114]. These behaviors persist despite severe adverse health outcomes and profound social consequences. Addiction typically arises following repeated drug administration and is modulated by a complex interplay of genetic predisposition and environmental influences [115]. In recent decades, growing attention has been devoted to the role of glutamate. As a ubiquitous excitatory neurotransmitter, glutamate mediates a wide range of physiological functions in the central nervous system [116], and its role in addiction is particularly complex [117]. All these processes are closely intertwined with synaptic plasticity, the capacity of the brain to adapt to external stimuli, which is mainly governed by AMPARs via long-term potentiation (LTP) and long-term depression (LTD) [118]. Notably, both LTP and LTD are precisely modulated by metaplasticity, a higher-order regulatory process that governs synaptic plasticity dynamics. Robust dopamine release elicited by addictive drugs within mesocorticolimbic circuits is thought to trigger enduring neuroadaptations, establishing a persistent drug-associated memory that progressively strengthens addiction-related behaviors [119]. Repeated drug exposure alters both the AMPA/NMDA current ratio and glutamate receptor subunit composition, indicating that excitatory synapses are not simply strengthened, but are fundamentally reprogrammed in a manner that favors maladaptive behavioral output [120].

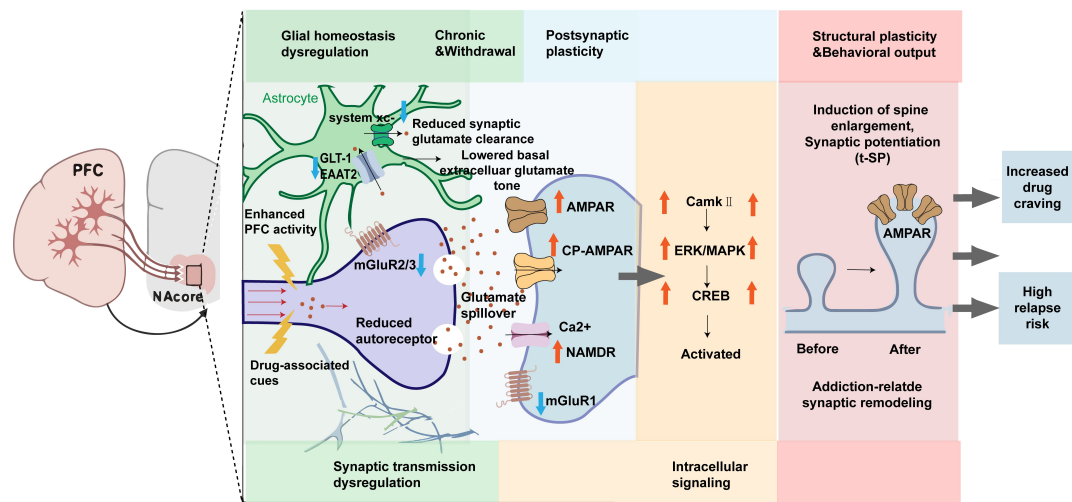
Accumulating evidence indicates that drug addiction is not merely a consequence of dysregulated dopaminergic reward signaling, but also a disorder of persistent glutamatergic maladaptation within the corticostriatal circuitry, particularly the projection from the PFC to the nucleus accumbens core (NAcore) (Fig. 2). Within this framework, impaired glutamate homeostasis is viewed as a core pathological event that diminishes top-down executive control over drug seeking and promotes cue-induced craving and relapse [121,122]. This does not merely reflect enhanced excitatory transmission, and addiction-related glutamatergic dysfunction involves coordinated alterations in astrocyte-dependent glutamate clearance, extrasynaptic glutamate tone, receptor composition, intracellular signaling, and structural synaptic plasticity [121,123].

Following prolonged exposure to addictive drugs such as cocaine, the expression or function of the primary glutamate transporters GLT-1/EAAT2 and system Xc<sup>-</sup> is decreased in the nucleus accumbens, leading to impaired glutamate clearance and dysregulated extracellular glutamate levels. This impairment decreases basal extrasynaptic glutamate levels while simultaneously weakening the capac-

ity of the perisynaptic environment to buffer transient increases in synaptic glutamate [124–126]. This glutamate spillover is now regarded as a key molecular trigger linking drug-associated cues to relapse-related synaptic events in the NAcore [125].

mGluR1 signaling in the NAcore appears to function as a brake on pathological synaptic maturation. Notably, reduced surface expression and activity of mGluR1 precede the accumulation of Ca<sup>2+</sup>-permeable AMPA receptors (CP-AMPA) during withdrawal, thereby facilitating the progression of such pathological changes [127,128]. In contrast, pharmacological enhancement of mGluR1 signaling can remove CP-AMPA from accumbal synapses and attenuate cue-induced cocaine craving, indicating that mGluR1 underlies addiction-related plasticity and represents a potential therapeutic target [129]. Conversely, presynaptic mGluR2/3 receptors act primarily through negative feedback mechanisms to suppress glutamate release. When chronic drug exposure lowers basal extrasynaptic glutamate levels, tonic activation of mGluR2/3 is reduced, thereby weakening presynaptic inhibitory control and enabling greater glutamate release during reinstatement [130,131]. This loss of presynaptic restraint further amplifies relapse-associated glutamatergic transmission within the PFC-NAcore pathway [132].

NMDARs also contribute to addiction-related glutamatergic plasticity by modulating Ca<sup>2+</sup>-dependent plasticity thresholds and downstream signaling cascades. Drug self-administration and withdrawal have been associated with changes in NMDAR subunit expression in the nucleus accumbens, which may influence coincidence detection, synaptic strengthening, and the persistence of drug-associated memory traces [133–135]. At the intracellular level, CaMKII, extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK), and cAMP response element-binding protein (CREB) are widely recognized as core effectors of glutamate-dependent neuroplasticity in addiction. Ca<sup>2+</sup> entry through AMPARs and NMDARs activates kinase cascades that regulate receptor phosphorylation, trafficking, cytoskeletal organization, and postsynaptic density assembly [136]. These events in turn modulate transcriptional programs involving immediate early genes and plasticity-related proteins, thereby translating repeated drug exposure into long-lasting molecular and structural adaptations [137]. Thus, glutamatergic dysregulation in addiction should be understood not only as aberrant neurotransmission, but also as a mechanism that drives durable synaptic and transcriptional reprogramming [138]. These molecular changes are accompanied by structural plasticity at the synaptic level. During cue-induced relapse, MSNs in the NAcore undergo a form



**Fig. 2. Schematic of addiction-related synaptic remodeling in the PFC-NAcore pathway.** This figure illustrates the molecular and cellular mechanisms underlying glutamatergic dysregulation in addiction, with a focus on the PFC-NAcore pathway. Astrocytes and glutamate transporters, including GLT-1/EAAT2 and system Xc<sup>-</sup>, are critical for preserving glutamate homeostasis. Chronic drug exposure impairs these transporters, leading to reduced glutamate clearance, lower basal extracellular glutamate levels, and weakened synaptic buffering capacity. This leads to glutamate spillover, activating presynaptic and postsynaptic mGluR1 and mGluR2/3, and further disrupting autoreceptor-mediated feedback control. As a result, postsynaptic activity is aberrantly enhanced, triggering extrasynaptic signaling pathways that mediate relapse-related behaviors. Chronic drug exposure also leads to reduced autoreceptor activity, causing abnormal activation of AMPA receptors and CP-AMPA receptors in MSNs within the NAcore. This activation, together with Ca<sup>2+</sup> influx via NMDA receptors, initiates intracellular signaling cascades, including the ERK/MAPK and CREB pathways. These pathways drive synaptic plasticity and structural changes, such as dendritic spine enlargement, which are linked to increased drug craving and relapse risk. The induction of t-SP in the NAcore, which strengthens drug-related synaptic responses and correlates with heightened drug-seeking behavior. This plastic remodeling contributes to the formation of addiction-related memories and the long-term persistence of drug craving. AMPAR,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CP-AMPA, Ca<sup>2+</sup>-permeable AMPA receptor; EAAT2, excitatory amino acid transporter 2; mGluR2/3, metabotropic glutamate receptor 2/3; mGluR1, metabotropic glutamate receptor 1; mGluR3, metabotropic glutamate receptor 3; PAM, positive allosteric modulator; t-SP, transient synaptic potentiation; PFC, prefrontal cortex; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NAcore, nucleus accumbens core; GLT-1, glutamate transporter 1.

of transient synaptic potentiation (t-SP), characterized by increased dendritic spine head diameter, enhanced AMPA-mediated transmission, and rapid strengthening of excitatory synapses. This relapse-associated t-SP depends on glutamate spillover from corticostriatal afferents and correlates with the intensity of reinstatement behavior, supporting the view that it is a mechanistic component of relapse rather than an epiphenomenon [139,140].

Taken together, these findings support a mechanistic cascade in which astrocytic transporter dysfunction and impaired system Xc<sup>-</sup> activity lead to reduced glutamate homeostasis, excessive glutamate spillover, abnormal AMPAR/NMDAR/mGluR signaling, activation of intracellular plasticity pathways, and ultimately craving incubation and relapse vulnerability.

### Glutamate-Mediated Molecular Mechanisms in Drug Addiction and Therapeutic Strategies

Building on these findings regarding molecular mechanisms, glutamate-targeted interventions have emerged as a promising therapeutic strategy for substance use disorders (SUDs) [141]. Rather than globally suppressing excitatory transmission, these interventions aim to restore glutamate homeostasis, normalize receptor-dependent plasticity, and dampen relapse-associated synaptic reactivity. Restoring glutamate balance via modulation of glutamate transporters and receptors represents a viable therapeutic strategy to prevent reinstatement of drug-seeking behavior in preclinical models [122]. Current glutamatergic therapeutic approaches can be broadly classified into three categories: (i) agents that restore astrocyte-synapse glutamate homeostasis, (ii) agents that modulate ionotropic or mGluRs, and (iii) compounds that indirectly reshape

glutamate-dependent plasticity. These strategies aim to reestablish proper glutamatergic function, thereby reducing relapse and promoting long-term recovery [142]. Studies using glutamatergic agents in preclinical models and clinical trials of addiction are summarized in Table 3 (Ref. [147,155–157]).

Another therapeutic strategy involves enhancing glutamate uptake to normalize the perisynaptic environment. Ceftriaxone has garnered considerable interest because it upregulates GLT-1 expression and improves glutamate clearance in the NAc, which restores glutamate homeostasis and normalizes synaptic transmission [143]. In animal studies, ceftriaxone has been demonstrated to reduce reinstatement-like behavior induced by various drugs of abuse, highlighting its potential in treating SUDs [144]. However, the translational value of ceftriaxone in clinical addiction treatment remains uncertain, largely owing to its antibiotic properties and the lack of direct long-term clinical application. The therapeutic significance of ceftriaxone lies in validating GLT-1 upregulation as a relevant mechanism, instead of in immediate clinical application [145].

Targeting mGluRs represents another promising pharmacological strategy. Because mGluR2/3 inhibit glutamate release through presynaptic negative feedback, restoring their function may help attenuate the excessive glutamatergic drive linked to relapse [146]. Preclinical studies have demonstrated that the mGluR2/3 agonist LY379268 reduces cue-induced reinstatement of cocaine seeking, suggesting that re-establishing presynaptic inhibition of glutamate release can be an effective anti-relapse strategy [147,148]. Chronic exposure to alcohol and other addictive substances has been shown to reduce mGluR2 expression and function, indicating that interventions targeting mGluR2 may have broad applicability across multiple SUDs [149]. The mGluR1-targeted interventions more directly counteract pathological postsynaptic plasticity. Activation of mGluR1 promotes the removal of CP-AMPA receptors from accumbal synapses, which may help reverse the synaptic adaptations underlying the incubation of craving [150]. Preclinical evidence suggests that mGluR2/3-directed therapies are more likely to reduce glutamate release, while mGluR1-directed therapies may reset the pathological state of excitatory synapses themselves. These two strategies target distinct but complementary stages in the relapse cascade [131,151].

In recent years, ketamine and other NMDAR-modulating interventions have been investigated as potential treatments for SUDs. Initial evidence suggests that ketamine may influence maladaptive reward learning and synaptic plasticity through rapid glutamatergic remodel-

ing, though existing research is limited by small sample sizes and heterogeneous study designs [42,152]. In animal models of addiction, glutamatergic interventions offer an important therapeutic framework distinct from traditional dopamine or opioid based approaches. The primary advantage of these strategies lies in their direct targeting of relapse vulnerability, cue-induced craving, and maladaptive synaptic plasticity—all of which are central features of the chronic and recurrent nature of addiction [153,154]. Future advances will likely depend on stratified treatment strategies that account for substance type, abstinence status, relapse risk, and circuit-level neurobiological phenotypes, as well as combining glutamatergic agents with behavioral or other pharmacological therapies. In this regard, glutamate-targeted therapies hold value not merely through novel pharmacological candidates, but by redefining addiction treatment as the restoration of pathological neuroplasticity, instead of simply dampening reward or withdrawal symptoms.

## Challenges in Translating Glutamatergic Therapies

Despite strong theoretical rationale and promising preclinical data, the translation of glutamatergic therapies into approved treatments for psychiatric and neurodegenerative disorders has been exceptionally difficult. Several glutamate-targeted compounds have failed in late-phase clinical trials, highlighting critical gaps between preclinical models and patient outcomes.

### *Disease Heterogeneity and Lack of Patient Stratification*

Psychiatric diagnoses such as SCZ are clinical syndromes that encompass significant biological heterogeneity. Recent genome-wide association studies have demonstrated that these disorders are the product of complex genetics involving hundreds of risk genes, indicating that current diagnostic labels encompass many etiologically distinct conditions [158,159]. This heterogeneity likely underlies the failure of multiple late-phase clinical trials of glutamatergic drugs. A notable example is pomaglumetad methionil, an mGluR2/3 agonist that failed to meet primary endpoints in Phase III SCZ trials [107]. However, subsequent analysis of machine-learning models applied to electroencephalography (EEG) data from these failed trials identified a subgroup of patients who had responded substantially to the drug, with accuracy rates over 90%, suggesting that the efficacy signal was diluted by non-responders who did not share the same underlying glutamatergic pathology [160]. As a 2024 review concluded, the

| Drug             | Addiction type                  | Mechanism of action                                 | Principal effect                                                                                                               | Development stage | Study subjects | References                    |
|------------------|---------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------|-------------------------------|
| N-acetylcysteine | Cocaine dependence              | Indirectly modulating mGluR2/3 and mGluR5 pathways. | In animals, it reduces reinstatement-like behavior.                                                                            | Preclinical study | Humans         | Kupchik <i>et al.</i> [155]   |
| Memantine        | Opioid dependence               | NMDAR noncompetitive antagonist                     | It can attenuate the expression of physical opioid dependence and withdrawal in humans.                                        | Clinical study    | Humans         | Bisaga <i>et al.</i> [156]    |
| D-cycloserine    | Nicotine dependence             | NMDAR                                               | It attenuates reactivity to smoking cues and appears to preferentially facilitate extinction learning or cue exposure therapy. | Clinical study    | Humans         | Santa Ana <i>et al.</i> [157] |
| LY379268         | Cocaine/Nicotine re-instatement | mGluR2/3                                            | It inhibits conditioned reinstatement and certain forms of self-administration behavior.                                       | Preclinical study | Rodent models  | Baptista <i>et al.</i> [147]  |

mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor. LY379268: a selective orthosteric agonist of mGluR2/3 receptors. N-acetylcysteine: a prodrug of cysteine and precursor to glutathione; its effects on glutamatergic signaling are mediated in part through modulation of mGluR2/3 and mGluR5. D-cycloserine: a partial agonist at the glycine-binding site of the NMDAR, used experimentally to facilitate fear extinction and cue-exposure therapy in addiction.

definition of the responsive subject population and development of response-predicting biomarkers are among the main avenues for further research in targeting glutamatergic receptors [161].

#### *Absence of Validated Target-Engagement Biomarkers*

A key limitation for glutamate-based treatment development is the lack of functional biomarkers to verify that investigational drugs engage their intended targets in the human brain. A randomized clinical trial evaluated three potential imaging-based biomarkers—pharmacological blood oxygenation level dependent (pharmacobOLD), proton magnetic resonance spectroscopy ( $^1\text{H}$  MRS), and task-based fMRI—for detecting ketamine-induced changes in brain glutamate function [162]. The results demonstrated that pharmacobOLD produced a highly robust and consistent response across study sites, with a very large effect size (Cohen  $d = 5.4$ ), supporting its utility for definitive assessment of functional target engagement. In contrast,  $^1\text{H}$  MRS showed only a small but significant signal (Cohen  $d = 0.64$ ), while task-based fMRI failed to detect any significant differences [162]. The lack of validated target-engagement biomarkers has hampered translation between preclinical and early-stage clinical studies, making it difficult to determine whether a failed trial reflects an invalid mechanism, an inadequate compound, or simply insufficient target exposure.

#### *Disease Stage-Dependent Glutamatergic Dysfunction*

Glutamatergic abnormalities evolve with disease progression, yet most clinical trials fail to stratify patients by illness stage. In SCZ, elevated glutamatergic metabolites are most consistently observed in early psychosis, while chronic illness often shows normal or reduced levels [163]. Depression may similarly show stage-dependent glutamatergic involvement [164]. Including patients across different stages without stratification likely obscures treatment signals and contributes to failed trials.

#### *Dose-Limiting Side Effects*

The widespread expression of glutamate receptors creates a narrow therapeutic window for most glutamatergic agents. Non-selective NMDAR antagonists produce psychotomimetic effects, sedation, and cognitive impairment [62]. AMPAR positive allosteric modulators carry proconvulsant risks [165]. mGluR5 negative allosteric modulators have shown dose-limiting dizziness and somnolence [166].

Separating desired therapeutic effects from on-target side effects mediated by the same receptors in different brain circuits remains a fundamental challenge. Subtype-selective agents and peripheral-restricted compounds offer partial solutions, but chronic modulation of glutamatergic signaling inevitably risks disrupting normal cognitive and synaptic function.

Collectively, without biomarkers to confirm target engagement and without validated methods to identify responsive patient subgroups, the glutamatergic field continues to struggle to translate decades of preclinical research into clinical success.

## **Conclusions**

This review has synthesized evidence demonstrating that glutamatergic dysregulation is a central, transdiagnostic mechanism spanning depression, SCZ, and drug addiction. Despite their distinct clinical presentations, these three disorders share a core set of interconnected pathologies: disrupted glutamate homeostasis, aberrant ionotropic and metabotropic receptor signaling, impaired astrocytic clearance and metabolic support, and a self-perpetuating cycle of neuroinflammation and excitotoxicity. Across all conditions, the delicate balance between synaptic and extrasynaptic glutamate signaling is disrupted, leading to impaired neuroplasticity that compromises emotional regulation, cognitive function, and behavioral control.

However, the nature of glutamatergic dysfunction is critically disease-specific. In depression, chronic stress drives NMDAR overactivation and neuroinflammatory cascades that compromise AMPAR trafficking and BDNF signaling, producing synaptic weakening and dendritic spine loss in prefrontal and hippocampal circuits. SCZ involves a fundamentally different mechanism: NMDAR hypofunction on parvalbumin-positive GABAergic interneurons disinhibits cortical pyramidal neurons, creating a glutamate excitotoxicity and excitation-inhibition imbalance that disrupts network oscillations and downstream dopaminergic signaling. Addiction is characterized by drug-induced downregulation of astrocytic glutamate transporters and system  $\text{Xc}^-$  in the nucleus accumbens, leading to glutamate spillover, pathological accumulation of  $\text{Ca}^{2+}$ -permeable AMPAR, and synaptic metaplasticity that encodes persistent craving and relapse vulnerability.

The translational history of glutamatergic therapies reveals several common reasons for the gap between preclinical promise and clinical outcomes. First, many agents strongly engage their molecular target, such as NMDAR co-

agonists or mGluR2/3 agonists, yet fail to produce meaningful clinical improvement, often because the downstream circuit consequences in the intact human brain remain incompletely understood. Second, profound patient heterogeneity means that the same intervention may normalize hyperglutamatergic tone in one individual while worsening hypofunction in another. Third, compensatory neuroadaptations can counteract therapeutic effects over time as homeostatic mechanisms resist the induced pharmacological change. Fourth, glutamatergic agents typically have narrow therapeutic windows, where insufficient modulation yields no benefit but excessive modulation impairs physiological plasticity, producing cognitive or psychotomimetic side effects. Finally, the absence of validated biomarkers prevents the stratification of patients most likely to benefit from a given intervention.

Addressing these challenges requires several interconnected strategies. Clinically deployable biomarkers are urgently needed, including advanced magnetic resonance spectroscopy, positron emission tomography (PET) ligands for specific receptor subtypes, and EEG-based indices of excitation-inhibition balance to guide patient selection and monitor target engagement. Pharmacologically, the field should move toward subtype-selective allosteric modulators for specific mGluRs and NMDAR/AMPA subunits, as these offer greater precision than broad-acting orthosteric agents. Multi-target approaches that simultaneously address receptor dysfunction, astrocytic homeostasis, and neuroinflammation may better reflect the inherently multimodal nature of glutamatergic pathology. Integration of pharmacological strategies with circuit-based interventions such as repetitive transcranial magnetic stimulation, which can prime or consolidate plasticity, represents another promising avenue. Preclinical models must better align with the chronic, stage-dependent nature of human disease by incorporating disease-relevant genetic backgrounds and clinically meaningful endpoints. Ultimately, the success of glutamatergic therapeutics will depend on precision psychiatry frameworks that integrate clinical phenotyping, neuroimaging, genetics, and biomarkers to match the right glutamatergic agent to the right patient at the right stage of illness, thereby fulfilling the considerable promise of targeting this system across the spectrum of psychiatric and neurodegenerative disorders.

### Availability of Data and Materials

Not applicable.

### Author Contributions

WJS: Conceptualization, Data curation, Investigation, Writing—original draft, Visualization; JB: Conceptualization, Supervision, Writing—review and editing, Funding acquisition. Both authors reviewed the manuscript. All authors gave final approval of the version to be published. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

### Ethics Approval and Consent to Participate

Not applicable.

### Acknowledgment

Not applicable.

### Funding

This study was supported by the National Natural Science Foundation of China (No. 82371271), the innovation team of stress and defense of Yunnan Province (202305AS350011).

### Conflict of Interest

The authors declare no conflict of interest.

### References

- [1] Gao K, Cheung-Hoi Yu A. Glutamate, a Key for Astrocytes to Participate in Brain Function and Diseases. *Neurochemical Research*. 2025; 50: 166. <http://doi.org/10.1007/s11064-025-04418-7>.
- [2] Wierońska JM, Stachowicz K. Special issue: Glutamate—physiology, pathology, therapy. *Pharmacological Reports*. 2024; 76: 1197–1198. <http://doi.org/10.1007/s43440-024-00670-w>.
- [3] Wennagel D, Charrier C. Trans-synaptic functions of non-canonical ionotropic glutamate receptors in circuit wiring and plasticity. *Current Opinion in Neurobiology*. 2025; 93: 103053. <http://doi.org/10.1016/j.conb.2025.103053>.
- [4] Ma L, Ma X, Huang W, Wang J, Yue S, Xu L, *et al.*  $\gamma$ -Aminobutyric acid and glutamate dysregulation in the dorsolateral prefrontal cortex of adolescents with first-episode major depressive disorder and the modulatory effects of repetitive transcranial magnetic stimulation.

- Psychoradiology. 2026; 6: kkaf034. <http://doi.org/10.1093/psyrad/kkaf034>.
- [5] Parker N, Koch E, Shadrin AA, Fuhrer J, Hindley GFL, Stinson SE, *et al.* Leveraging the genetics of psychiatric disorders to prioritize potential drug targets and compounds. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*. 2026; 51: 1300–1309. <http://doi.org/10.1038/s41386-026-02380-8>.
  - [6] Górska AM, Santos-García I, Kvasnička A, Dobešová D, Friedecký D, Gildenblat J, *et al.* ABCA7 deficiency exacerbates glutamate excitotoxicity in Alzheimer's disease mice—A new pharmacological target for Glu-related neurotoxicity. *Progress in Neurobiology*. 2026; 259: 102891. <http://doi.org/10.1016/j.pneurobio.2026.102891>.
  - [7] Nakajima W, Hatano M, Ohtani Y, Tani H, Yatomi T, Tsuchimoto S, *et al.* The dynamics of AMPA receptors underlies the efficacy of ketamine in treatment resistant patients with depression. *Molecular Psychiatry*. 2026; 31: 3801–3810. <http://doi.org/10.1038/s41380-026-03510-w>.
  - [8] Mancuso M, Mezzalana F, Vignoli B, Greotti E. Mitochondrial Ca<sup>2+</sup> Signaling at the Tripartite Synapse: A Unifying Framework for Glutamate Homeostasis, Metabolic Coupling, and Network Vulnerability. *Biomolecules*. 2026; 16: 171. <http://doi.org/10.3390/biom16010171>.
  - [9] de León-López CAM, Carretero-Rey M, Khan ZU. AMPA Receptors in Synaptic Plasticity, Memory Function, and Brain Diseases. *Cellular and Molecular Neurobiology*. 2025; 45: 14. <http://doi.org/10.1007/s10571-024-01529-7>.
  - [10] Vardalaki D, Yaeger CE, Harnett MT. Silent Synapses in the Adult Brain. *Annual Review of Neuroscience*. 2025; 48: 169–189. <http://doi.org/10.1146/annurev-neuro-112723-032924>.
  - [11] Brunetti V, Soda T, Berra-Romani R, De Sarro G, Guerra G, Scarpellino G, *et al.* Two Signaling Modes Are Better than One: Flux-Independent Signaling by Ionotropic Glutamate Receptors Is Coming of Age. *Biomedicines*. 2024; 12: 880. <http://doi.org/10.3390/biomedicines12040880>.
  - [12] Vialko A, Chałupnik P, Szymańska E. Positive AMPA and Kainate Receptor Modulators and Their Therapeutic Potential in CNS Diseases: A Comprehensive Review. *International Journal of Molecular Sciences*. 2025; 26: 6450. <http://doi.org/10.3390/ijms26136450>.
  - [13] Barone A, Vellucci L, Nasti A, Mazza B, Iannotta F, Iasevoli F, *et al.* Glutamate Metabotropic Receptors-Linked Postsynaptic Density Proteins: An Emergent Hub for Antipsychotics' Regulation of Synaptic Plasticity and Metaplasticity. *Biomolecules*. 2026; 16: 324. <http://doi.org/10.3390/biom16020324>.
  - [14] Zhang Y, Liu W, Huang T, Liu L, Chen X. Neuroprotective role of GLT-1/EAAT2 in glutamate-induced excitotoxicity. *Behavioural Brain Research*. 2025; 495: 115804. <http://doi.org/10.1016/j.bbr.2025.115804>.
  - [15] Zhang G, Huang S, Wei M, Wu Y, Wang J. Excitatory Amino Acid Transporters as Therapeutic Targets in the Treatment of Neurological Disorders: Their Roles and Therapeutic Prospects. *Neurochemical Research*. 2025; 50: 155. <http://doi.org/10.1007/s11064-025-04400-3>.
  - [16] Lin W, Wang C, Liu G, Bi C, Wang X, Zhou Q, *et al.* SLC7A11/xCT in cancer: biological functions and therapeutic implications. *American Journal of Cancer Research*. 2020; 10: 3106–3126.
  - [17] Chen Y, Xiao W, Qian C, Huang L, Lv J, Wang Z, *et al.* System Xc<sup>−</sup> pathway as a potential regulatory target in neurological disorders. *Frontiers in Pharmacology*. 2026; 16: 1701320. <http://doi.org/10.3389/fphar.2025.1701320>.
  - [18] Bridges R, Lutgen V, Lobner D, Baker DA. Thinking outside the cleft to understand synaptic activity: contribution of the cystine-glutamate antiporter (System Xc<sup>−</sup>) to normal and pathological glutamatergic signaling. *Pharmacological Reviews*. 2012; 64: 780–802. <http://doi.org/10.1124/pr.110.003889>.
  - [19] Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012; 62: 63–77. <http://doi.org/10.1016/j.neuropharm.2011.07.036>.
  - [20] Carmellini P, Pinzi M, Rescaili MB, Cuomo A. The Connectomic Glutamate Framework for Depression: Bridging Molecular Plasticity and Network Reorganization. *Brain Sciences*. 2025; 16: 8. <http://doi.org/10.3390/brainsci16010018>.
  - [21] Chen M, Jin J, Bi H, Zhang Y, Sun M, Li X, *et al.* Advances in the study of NMDA receptors in depression pathogenesis and the antidepressant efficacy of their antagonists. *Asian Journal of Psychiatry*. 2025; 108: 104502. <http://doi.org/10.1016/j.ajp.2025.104502>.
  - [22] Comai S, De Martin S, Mattarei A, Guidetti C, Pappagallo M, Folli F, *et al.* N-methyl-D-aspartate Receptors and Depression: Linking Psychopharmacology, Pathology and Physiology in a Unifying Hypothesis for the Epigenetic Code of Neural Plasticity. *Pharmaceuticals*. 2024; 17: 1618. <http://doi.org/10.3390/ph17121618>.
  - [23] Cao K, Zhong J, Wang S, Shi Y, Bai S, Zhao J, *et al.* SiNiSan exerts antidepressant effects by modulating serotonergic/GABAergic neuron activity in the dorsal raphe nucleus region through NMDA receptor in the adolescent depression mouse model. *Journal of Ethnopharmacology*. 2024; 328: 118040. <http://doi.org/10.1016/j.jep.2024.118040>.
  - [24] Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, *et al.* NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; 475: 91–95. <http://doi.org/10.1038/nature10130>.
  - [25] Suzuki K, Monteggia LM. The role of eEF2 kinase in the rapid antidepressant actions of ketamine. *Advances in Pharmacology*. 2020; 89: 79–99. <http://doi.org/10.1016/bs.apha.2020.04.005>.
  - [26] Gerhard DM, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, *et al.* GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *The Journal of Clinical Investigation*. 2020; 130: 1336–1349. <http://doi.org/10.1172/jci130808>.
  - [27] Pałucha-Poniewiera A. Modulation of Metabotropic Glutamate Receptors as a Strategy to Improve the Efficacy and Safety of Ketamine as an Antidepressant. *Cells*. 2025; 14: 1967.
  - [28] He C, Zhang J, Wang J, Zhu G, Yang S. Metabotropic glutamate receptor 5 in depression: Mechanisms and therapeutic potential. *European Journal of Medicinal Chemistry*. 2025; 297: 117976. <http://doi.org/10.1016/j.ejmech.2025.117976>.
  - [29] Elmeseiny OSA, Müller HK. A molecular perspective on mGluR5 regulation in the antidepressant effect of ketamine. *Pharmacological Research*. 2024; 200: 107081. <http://doi.org/10.1016/j.phrs.2024.107081>.
  - [30] McCarthy CI, Zack Ma Z, Monteggia LM, Kavalali ET. Spontaneous glutamate release activates mGluR signaling to drive rapid antidepressant responses. *Proceedings of the National Academy of Sciences*.

- ences of the United States of America. 2025; 122: e2510642122. <http://doi.org/10.1073/pnas.2510642122>.
- [31] Pałucha-Poniewiera A, Rafał-Ulińska A, Santocki M, Babii Y, Kaczorowska K. Partial mGlu<sub>5</sub> receptor NAM, M-5MPEP, induces rapid and sustained antidepressant-like effects in the BDNF-dependent mechanism and enhances (R)-ketamine action in mice. *Pharmacological Reports: PR*. 2024; 76: 504–518. <http://doi.org/10.1007/s43440-024-00588-3>.
- [32] Pinzi M, Fagiolini A, Koukouna D, Gualtieri G, Rescalli MB, Pierini C, *et al.* Inflammatory and Immune Biomarkers in Mood Disorders: From Mechanistic Pathways to Clinical Translation. *Cells*. 2025; 14: 1558. <http://doi.org/10.3390/cells14191558>.
- [33] Zhang N, Han K, Sheng L, Wang F, He M, Wu M, *et al.* Neuropharmacological Insights into Glutamate Homeostasis in Post-stroke Depression Regulated by Astrocytes. *Current Neuropharmacology*. 2026; 24: 601–611. <http://doi.org/10.2174/011570159x379476250611052236>.
- [34] Schmitz CN, Sammer G, Neumann E, Blecker C, Gründer G, Adolphi H, *et al.* Functional resting state connectivity is differentially associated with IL-6 and TNF- $\alpha$  in depression and in healthy controls. *Scientific Reports*. 2025; 15: 1769. <http://doi.org/10.1038/s41598-025-85514-0>.
- [35] Gao M, Song Y, Liu Y, Miao Y, Guo Y, Chai H. TNF- $\alpha$ /TNFR1 activated astrocytes exacerbate depression-like behavior in CUMS mice. *Cell Death Discovery*. 2024; 10: 220. <http://doi.org/10.1038/s41420-024-01987-4>.
- [36] Chai H, Zhao K, Hu W, Liu B. Wogonin Mitigates Depression by Inhibiting TNF- $\alpha$ /TNFR1/CXCL1 Signalling-Mediated Astrocyte Activation. *Journal of Cellular and Molecular Medicine*. 2026; 30: e71116. <http://doi.org/10.1111/jcmm.71116>.
- [37] Guo F, Fan J, Liu JM, Kong PL, Ren J, Mo JW, *et al.* Astrocytic ALKBH5 in stress response contributes to depressive-like behaviors in mice. *Nature Communications*. 2024; 15: 4347. <http://doi.org/10.1038/s41467-024-48730-2>.
- [38] White AJ, Robinson JL, Wilson AE, Reid MA. Neurometabolites of the anterior cingulate cortex (ACC) in major depressive disorder (MDD): A systematic review and meta-analysis. *NeuroImage. Clinical*. 2026; 49: 103959. <http://doi.org/10.1016/j.nicl.2026.103959>.
- [39] Li WW, Xiao R, Chen XY, Pu JC, Chen JJ, Wang HY, *et al.* Multi-Omics Analysis Reveals Disturbances of Purine Metabolism and Glutamate Metabolism in the Hippocampus of Lipopolysaccharide-Induced Mouse Model of Depression. *Brain and Behavior*. 2025; 15: e70549. <http://doi.org/10.1002/brb3.70549>.
- [40] Zhu W, Chang J, Tian L, Yang X, Li W. Depletion of HSP60 in Microglia Leads to Synaptic Dysfunction and Depression-Like Behaviors Through Enhanced Synaptic Pruning in Male Mice. *CNS Neuroscience & Therapeutics*. 2025; 31: e70394. <http://doi.org/10.1111/cns.70394>.
- [41] Freudenberg F, Reif-Leonhard C, Dawson GR, McKernan RM, Reif A. All roads lead to glutamate: NMDA and AMPA receptors as targets for rapid-acting antidepressants. *Pharmacological Research*. 2025; 220: 107918. <http://doi.org/10.1016/j.phrs.2025.107918>.
- [42] Palhas M, Corne R, Mongeau R. Changing your mind: neuroplastic mechanisms underlying the therapeutic effect of psychedelics in depression, PTSD, and addiction. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2025; 142: 111533. <http://doi.org/10.1016/j.pnpbp.2025.111533>.
- [43] Sanacora G, Ahmed M, Brown B, Cabrera P, Doherty T, Himedani M, *et al.* Real-World Safety of Esketamine Nasal Spray: A Comprehensive Analysis Almost 5 Years After First Approval. *The American Journal of Psychiatry*. 2025; 182: 913–921. <http://doi.org/10.1176/appi.ajp.20240655>.
- [44] McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrrough JW, Berk M, *et al.* Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *The American Journal of Psychiatry*. 2021; 178: 383–399. <http://doi.org/10.1176/appi.ajp.2020.20081251>.
- [45] Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *The American Journal of Psychiatry*. 2022; 179: 490–499. <http://doi.org/10.1176/appi.ajp.21080800>.
- [46] Xiao N, Yin L, Teopiz KM, Kwan ATH, Le GH, Wong S, *et al.* The sigma-1 receptor: a mechanistically-informed therapeutic target for antidepressants. *Expert Opinion on Therapeutic Targets*. 2025; 29: 345–359. <http://doi.org/10.1080/14728222.2025.2500424>.
- [47] Chaki S, Watanabe M. mGlu2/3 receptor antagonists for depression: overview of underlying mechanisms and clinical development. *European Archives of Psychiatry and Clinical Neuroscience*. 2023; 273: 1451–1462. <http://doi.org/10.1007/s00406-023-01561-6>.
- [48] Freudenberg F, Reif-Leonhard C, Reif A. Advancing past ketamine: emerging glutamatergic compounds for the treatment of depression. *European Archives of Psychiatry and Clinical Neuroscience*. 2025; 275: 1547–1557. <http://doi.org/10.1007/s00406-024-01875-z>.
- [49] Umbricht D, Niggli M, Sanwald-Ducray P, Deptula D, Moore R, Grünbauer W, *et al.* Randomized, Double-Blind, Placebo-Controlled Trial of the mGlu2/3 Negative Allosteric Modulator Decoglurant in Partially Refractory Major Depressive Disorder. *The Journal of Clinical Psychiatry*. 2020; 81: 18m12470. <http://doi.org/10.4088/JCP.18m12470>.
- [50] Parent HH, Niswender CM. Therapeutic Potential for Metabotropic Glutamate Receptor 7 Modulators in Cognitive Disorders. *Molecular Pharmacology*. 2024; 105: 348–358. <http://doi.org/10.1124/molpharm.124.000874>.
- [51] Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, *et al.* Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*. 2000; 47: 351–354. [http://doi.org/10.1016/s0006-3223\(99\)00230-9](http://doi.org/10.1016/s0006-3223(99)00230-9).
- [52] Kang MJY, Hawken E, Vazquez GH. The Mechanisms Behind Rapid Antidepressant Effects of Ketamine: A Systematic Review With a Focus on Molecular Neuroplasticity. *Frontiers in Psychiatry*. 2022; 13: 860882. <http://doi.org/10.3389/fpsy.2022.860882>.
- [53] Iosifescu DV, Jones A, O’Gorman C, Streicher C, Feliz S, Fava M, *et al.* Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *The Journal of Clinical Psychiatry*. 2022; 83: 21m14345. <http://doi.org/10.4088/JCP.21m14345>.
- [54] Quiroz JA, Tamburri P, Deptula D, Banken L, Beyer U, Rabbia M, *et al.* Efficacy and Safety of Basimglurant as Adjunctive Therapy for Major Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2016; 73: 675–684. <http://doi.org/10.1001/jamapsychiatry.2016.0838>.
- [55] Donello JE, Banerjee P, Li YX, Guo YX, Yoshitake T, Zhang XL,

- et al.* Positive N-Methyl-D-Aspartate Receptor Modulation by Rapastinel Promotes Rapid and Sustained Antidepressant-Like Effects. *International Journal of Neuropsychopharmacology*. 2019; 22: 247–259. <http://doi.org/10.1093/ijnp/pyy101>.
- [56] Moskal JR, Burch R, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, *et al.* GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. *Expert Opinion on Investigational Drugs*. 2014; 23: 243–254. <http://doi.org/10.1517/13543784.2014.852536>.
- [57] Pałucha-Poniewiera A, Wierońska JM, Brański P, Stachowicz K, Chaki S, Pilc A. On the mechanism of the antidepressant-like action of group II mGlu receptor antagonist, MGS0039. *Psychopharmacology*. 2010; 212: 523–535. <http://doi.org/10.1007/s00213-010-1978-5>.
- [58] Tatarczyńska E, Kłodzińska A, Chojnacka-Wójcik E, Pałucha A, Gasparini F, Kuhn R, *et al.* Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. *British Journal of Pharmacology*. 2001; 132: 1423–1430. <http://doi.org/10.1038/sj.bjp.0703923>.
- [59] Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 2014; 383: 1677–1687. [http://doi.org/10.1016/s0140-6736\(13\)62036-x](http://doi.org/10.1016/s0140-6736(13)62036-x).
- [60] Bojesen KB, Lemvig CK, Sigvard AK, Vestergaard MB, Larsson HBW, Rostrup E, *et al.* Cerebral glutamate levels over two years in initially antipsychotic-naïve first-episode patients with psychosis are related to clinical symptoms and cognition. *Molecular Psychiatry*. 2025; 30: 5652–5663. <http://doi.org/10.1038/s41380-025-03234-3>.
- [61] Coyle JT. Passing the torch: The ascendance of the glutamatergic synapse in the pathophysiology of schizophrenia. *Biochemical Pharmacology*. 2024; 228: 116376. <http://doi.org/10.1016/j.bcp.2024.116376>.
- [62] Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry*. 1994; 51: 199–214. <http://doi.org/10.1001/archpsyc.1994.03950030035004>.
- [63] Kokkinou M, Ashok AH, Howes OD. The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. *Molecular Psychiatry*. 2018; 23: 59–69. <http://doi.org/10.1038/mp.2017.190>.
- [64] Kantrowitz JT, Javitt DC. N-methyl-d-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? *Brain Research Bulletin*. 2010; 83: 108–121. <http://doi.org/10.1016/j.brainresbull.2010.04.006>.
- [65] Carlén M, Meletis K, Siegle JH, Cardin JA, Futai K, Vierling-Claassen D, *et al.* A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Molecular Psychiatry*. 2012; 17: 537–548. <http://doi.org/10.1038/mp.2011.31>.
- [66] Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biological Psychiatry*. 2015; 77: 1031–1040. <http://doi.org/10.1016/j.biopsych.2015.03.010>.
- [67] Dogra S, Aguayo C, Xiang Z, Putnam J, Smith J, Johnston C, *et al.* Activation of Metabotropic Glutamate Receptor 3 Modulates Thalamo-accumbal Transmission and Rescues Schizophrenia-Like Physiological and Behavioral Deficits. *Biological Psychiatry*. 2024; 96: 230–242. <http://doi.org/10.1016/j.biopsych.2023.11.023>.
- [68] Luessen DJ, Gallinger IM, Ferranti AS, Foster DJ, Melancon BJ, Lindsley CW, *et al.* mGlu<sub>1</sub>-mediated restoration of prefrontal cortex inhibitory signaling reverses social and cognitive deficits in an NMDA hypofunction model in mice. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*. 2022; 47: 1826–1835. <http://doi.org/10.1038/s41386-022-01350-0>.
- [69] Zehnder T, Petrelli F, Romanos J, De Oliveira Figueiredo EC, Lewis TL, Déglon N, *et al.* Mitochondrial biogenesis in developing astrocytes regulates astrocyte maturation and synapse formation. *Cell Reports*. 2021; 35: 108952. <http://doi.org/10.1016/j.celrep.2021.108952>.
- [70] Kim J, Lee J, Song H, Koo JW, Kang S. mGluR5 as a Potential Orchestrator of Astrocyte Interactions in Neurological Disorders. *Neural Plasticity*. 2025; 2025: 7259018. <http://doi.org/10.1155/np/7259018>.
- [71] Fuxe K, Agnati LF, Jacobsen K, Hillion J, Canals M, Torvinen M, *et al.* Receptor heteromerization in adenosine A2A receptor signaling: Relevance for striatal function and Parkinson's disease. *Neurology*. 2003; 61: S19–S23. <http://doi.org/10.1212/01.wn.1.0000095206.44418.5c>.
- [72] Zoicas I, Kornhuber J. The Role of Metabotropic Glutamate Receptors in Social Behavior in Rodents. *International Journal of Molecular Sciences*. 2019; 20: 1412. <http://doi.org/10.3390/ijms20061412>.
- [73] Copeland CS, Neale SA, Nisenbaum ES, Salt TE. Group II metabotropic glutamate receptor (mGlu<sub>2</sub> and mGlu<sub>3</sub>) roles in thalamic processing. *British Journal of Pharmacology*. 2022; 179: 1607–1619. <http://doi.org/10.1111/bph.15640>.
- [74] Nicoletti F, Orlando R, Di Menna L, Cannella M, Notartomaso S, Mascio G, *et al.* Targeting mGlu Receptors for Optimization of Antipsychotic Activity and Disease-Modifying Effect in Schizophrenia. *Frontiers in Psychiatry*. 2019; 10: 49. <http://doi.org/10.3389/fpsy.2019.00049>.
- [75] Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annual Review of Pharmacology and Toxicology*. 2010; 50: 295–322. <http://doi.org/10.1146/annurev.pharmtox.011008.145533>.
- [76] Harrison PJ, Lyon L, Sartorius LJ, Burnet PWJ, Lane TA. The group II metabotropic glutamate receptor 3 (mGluR3, mGlu3, GRM3): expression, function and involvement in schizophrenia. *Journal of Psychopharmacology*. 2008; 22: 308–322. <http://doi.org/10.1177/0269881108089818>.
- [77] Dogra S, Stansley BJ, Xiang Z, Qian W, Gogliotti RG, Nicoletti F, *et al.* Activating mGlu<sub>3</sub> Metabotropic Glutamate Receptors Rescues Schizophrenia-like Cognitive Deficits Through Metaplastic Adaptations Within the Hippocampus. *Biological Psychiatry*. 2021; 90: 385–398. <http://doi.org/10.1016/j.biopsych.2021.02.970>.
- [78] Li J, Ryan SK, Deboer E, Cook K, Fitzgerald S, Lachman HM, *et al.* Mitochondrial deficits in human iPSC-derived neurons from patients with 22q11.2 deletion syndrome and schizophrenia. *Translational Psychiatry*. 2019; 9: 302. <http://doi.org/10.1038/s41398-019-0643-y>.

- [79] Devaraju P, Zakharenko SS. Mitochondria in complex psychiatric disorders: Lessons from mouse models of 22q11.2 deletion syndrome: Hemizygous deletion of several mitochondrial genes in the 22q11.2 genomic region can lead to symptoms associated with neuropsychiatric disease. *BioEssays*. 2017; 39: 1600177. <http://doi.org/10.1002/bies.201600177>.
- [80] Ling E, Nemesh J, Goldman M, Kamitaki N, Reed N, Handsaker RE, *et al.* A concerted neuron-astrocyte program declines in ageing and schizophrenia. *Nature*. 2024; 627: 604–611. <http://doi.org/10.1038/s41586-024-07109-5>.
- [81] Li J, Tran OT, Crowley TB, Moore TM, Zackai EH, Emanuel BS, *et al.* Association of Mitochondrial Biogenesis With Variable Penetration of Schizophrenia. *JAMA Psychiatry*. 2021; 78: 911–921. <http://doi.org/10.1001/jamapsychiatry.2021.0762>.
- [82] 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. *World Journal of Psychiatry*. 2018; 8: 51–63. <http://doi.org/10.5498/wjp.v8.i2.51>.
- [83] McCullumsmith RE, O'Donovan SM, Drummond JB, Benesh FS, Simmons M, Roberts R, *et al.* Cell-specific abnormalities of glutamate transporters in schizophrenia: sick astrocytes and compensating relay neurons? *Molecular Psychiatry*. 2016; 21: 823–830. <http://doi.org/10.1038/mp.2015.148>.
- [84] O'Donovan SM, Shan D, Wu X, Choi JH, McCullumsmith RE. Dysregulated Transcript Expression but Not Function of the Glutamate Transporter EAAT2 in the Dorsolateral Prefrontal Cortex in Schizophrenia. *Schizophrenia Bulletin*. 2025; 51: 531–542. <http://doi.org/10.1093/schbul/sbae092>.
- [85] Marx W, McGuinness AJ, Rocks T, Ruusunen A, Cleminson J, Walker AJ, *et al.* The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: a meta-analysis of 101 studies. *Molecular Psychiatry*. 2021; 26: 4158–4178. <http://doi.org/10.1038/s41380-020-00951-9>.
- [86] Stone TW. Kynurenic acid antagonists and kynurenine pathway inhibitors. *Expert Opinion on Investigational Drugs*. 2001; 10: 633–645. <http://doi.org/10.1517/13543784.10.4.633>.
- [87] Hilmas C, Pereira EF, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX. The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. 2001; 21: 7463–7473. <http://doi.org/10.1523/jneurosci.21-19-07463.2001>.
- [88] Stone TW, Darlington LG. The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders. *British Journal of Pharmacology*. 2013; 169: 1211–1227. <http://doi.org/10.1111/bph.12230>.
- [89] Almulla AF, Vasupanrajit A, Tunvirachaisakul C, Al-Hakeim HK, Solmi M, Verkerk R, *et al.* The tryptophan catabolite or kynurenine pathway in schizophrenia: Meta-analysis reveals dissociations between central, serum, and plasma compartments. *Molecular Psychiatry*. 2022; 27: 3679–3691. <http://doi.org/10.1038/s41380-022-01552-4>.
- [90] Sapienza J, Agostoni G, Repaci F, Spangaro M, Comai S, Bosia M. Metabolic Syndrome and Schizophrenia: Adding a Piece to the Interplay Between the Kynurenine Pathway and Inflammation. *Metabolites*. 2025; 15: 176. <http://doi.org/10.3390/metabo15030176>.
- [91] Rampino A, Garofalo M, Nuzzo T, Favia M, Saltarelli S, Masellis R, *et al.* Variations of blood D-serine and D-aspartate homeostasis track psychosis stages. *Schizophrenia*. 2024; 10: 115. <http://doi.org/10.1038/s41537-024-00537-2>.
- [92] Fadgyas-Stanculete M, Capatina OO. Glutamate-Based Therapeutic Strategies for Schizophrenia: Emerging Approaches Beyond Dopamine. *International Journal of Molecular Sciences*. 2025; 26: 4331. <http://doi.org/10.3390/ijms26094331>.
- [93] Okubo R, Okada M, Motomura E. Dysfunction of the NMDA Receptor in the Pathophysiology of Schizophrenia and/or the Pathomechanisms of Treatment-Resistant Schizophrenia. *Biomolecules*. 2024; 14: 1128. <http://doi.org/10.3390/biom14091128>.
- [94] Sehatpour P, Kantrowitz JT. Finding the Right Dose: NMDA Receptor-Modulating Treatments for Cognitive and Plasticity Deficits in Schizophrenia and the Role of Pharmacodynamic Target Engagement. *Biological Psychiatry*. 2025; 97: 128–138. <http://doi.org/10.1016/j.biopsych.2024.08.019>.
- [95] Wolosker H, Balu DT, Coyle JT. The Rise and Fall of the D-Serine-Mediated Gliotransmission Hypothesis. *Trends in Neurosciences*. 2016; 39: 712–721. <http://doi.org/10.1016/j.tins.2016.09.007>.
- [96] Kantrowitz JT, Malhotra AK, Cornblatt B, Silipo G, Balla A, Suckow RF, *et al.* High dose D-serine in the treatment of schizophrenia. *Schizophrenia Research*. 2010; 121: 125–130. <http://doi.org/10.1016/j.schres.2010.05.012>.
- [97] Chaki S, Shimazaki T, Karasawa J, Aoki T, Kaku A, Iijima M, *et al.* Efficacy of a glycine transporter 1 inhibitor TASP0315003 in animal models of cognitive dysfunction and negative symptoms of schizophrenia. *Psychopharmacology*. 2015; 232: 2849–2861. <http://doi.org/10.1007/s00213-015-3920-3>.
- [98] Rosenbrock H, Desch M, Wunderlich G. Development of the novel GlyT1 inhibitor, iclepertin (BI 425809), for the treatment of cognitive impairment associated with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*. 2023; 273: 1557–1566. <http://doi.org/10.1007/s00406-023-01576-z>.
- [99] Pinna A, Palasz A. Modulation of glycine transporters as a novel therapeutic strategy in neuropsychiatry. *Psychopharmacology*. 2026; 243: 495–512. <http://doi.org/10.1007/s00213-025-06915-7>.
- [100] Guastella J, Brecha N, Weigmann C, Lester HA, Davidson N. Cloning, expression, and localization of a rat brain high-affinity glycine transporter. *Proceedings of the National Academy of Sciences of the United States of America*. 1992; 89: 7189–7193. <http://doi.org/10.1073/pnas.89.15.7189>.
- [101] Seetharam JC, Maiti R, Mishra A, Mishra BR. Efficacy and safety of add-on sodium benzoate, a D-amino acid oxidase inhibitor, in treatment of schizophrenia: A systematic review and meta-analysis. *Asian Journal of Psychiatry*. 2022; 68: 102947. <http://doi.org/10.1016/j.ajp.2021.102947>.
- [102] Liang CW, Cheng HY, Tseng MM. Augmentation with glutamatergic modulators for schizophrenia: A network meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2025; 142: 111495. <http://doi.org/10.1016/j.pnpb.2025.111495>.
- [103] Terry-Lorenzo RT, Fan RH, Khin NA, Singh JB. Therapeutic potential of D-amino acid oxidase inhibitors for cognitive impairment associated with schizophrenia: learnings from luvadaxistat. *International Journal of Neuropsychopharmacology*. 2024; 28: pyae066. <http://doi.org/10.1093/ijnp/pyae066>.

- [104] Hamilton A, Esseltine JL, DeVries RA, Cregan SP, Ferguson SS. Metabotropic glutamate receptor 5 knockout reduces cognitive impairment and pathogenesis in a mouse model of Alzheimer's disease. *Molecular Brain*. 2014; 7: 40. <http://doi.org/10.1186/1756-6606-7-40>.
- [105] Conn PJ, Lindsley CW, Jones CK. Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends in Pharmacological Sciences*. 2009; 30: 25–31. <http://doi.org/10.1016/j.tips.2008.10.006>.
- [106] Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, *et al.* Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized Phase 2 clinical trial. *Nature Medicine*. 2007; 13: 1102–1107. <http://doi.org/10.1038/nm1632>.
- [107] Aboushawab H, Abbas OF, Ghabour H, Hassan O, Shalbaya AN, Abdelsalam R, *et al.* Pomaglutam methionil (LY2140023) in schizophrenia patients: a systematic review and meta-analysis. *BMC Psychiatry*. 2025; 25: 775. <http://doi.org/10.1186/s12888-025-07199-z>.
- [108] Javitt DC, Zylberman I, Zukin SR, Heresco-Levy U, Lindenmayer JP. Amelioration of negative symptoms in schizophrenia by glycine. *The American Journal of Psychiatry*. 1994; 151: 1234–1236. <http://doi.org/10.1176/ajp.151.8.1234>.
- [109] Tsai G, Yang P, Chung LC, Lange N, Coyle JT. D-serine added to antipsychotics for the treatment of schizophrenia. *Biological Psychiatry*. 1998; 44: 1081–1089. [http://doi.org/10.1016/s0006-3223\(98\)00279-0](http://doi.org/10.1016/s0006-3223(98)00279-0).
- [110] Lane HY, Lin CH, Huang YJ, Liao CH, Chang YC, Tsai GE. A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. *International Journal of Neuropsychopharmacology*. 2010; 13: 451–460. <http://doi.org/10.1017/s1461145709990939>.
- [111] Rorick-Kehn LM, Johnson BG, Knitowski KM, Salhoff CR, Witkin JM, Perry KW, *et al.* In vivo pharmacological characterization of the structurally novel, potent, selective mGlu2/3 receptor agonist LY404039 in animal models of psychiatric disorders. *Psychopharmacology*. 2007; 193: 121–136. <http://doi.org/10.1007/s00213-007-0758-3>.
- [112] Uslaner JM, Parmentier-Batteur S, Flick RB, Surles NO, Lam JS, McNaughton CH, *et al.* Dose-dependent effect of CDPPE, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. *Neuropharmacology*. 2009; 57: 531–538. <http://doi.org/10.1016/j.neuropharm.2009.07.022>.
- [113] Yang F, Snyder LB, Balakrishnan A, Brown JM, Sivarao DV, Easton A, *et al.* Discovery and Preclinical Evaluation of BMS-955829, a Potent Positive Allosteric Modulator of mGluR5. *ACS Medicinal Chemistry Letters*. 2016; 7: 289–293. <http://doi.org/10.1021/acsmcmedchemlett.5b00450>.
- [114] Uhl GR, Koob GF, Cable J. The neurobiology of addiction. *Annals of the New York Academy of Sciences*. 2019; 1451: 5–28. <http://doi.org/10.1111/nyas.13989>.
- [115] Hrickova M, Ruda-Kucerova J. Do AMPA/kainate antagonists possess potential in the treatment of addiction? Evidence from animal behavioural studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2025; 138: 111355. <http://doi.org/10.1016/j.pnpbp.2025.111355>.
- [116] Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *The Journal of Nutrition*. 2000; 130: 1007s–1015s. <http://doi.org/10.1093/jn/130.4.1007S>.
- [117] Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. *Biochemical Pharmacology*. 2008; 75: 218–265. <http://doi.org/10.1016/j.bcp.2007.06.039>.
- [118] Diering GH, Huganir RL. The AMPA Receptor Code of Synaptic Plasticity. *Neuron*. 2018; 100: 314–329. <http://doi.org/10.1016/j.neuron.2018.10.018>.
- [119] Chiamulera C, Piva A, Abraham WC. Glutamate receptors and metaplasticity in addiction. *Current Opinion in Pharmacology*. 2021; 56: 39–45. <http://doi.org/10.1016/j.coph.2020.09.005>.
- [120] Kourrich S, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. 2007; 27: 7921–7928. <http://doi.org/10.1523/jneurosci.1859-07.2007>.
- [121] Kalivas PW. The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*. 2009; 10: 561–572. <http://doi.org/10.1038/nrn2515>.
- [122] Scofield MD, Heinsbroek JA, Gipson CD, Kupchik YM, Spencer S, Smith AC, *et al.* The Nucleus Accumbens: Mechanisms of Addiction across Drug Classes Reflect the Importance of Glutamate Homeostasis. *Pharmacological Reviews*. 2016; 68: 816–871. <http://doi.org/10.1124/pr.116.012484>.
- [123] Scofield MD, Kalivas PW. Astrocytic dysfunction and addiction: consequences of impaired glutamate homeostasis. *The Neuroscientist*. 2014; 20: 610–622. <http://doi.org/10.1177/1073858413520347>.
- [124] Knackstedt LA, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. *Biological Psychiatry*. 2010; 67: 81–84. <http://doi.org/10.1016/j.biopsych.2009.07.018>.
- [125] LaCrosse AL, O'Donovan SM, Sepulveda-Orengo MT, McCullumsmith RE, Reissner KJ, Schwendt M, *et al.* Contrasting the Role of xCT and GLT-1 Upregulation in the Ability of Ceftriaxone to Attenuate the Cue-Induced Reinstatement of Cocaine Seeking and Normalize AMPA Receptor Subunit Expression. *The Journal of Neuroscience: The official journal of the Society for Neuroscience*. 2017; 37: 5809–5821. <http://doi.org/10.1523/jneurosci.3717-16.2017>.
- [126] Roberts-Wolfe DJ, Kalivas PW. Glutamate Transporter GLT-1 as a Therapeutic Target for Substance Use Disorders. *CNS & Neurological Disorders Drug Targets*. 2015; 14: 745–756. <http://doi.org/10.2174/1871527314666150529144655>.
- [127] Funke JR, Hwang EK, Wunsch AM, Baker R, Engeln KA, Murray CH, *et al.* Persistent Neuroadaptations in the Nucleus Accumbens Core Accompany Incubation of Methamphetamine Craving in Male and Female Rats. *eNeuro*. 2023; 10: ENEURO.0480-22.2023. <http://doi.org/10.1523/eneuro.0480-22.2023>.
- [128] Chow JJ, Pitts KM, Negishi K, Madangopal R, Dong Y, Wolf ME, *et al.* Neurobiology of the incubation of drug craving: An update. *Pharmacological Reviews*. 2025; 77: 100022. <http://doi.org/10.1016/j.pharmr.2024.100022>.
- [129] Loweth JA, Scheyer AF, Milovanovic M, LaCrosse AL, Flores-Barrera E, Werner CT, *et al.* Synaptic depression via mGluR1 positive allosteric modulation suppresses cue-induced cocaine craving. *Nature Neuroscience*. 2014; 17: 73–80. <http://doi.org/10.1038/nn.3590>.

- [130] Niedzińska-Andres E, Pomierny-Chamioło L, Andres M, Walczak M, Knackstedt LA, Filip M, *et al.* Cocaine use disorder: A look at metabotropic glutamate receptors and glutamate transporters. *Pharmacology & Therapeutics*. 2021; 221: 107797. <http://doi.org/10.1016/j.pharmthera.2020.107797>.
- [131] Olive MF. Metabotropic glutamate receptor ligands as potential therapeutics for addiction. *Current Drug Abuse Reviews*. 2009; 2: 83–98. <http://doi.org/10.2174/1874473710902010083>.
- [132] Amorim Moreira Alves G, Teranishi M, Teixeira de Castro Gonçalves Ortega AC, James F, Perera Molligoda Arachchige AS. Mechanisms of GLP-1 in Modulating Craving and Addiction: Neurobiological and Translational Insights. *Medical Sciences*. 2025; 13: 136. <http://doi.org/10.3390/medsci13030136>.
- [133] Smaga I, Wydra K, Frankowska M, Fumagalli F, Sanak M, Filip M. Cocaine Self-Administration and Abstinence Modulate NMDA Receptor Subunits and Active Zone Proteins in the Rat Nucleus Accumbens. *Molecules*. 2020; 25: 3480. <http://doi.org/10.3390/molecules25153480>.
- [134] Ortinski PI. Cocaine-induced changes in NMDA receptor signaling. *Molecular Neurobiology*. 2014; 50: 494–506. <http://doi.org/10.1007/s12035-014-8636-6>.
- [135] Christian DT, Stefanik MT, Bean LA, Loweth JA, Wunsch AM, Funke JR, *et al.* GluN3-Containing NMDA Receptors in the Rat Nucleus Accumbens Core Contribute to Incubation of Cocaine Craving. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. 2021; 41: 8262–8277. <http://doi.org/10.1523/jneurosci.0406-21.2021>.
- [136] Luo Y, Yu Y, Zhang M, He H, Fan N. Chronic administration of ketamine induces cognitive deterioration by restraining synaptic signaling. *Molecular Psychiatry*. 2021; 26: 4702–4718. <http://doi.org/10.1038/s41380-020-0793-6>.
- [137] Salery M, Trifilieff P, Caboche J, Vanhoutte P. From Signaling Molecules to Circuits and Behaviors: Cell-Type-Specific Adaptations to Psychostimulant Exposure in the Striatum. *Biological Psychiatry*. 2020; 87: 944–953. <http://doi.org/10.1016/j.biopsych.2019.11.001>.
- [138] Egervari G, Landry J, Callens J, Fullard JF, Roussos P, Keller E, *et al.* Striatal H3K27 Acetylation Linked to Glutamatergic Gene Dysregulation in Human Heroin Abusers Holds Promise as Therapeutic Target. *Biological Psychiatry*. 2017; 81: 585–594. <http://doi.org/10.1016/j.biopsych.2016.09.015>.
- [139] Gipson CD, Kupchik YM, Shen H, Reissner KJ, Thomas CA, Kalivas PW. Relapse induced by cues predicting cocaine depends on rapid, transient synaptic potentiation. *Neuron*. 2013; 77: 867–872. <http://doi.org/10.1016/j.neuron.2013.01.005>.
- [140] Garcia-Keller C, Neuhofer D, Bobadilla AC, Spencer S, Chioma VC, Monforton C, *et al.* Extracellular Matrix Signaling Through  $\beta 3$  Integrin Mediates Cocaine Cue-Induced Transient Synaptic Plasticity and Relapse. *Biological Psychiatry*. 2019; 86: 377–387. <http://doi.org/10.1016/j.biopsych.2019.03.982>.
- [141] Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *The American Journal of Psychiatry*. 2005; 162: 1403–1413. <http://doi.org/10.1176/appi.ajp.162.8.1403>.
- [142] Reiner A, Levitz J. Glutamatergic Signaling in the Central Nervous System: Ionotropic and Metabotropic Receptors in Concert. *Neuron*. 2018; 98: 1080–1098. <http://doi.org/10.1016/j.neuron.2018.05.018>.
- [143] Sari Y, Swiss GMS, Alrashedi FA, Baeshen KA, Alshammari SA, Alsharari SD, *et al.* Effects of novel beta-lactam, MC-100093, and ceftriaxone on astrocytic glutamate transporters and neuroinflammatory factors in nucleus accumbens of C57BL/6 mice exposed to escalated doses of morphine. *Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society*. 2024; 32: 102108. <http://doi.org/10.1016/j.jsps.2024.102108>.
- [144] Shen HW, Scofield MD, Boger H, Hensley M, Kalivas PW. Synaptic glutamate spillover due to impaired glutamate uptake mediates heroin relapse. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. 2014; 34: 5649–5657. <http://doi.org/10.1523/jneurosci.4564-13.2014>.
- [145] Abulseoud OA, Alasmari F, Hussein AM, Sari Y. Ceftriaxone as a Novel Therapeutic Agent for Hyperglutamatergic States: Bridging the Gap Between Preclinical Results and Clinical Translation. *Frontiers in Neuroscience*. 2022; 16: 841036. <http://doi.org/10.3389/fnins.2022.841036>.
- [146] Caprioli D, Justinova Z, Venniro M, Shaham Y. Effect of Novel Allosteric Modulators of Metabotropic Glutamate Receptors on Drug Self-administration and Relapse: A Review of Preclinical Studies and Their Clinical Implications. *Biological Psychiatry*. 2018; 84: 180–192. <http://doi.org/10.1016/j.biopsych.2017.08.018>.
- [147] Baptista MA, Martin-Fardon R, Weiss F. Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*. 2004; 24: 4723–4727. <http://doi.org/10.1523/jneurosci.0176-04.2004>.
- [148] Cannella N, Halbout B, Uhrig S, Evrard L, Corsi M, Corti C, *et al.* The mGluR2/3 agonist LY379268 induced anti-reinstatement effects in rats exhibiting addiction-like behavior. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*. 2013; 38: 2048–2056. <http://doi.org/10.1038/npp.2013.106>.
- [149] Mao LM, Puthumana E, Wang JQ. mGlu2 Receptors in the Basal Ganglia: A New Frontier in Addiction Therapy. *Frontiers in Bioscience-Landmark*. 2025; 30: 26637. <http://doi.org/10.31083/fb126637>.
- [150] Murray CH, Loweth JA, Milovanovic M, Stefanik MT, Caccamise AJ, Dolubizno H, *et al.* AMPA receptor and metabotropic glutamate receptor 1 adaptations in the nucleus accumbens core during incubation of methamphetamine craving. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*. 2019; 44: 1534–1541. <http://doi.org/10.1038/s41386-019-0425-5>.
- [151] Loweth JA, Tseng KY, Wolf ME. Using metabotropic glutamate receptors to modulate cocaine's synaptic and behavioral effects: mGluR1 finds a niche. *Current Opinion in Neurobiology*. 2013; 23: 500–506. <http://doi.org/10.1016/j.conb.2013.01.009>.
- [152] Janssen-Aguilar R, Meshkat S, Demchenko I, Zhang Y, Greenshaw A, Dunn W, *et al.* Role of ketamine in the treatment of substance use disorders: A systematic review. *Journal of Substance Use and Addiction Treatment*. 2025; 175: 209705. <http://doi.org/10.1016/j.josat.2025.209705>.
- [153] Wolf ME. Targeting Neuroplasticity in Substance Use Disorders: Implications for Therapeutics. *Annual Review of Pharmacology and Toxicology*. 2025; 65: 259–280. <http://doi.org/10.1146/annurev-pharmtox-061724-080548>.

- [154] Estrada-Medina R, Briones-Llamoctanta BE, Turpo-Chaparro JE. Neuroplasticity and recovery of the brain affected by substance use disorder: multilevel mechanisms and new therapeutic strategies (2020–2025). *Frontiers in Molecular Neuroscience*. 2026; 19: 1760387. <http://doi.org/10.3389/fnmol.2026.1760387>.
- [155] Kupchik YM, Moussawi K, Tang XC, Wang X, Kalivas BC, Kolokithas R, *et al.* The effect of N-acetylcysteine in the nucleus accumbens on neurotransmission and relapse to cocaine. *Biological psychiatry*. 2012; 71: 978–986. <http://doi.org/10.1016/j.biopsy.ch.2011.10.024>.
- [156] Bisaga A, Comer SD, Ward AS, Popik P, Kleber HD, Fischman MW. The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. *Psychopharmacology*. 2001; 157: 1–10. <http://doi.org/10.1007/s002130100739>.
- [157] Santa Ana EJ, Rounsaville BJ, Frankforter TL, Nich C, Babuscio T, Poling J, *et al.* D-Cycloserine attenuates reactivity to smoking cues in nicotine dependent smokers: a pilot investigation. *Drug and Alcohol Dependence*. 2009; 104: 220–227. <http://doi.org/10.1016/j.drugalcdep.2009.04.023>.
- [158] Wendt FR, Pathak GA, Tylee DS, Goswami A, Polimanti R. Heterogeneity and Polygenicity in Psychiatric Disorders: A Genome-Wide Perspective. *Chronic Stress*. 2020; 4: 2470547020924844. <http://doi.org/10.1177/2470547020924844>.
- [159] Sullivan PF, Yao S, Hjerling-Leffler J. Schizophrenia genomics: genetic complexity and functional insights. *Nature Reviews Neuroscience*. 2024; 25: 611–624. <http://doi.org/10.1038/s41583-024-00837-7>.
- [160] Siekmeier PJ, Coyle JT. Novel electroencephalographic biomarkers for the prediction of responders to an experimental glutamatergic agent in patients with schizophrenia. *Translational Psychiatry*. 2025; 15: 390. <http://doi.org/10.1038/s41398-025-03604-z>.
- [161] Magdaleno Roman JY, Chapa González C. Glutamate and excitotoxicity in central nervous system disorders: ionotropic glutamate receptors as a target for neuroprotection. *Neuroprotection*. 2024; 2: 137–150. <http://doi.org/10.1002/nep3.46>.
- [162] Javitt DC, Carter CS, Krystal JH, Kantrowitz JT, Girgis RR, Kegeles LS, *et al.* Utility of Imaging-Based Biomarkers for Glutamate-Targeted Drug Development in Psychotic Disorders: A Randomized Clinical Trial. *JAMA Psychiatry*. 2018; 75: 11–19. <http://doi.org/10.1001/jamapsychiatry.2017.3572>.
- [163] Merritt K, Egerton A, Kempton MJ, Taylor MJ, McGuire PK. Nature of Glutamate Alterations in Schizophrenia: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies. *JAMA Psychiatry*. 2016; 73: 665–674. <http://doi.org/10.1001/jamapsychiatry.2016.0442>.
- [164] de Diego-Adelino J, Portella MJ, Gómez-Ansón B, López-Moruelo O, Serra-Blasco M, Vives Y, *et al.* Hippocampal abnormalities of glutamate/glutamine, N-acetylaspartate and choline in patients with depression are related to past illness burden. *Journal of Psychiatry & Neuroscience: JPN*. 2013; 38: 107–116. <http://doi.org/10.1503/jpn.110185>.
- [165] Ward SE, Harries MH, Aldegheri L, Bradford AM, Ballini E, Dawson L, *et al.* Pharmacological characterisation of MDI-222, a novel AMPA receptor positive allosteric modulator with an improved safety profile. *Journal of Psychopharmacology/British Association for Psychopharmacology*. 2020; 34: 93–102. <http://doi.org/10.1177/0269881119872198>.
- [166] Tison F, Keywood C, Wakefield M, Durif F, Corvol JC, Eggert K, *et al.* A Phase 2A Trial of the Novel mGluR5-Negative Allosteric Modulator Dipraglurant for Levodopa-Induced Dyskinesia in Parkinson's Disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2016; 31: 1373–1380. <http://doi.org/10.1002/mds.26659>.