



The neuroprotective and neuroplastic potential of glutamatergic therapeutic drugs in bipolar disorder

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ABSTRACT

The monoamine hypothesis has dominated research on the pathophysiology of mood disorders as well as the development of therapeutic drugs by over half a century. Nowadays a change of perspective is taking place. The glutamate system is increasingly implicated in the pathophysiology of mood disorders. The evidence spans from animal, post-mortem, imaging, pharmacological and genome-wide association studies. Bipolar disorder has been recently re-conceptualized as a synaptic plasticity-related disorder rather than simply as a result of deficits or excesses in individual neurotransmitters. A paradigm shift from a monoamine hypothesis to a neuroplasticity hypothesis focused on glutamate may represent a substantial advancement in the research for new drugs and therapies. In this review we summarize data from clinical and pre-clinical studies that have addressed glutamatergic alterations in bipolar disorder. Along with an in-depth discussion of glutamatergic alterations in bipolar disorder, we also report available data on the neuroprotective and neuroplastic potential of the classic mood stabilizers, ketamine, and psychedelics. The glutamatergic mechanisms underlying the efficacy of these drugs are described and discussed.

1. Introduction

Bipolar disorder (BD) is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide. Growing evidence suggests that the glutamatergic system is central to the neurobiology and treatment of this disorder and more broadly, mood disorders (Table 1). Glutamate (Glu) is the most abundant excitatory neurotransmitter in the brain, and acts in three different cell compartments, the pre- and postsynaptic neurons and glia. Physiological activity in the glial-neuronal Glu-glutamine cycle includes the uptake and inactivation of Glu after its actions as a neurotransmitter have been completed, an effect that aims to prevent toxic effects secondary to overexposure to high Glu levels (Machado-Vieira et al., 2012). Numerous sources of evidence have shown that in BD, Glu neurotransmission is highly affected in different brain regions, leading to alterations in synaptic signal transmission. In line with what happens during brain development, studies identified the glutamatergic neurotransmission as an essential mechanism for an activity-dependent modulation of synapses and neural networks. Indeed, the Ca²⁺ influx at postsynaptic N-methyl-D-aspartate receptors (NMDARs) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) is

essential for the formation and stabilization of the synapse. Notably, AMPARs exist as calcium-impermeable (CI-) and calcium-permeable (CP-) subtypes, the latter of which lacks the GluA2 subunit (Cull-Candy and Farrant, 2021). Activation of AMPAR (CI-) and induced depolarization increases Ca²⁺ influx through NMDA-Rs and L-type Ca²⁺ channels. If the intracellular Ca²⁺ level rises too far, neuronal death will result (Li and Wang, 2016). Thus, the amount of Ca²⁺ increase after Glu stimulation determines whether and which molecular changes will be activated in the neuron. This triggers the activity-dependent vesicular release of BDNF into the synaptic space that binds to and activates its surface receptor TrkB which in turn activates downstream signalling cascades involving ERK and Akt. These 2 pathways converge on mTOR, which is a key regulator of protein synthesis and synaptic plasticity (Fig. 1) This is ultimately associated with structural changes in the synapse. These structural alterations can have a clear impact on synaptic neurotransmission and plasticity.

The discovery of ketamine as a rapid antidepressant has caused a paradigm shift in depression research and treatment. Ketamine effects in bipolar depression have been studied in several studies (Diazgranados et al., 2010; Ionescu et al., 2015; Lally et al., 2014; Nugent et al., 2014; Permoda-Osip et al., 2013; Permoda-Osip et al., 2014; Rybakowski et al.,

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Table 1
Summary of major glutamatergic dysfunctions in BD and MDD.

	Bipolar Disorder	Major depression
Genetic	Glutamate receptor signaling (GRM7, GRM1, GNG2)*	Glutamate receptor signaling (GRIA3, GRIK2, GRIK4, GRM7)
Blood and urine	↑Anti-NMDAR antibodies* ↓kynurenic acid* ↓plasma glutathione ↑ NO*	↓kynurenic acid* ↑ glutamate* ↓plasma glutathione
CSF	↓urinary 2,4-dihydroxypyrimidine ↑kynurenic acid*	↑GLN to GLU ratio ↑ glutamate (PFC)
Post-Mortem	↓ expression of NMDA, AMPA, and kainite ↓NR1 subunit of the NMDA ↓ expression of EAAT3 and EAAT4 ↑ expression of NOS1AP	↓ NR1 subunit of the NMDA ↑mGluR2/3 receptors (PFC) ↓expression of EAAT1 and EAAT2 ↓expression of EAAT3 and EAAT4 ↓glutamine synthetase ↓ Glx (PFC*, ACC*) ↓ Glutamate (ACC*)
Neuroimaging	↑Glx (PFC*) ↓NAA*	

ACC anterior cingulate cortex; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; EAAT, Excitatory amino acid transporter; GLN glutamine; Glx, Glutamate – Glutamine; GRM7, Metabotropic glutamate receptor 7; GRM1, Metabotropic glutamate receptor 1; GNG2, Guanine nucleotide-binding protein subunit gamma 2; GRIA3 Glutamate Ionotropic Receptor AMPA Type Subunit 3; GRIK2 Glutamate Ionotropic Receptor Kainate Type Subunit 2; GRIK4 Glutamate Ionotropic Receptor Kainate Type Subunit 4; NAA, N-acetylaspartate; NMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; NOS1AP, Nitric Oxide Synthase 1 Adaptor Protein; PFC, Prefrontal Cortex;

*Supported by at least one meta-analysis

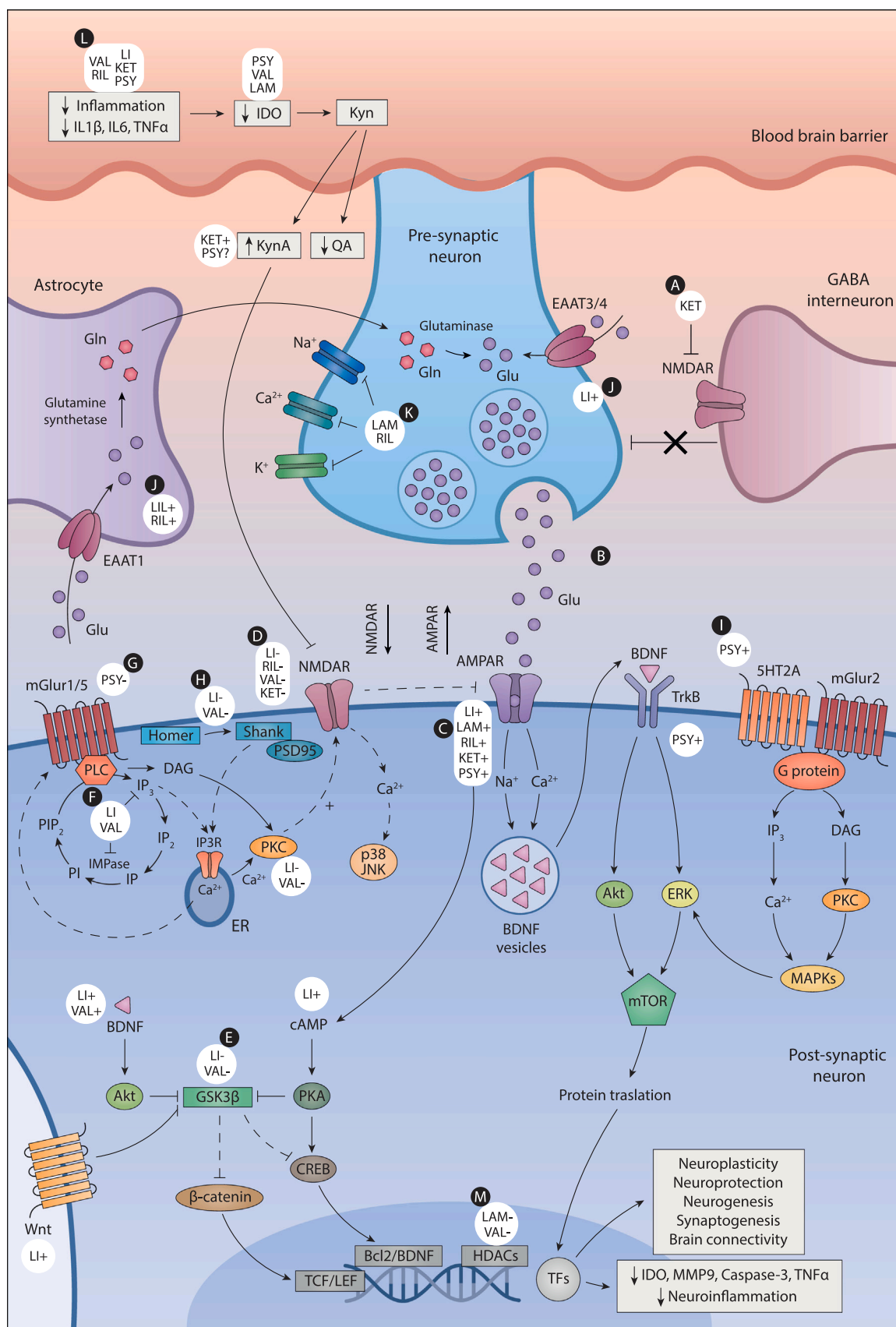
2017; Rybakowski et al., 2013; Zarate et al., 2012) (Table 2). The study of the antidepressant action of ketamine is one of the main factors that led to the glutamatergic hypothesis of mood disorders. This hypothesis postulates that disrupted Glu neurotransmission may mediate psychopathological features and psychosocial impairments by affecting the glutamatergic connections in the brain. The development of this hypothesis has also increased research interest in other therapeutic strategies that can modulate the GLU system and consequently neuroprotection and neuroplasticity in mood disorders. Psychedelics have classically been seen as serotonergic substances. However, there is increasing evidence that their mode of action is closely related to the glutamatergic system and to neuroplasticity. Psychedelics robustly promote structural and functional neural plasticity in key circuits relevant to brain health and mood. Recent findings demonstrate that the 5-HT_{2A}-mGluR2 complex is critical for the hallucinogen-like behaviors induced by 5-HT_{2A} agonists. Notably, head-twitch behavior induced by hallucinogenic 5HT_{2A} agonists is abolished in mGluR2-KO mice as well as the cellular response (Moreno et al., 2011). The translational potential of these findings is suggested by the significant involvement of mGluR signalling in BD (Nurnberger et al., 2014). At the same time, clinical and pre-clinical evidence support the role of Dextromethorphan (DXM) in depression. DXM is a non-opioid antitussive agent and similar to ketamine, it is established that DXM inhibits NMDA receptors and has effects at serotonin and norepinephrine transporters, and nicotinic and sigma-1 receptors (Nguyen et al., 2016). Clinical studies indicate that DXM is well tolerated and exhibits clinically significant antidepressant effects. Its efficacy has been preliminarily reported in adults with bipolar depression (Majeed et al., 2021).

There are at least five glutamate pathways in the brain connecting the frontal cortex to brainstem, midbrain, and limbic areas (for a review see Schwartz et al., 2012). Given that the therapeutics used to treat BD enhance neuroprotection, it is not surprising that accumulating evidence links mood disorders to the dysregulation of neuronal resilience,

survival and plasticity cascades. Changes in brain connectivity in BD could be related to altered levels of Glu. Unlike the monoamine systems that have more restricted roles, Glu is the key excitatory neurotransmitter with both intrinsic and extrinsic control of information flow in the brain. Preclinical studies in rodents and nonhuman primates have reported structural alterations, including atrophy of neurons in the hippocampus and prefrontal cortex (PFC), in chronic stress models (Duman et al., 2016; McEwen et al., 2015). Structural and functional alterations, including decreased volume and connectivity of both the hippocampus and PFC, have also been reported in depressed patients (MacQueen and Frodl, 2011). In particular, prolonged stress has been associated with neuronal atrophy and overall synaptic depression in the PFC (subgenual and anterior cingulate cortex) and the hippocampus. It has been proposed that down-regulation of PFC activity leads to gain of function in other brain regions negatively controlled by the PFC, such as the amygdala, a brain region associated with increased anxiety and hypothalamic-pituitary-adrenal axis reactivity. In this model, prefrontal synaptic deficits and the subsequent neuronal dysconnectivity are critical to the progress and treatment of mood disorders. These synaptic changes are believed to result from stress-induced altered Glu release and astroglial loss, leading to neurotrophic factor deficits and to sustained increase in extracellular Glu. The excess Glu precipitates excitotoxicity, altered synaptic strength, reduced dendritic spine density, dendritic retraction, and reduced dendritic branching in the PFC (Abdallah et al., 2015). It has been found that synaptic deficits are precipitated by reduction in neurotrophic factors such as BDNF and by inhibition of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway (Luo et al., 2021; Mariga et al., 2017). Together these data posit that enhancement of BDNF and mTORC1 signaling leads to prefrontal synaptic formation (synaptogenesis), and that reversal of stress-induced neuronal atrophy and synaptic dysconnectivity is a potential pro-neuroplastic therapeutic mechanism.

Consistent with impaired neuroplasticity and synaptic connectivity in both BD and MDD showed significantly decreased cerebral-limbic functional connectivity (FC) located between the default mode network (DMN) [posterior cingulate gyrus (PCG) and precuneus] and limbic regions (hippocampus, amygdala and thalamus) than healthy controls (HC). Bipolar patients exhibited more decreased FC mainly in the cortical regions (middle temporal gyrus, PCG, medial superior frontal gyrus, inferior occipital gyrus and superior temporal gyrus), while depression is more associated with limbic alterations (putamen, pallidum, hippocampus, amygdala, thalamus) (Liu et al., 2019). The fronto-limbic disconnection has been proposed as a candidate reliable biomarker for BD, mediating the relationship between the underlying susceptibility genes and the clinical expression (Vai et al., 2019). The structural disruption of white matter (WM) connectivity has been consistently confirmed by meta-analyses (Vederine et al., 2011). Today, there is also direct evidence of how alterations in glutamatergic transmission can directly affect the structural disruption of WM connectivity in BD. Indeed, it has been found that the carriers of the G allele of the Glu transporter polymorphism EAAT2-181A > C (rs4354668) showed lower axial diffusivity compared to T/T homozygotes when exposed to high stress and higher axial diffusivity than T/T when exposed to low stress. The WM tracts involved include inferior and superior longitudinal fasciculus and the inferior fronto-occipital fasciculus. This suggest that G/G homozygotes are vulnerable to stress as a consequence of an excess of free Glu (Poletti et al., 2019). Moreover, the same group reported lower fractional anisotropy (FA) in bilateral frontal WM tracts, lower gray matter (GM), and higher BOLD fMRI neural responses to emotional stimuli in medial prefrontal cortex (mPFC) in AA risk genotype of the Homer rs7713917, along with long term effects of lithium on WM structure (Benedetti et al., 2018). As the Homer family of postsynaptic scaffolding proteins plays a crucial role in Glu-mediated synaptic plasticity (de Bartolomeis et al., 2014), these data highlight the importance of the association between genetics and connectivity changes in BD.

Importantly, studies on BD show that the glutamatergic synapses do



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Fig. 1. The different sites of action of glutamatergic drugs in bipolar disorder. A) At low doses ketamine is thought to preferentially bind to NMDARs on GABAergic interneurons decreasing interneurons activity which in turn causes disinhibition of glutamatergic neurons (Widman and McMahon, 2018); B) Increased depolarization of the presynaptic neuron leads to a surge of glutamate release that binds and activates postsynaptic AMPARs (CI- and CP- subtypes) which conduct Na⁺ and Ca²⁺ into the cell (Yamamoto et al., 2015). This triggers the activity-dependent vesicular release of BDNF into the synaptic space that binds to and activates its surface receptor TrkB which in turn activates downstream signaling cascades involving ERK and Akt. These 2 pathways converge on mTOR, which is a key regulator of protein synthesis and synaptic plasticity (Miller et al., 2014). C) Mood stabilizers, ketamine and psychedelics increase AMPAR surface expression on the post-synaptic glutamatergic neuron. At the same time they increased cAMP production that in turn acts on PKA which activates the transcription factor CREB. D) Blockade of the postsynaptic NMDA receptors protects the neuron from the neurotoxic effects of glutamate by limiting intracellular CA²⁺ levels. Moreover, basal NMDAR activity suppresses AMPAR-mediated synaptic transmission; thus, the blockade of NMDAR boosts synaptic transmission by increasing surface AMPAR insertion (Sutton et al., 2006). E) GSK-3 β in the active form inhibits transcription factors such as β -catenin and CREB. Lithium and valproate inhibit GSK-3 β allowing transcription factors to migrate into the nucleus where they form a transcription complex with TCF/LEF promoting neuroplasticity. Moreover, lithium and valproate activate the wnt/ β catenin and increase BDNF levels that help further disable GSK-3 β (Ryves and Harwood, 2001; De Sarno et al., 2002; Cechinel-Recco et al., 2012). F) Both lithium and valproate directly inhibit several key enzymes that regulate recycling of inositol-1,4,5-trisphosphate (IP₃). This implies a reduction in IP₃ and DAG levels, resulting in reduced intracellular calcium levels and reduced PKC activation (Malhi et al., 2013). These effects are thought to underlie the antimanic and neuroprotective actions of lithium. Psychedelics can have the same effect by directly inhibiting mGluRs 1/5 (Dakic et al., 2017) (G). H) Both lithium and valproate decrease Homer1b/c transcription inducing sustained neuroplastic changes by affecting mGluRs1/5 coupling to inositol 1,4,5-trisphosphate receptors (IP₃Rs) as well as the mGluRs1/5 targeting and clustering to dendritic spines. Moreover, Homer-mediated signal from mGluRs directly regulate NMDA function, so that its inhibition results in down regulation of NMDAR (de Bartolomeis et al., 2014). I) Psychedelics specifically act on the 5ht_{2a}-mGluR2 hetero-complex, inducing downstream signalling cascades involving MPAPKs and ERK (Moreno et al., 2011). These 2 pathways converge on mTOR, which is a key regulator of protein synthesis and synaptic plasticity. J) Lithium and Riluzole increase the uptake of extracellular glutamate by increasing EAATs transcription on astrocyte and pre-synaptic neuron (Frizzo et al., 2004). K) Lamotrigine and Riluzole block of Na⁺, K⁺ and Ca²⁺ channels in the pre-synaptic neuron prevent the exaggerated glutamate release (Brody et al., 2003). L) Ant inflammatory properties of these drugs induce reductions of inflammatory markers principally, IL-1 β , IL-6, and TNF- α . Particularly, ketamine activate the neuroprotective branch of the KYN pathway (Kadriu et al., 2019), increasing the level of kynurenic acid that exerts neuroprotective actions by inhibiting NMDARs. M) Valproate and Lamotrigine exert anti-inflammatory and neuroprotective actions via HDAC inhibition that increase the anti-apoptotic Bcl-2 protein expression and reduce inflammatory molecules' expression (Leng et al., 2013).

not appear to lose their plasticity during life. Indeed, the impaired glutamatergic synaptic plasticity can be at least partially normalized by medications. Interestingly, mood stabilizers, have well-documented neuroprotective and neurotrophic effects in vivo and in vitro. For example, long-term lithium treatment increases total GM volume (Moore et al., 2000b), enhances levels of N-acetyl-aspartate, a marker of neuronal viability (Moore et al., 2000a); and increases diffusion tensor imaging (DTI) measures of axial diffusivity (AD) in several WM fibre tracts, including interhemispheric, limbic, and large frontal, parietal, and fronto-occipital connections in the brains of bipolar patients, correlating with its clinical efficacy (Benedetti et al., 2013). In addition, there is increasing evidence that the antidepressant action of ketamine and hallucinogens is primarily due to glutamatergic neuroplasticity processes.

The purpose of this narrative review is to summarize data from clinical and pre-clinical studies that have addressed glutamatergic alterations in BD. Our priority was given to systematic review articles and meta-analyses, or recent research articles when analytical articles were not available. Along with an in-depth discussion of glutamatergic alterations in BD, we also report available data on the neuroprotective and neuroplastic potential of the classic mood stabilizers, ketamine, and hallucinogens. The glutamatergic mechanisms underlying the efficacy of these drugs are described and discussed.

2. Glutamate system alterations in BD

A growing body of evidence indicates that abnormalities of glutamatergic neurotransmission play an important role in the development of many major psychiatric disorders (e.g., schizophrenia, BD and MDD). In this section, we report evidence from recent genetic, molecular, post-mortem and neuroimaging studies about glutamatergic dysfunction in the pathophysiology of BD. In addition, Table 1 summarizes the main glutamatergic alterations in BD contrasting to unipolar depression. To date, the most robust findings about glutamatergic dysfunction in BD subjects include higher levels of Glx in frontal brain regions and reduced expression of iGluRs. Moreover, genetic studies have substantially reported reduced gene expression of Glu receptors in BD.

2.1. Genetic

Meta-analysis of genome-wide studies suggests that Glu receptor

signalling is importantly involved in BD (Nurnberger et al., 2014). Indeed, reduced gene expression of the NMDAR NR1 and NR2B subunits has been detected in the perirhinal cortex of patients with BD (Beneyto et al., 2007). Similar findings have been reported for AMPARs subunits, whose levels have been found decreased in cortical areas of subjects with mood disorders (Beneyto et al., 2007; Beneyto and Meador-Woodruff, 2006). Selective reduction in striatal gene expression of the AMPAR subunit GluR1 has been also observed in patients with BD (Meador-Woodruff et al., 2001). Other genetic studies have reported that patients with BD exhibit aberrant DNA copy number at several loci containing genes involved in Glu signalling, including the GluR7 gene that encodes for a kainate receptor subunit (Wilson et al., 2006). Indeed, polymorphisms in GRIN1, GRIN2A, and GRIN2B genes, encoding for NMDAR subunits, have been reported to confer susceptibility to BD (Itokawa et al., 2003; Martucci et al., 2006; Mundo et al., 2003).

Genetic studies on metabotropic glutamate receptors (mGluRs) have received less attention despite their potential mechanisms of crosstalk in the form of bridging between ionotropic (iGluRs) and mGluRs via synaptic scaffolding proteins that interact with both GluRs classes. Metabotropic glutamate receptors are G-protein coupled receptors (GPCRs) that have been categorized into three groups: Group I (mGlu₁ and mGlu₅ receptors), Group II (mGlu₂ and mGlu₃ receptors) and Group III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈ receptors) (Alexander et al., 2021). Group I mGluRs increase neuron excitability, whereas Groups II and III tend to suppress neuronal excitability (Conn and Pin, 1997). Both iGluRs and mGluRs can modulate the function of voltage-gated Ca²⁺ channels (VGCCs), providing many opportunities for crosstalk where Ca²⁺ signals act cooperatively to control cellular processes. Group I mGluRs and NMDARs interactions via Homer-SHANK-DLGAP-PSD-95 or competition for the same scaffold (e.g., PICK1, which contains a common binding site for mGluR7 and AMPARs) have been reported (Reiner and Levitz, 2018). Moreover, group I mGluR-mediates control of AMPAR internalization, which contributes to the long-term depression (LTD) at glutamatergic synapse (Reiner and Levitz, 2018). GRM3 is the most widely studied of the mGluRs genes with contrasting results. Only two studies (Kandaswamy et al., 2013; Sklar et al., 2008) have replicated the association of GRM3 SNPs with BD while others have found no associations (Blacketer et al., 2017). Genetic analyses suggest mGluR4 as a candidate gene for susceptibility to BD (Fabbri and Serretti, 2016). Data from different bipolar phenotypes, cyclothymic, and schizoaffective cases suggested that certain GRM4 SNPs (rs1109654, rs2499724,

Table 2
Studies of ketamine in bipolar depression.

Study	Design	Dosing	Measurement	Results	Side effects
Diazgranados et al. (2010)	Placebo controlled (n = 18)	IV ketamine 0.5 mg/kg Single infusion (40 min)	MADRS	Ketamine improved depressive symptoms compared to placebo (71% responded to ketamine, 6% to placebo, defined as $\geq 50\%$ reduction in MADRS score)	Manic symptoms induced by ketamine (n = 1) and by placebo (n = 1), most common were dissociative symptoms
Zarate et al. (2012)	Placebo controlled (n = 15)	IV ketamine 0.5 mg/kg Single infusion (40 min)	MADRS	Ketamine improved depressive symptoms compared to placebo (79% responded to ketamine, 0% to placebo, defined as $\geq 50\%$ reduction in MADRS score)	No serious adverse effects, most common were dissociative symptoms, ketamine did not increase manic symptoms
Rybakowski et al. (2013)	Open label (n = 25)	IV ketamine 0.5 mg/kg Single infusion (40 min)	HDRS	52% responders (defined as $\geq 50\%$ reduction in HDRS score), 12 patients remitted (defined as ≤ 7 score in HDRS) after 14 Days	not mentioned
Permoda-Osip et al. (2013)	Open label (n = 20)	IV ketamine 0.5 mg/kg Single infusion (40 min)	HDRS	50% responders (defined as $\geq 50\%$ reduction in HDRS score)	not mentioned
Permoda-Osip et al. (2014)	Open label (n = 42)	IV ketamine 0.5 mg/kg Single infusion (40 min)	HDRS	Ketamine significantly improved depressive symptoms, 52% responders (defined as $\geq 50\%$ reduction in HDRS score)	No serious adverse effects, most common were dissociation symptoms
Lally et al. (2014)	Placebo controlled (n = 36)	IV ketamine 0.5 mg/kg Single infusion (40 min)	MADRS and SHAPS	Ketamine rapidly reduced levels of anhedonia independent from reductions in general depressive symptoms	not mentioned
Nugent et al. (2014)	Placebo controlled (n = 21)	IV ketamine 0.5 mg/kg Single infusion (40 min)	MADRS	43% responders (defined as $\geq 50\%$ reduction in MADRS score)	dissociative symptoms
Ionescu et al. (2015)	Open label (n = 36)	IV ketamine 0.5 mg/kg Single infusion (40 min)	MADRS and HDRS	Ketamine induced an antidepressant response regardless of baseline anxiety status	dissociative symptoms
Rybakowski et al. (2017)	Open label (n = 53)	IV ketamine 0.5 mg/kg Single infusion (40 min)	HDRS	51% responders (defined as $\geq 50\%$ reduction in HDRS score)	Depersonalization experienced by 1/3 of patients during infusion

MADRS Montgomery–Åsberg Depression Rating Scale, HDRS Hamilton Depression Rating Scale, SHAPS Snaith–Hamilton Pleasure Scale, IV intravenous

rs2499726, rs9380406) were significantly associated with mood episode frequency ([Fabbri and Serretti, 2016](#)). Accumulating evidence suggests that GRM7 is associated with BD ([Kandaswamy et al., 2014](#)), as GRM7 SNP rs6769814 was significantly associated with BD in combined genotype data and meta-analysis ([Kandaswamy et al., 2014](#)). Post-mortem genetic studies have identified a significant reduction of mGluR5 protein levels in all the brain sites in BD and reduction of the mRNA levels for mGluR5 in the superior frontal cortex (Brodmann Area 9 [BA9]) of subjects with BD alongside a reduction of Fragile X mental retardation protein (FMRP) levels in all the brain sites of BD ([Fatemi et al., 2013](#)). Normally, FMRP decreases mGluR5-mediated signalling; thus, FMRP deficits should deregulate mGluR5 signalling ([Bear, 2005](#)). Further investigation is needed to establish why FMRP and mGluR5 protein levels decrease in BD, especially in light of normal FMR1 mRNA levels.

2.2. Blood and urine

Studies of Glu and related markers in blood and urine of subjects with BD have supported the hypothesis of glutamatergic dysfunctions, suggesting that they may not be limited to the brain. Increased plasma Glu levels have been observed in patients with BD compared to healthy controls ([Altamura et al., 1993](#); [Hoekstra et al., 2006](#)), although this has not been confirmed in subsequent studies ([Palsson et al., 2015](#)).

Peripheral Glu uptake by platelets was found to be increased in manic and euthymic bipolar patients versus controls, with no difference during depressive episodes ([Daniele et al., 2012](#)). An increase in Glu uptake might indicate a compensatory mechanism to reduce an excess of circulating Glu. Other studies found increased serum levels of glutamine (Gln), glycine and D-serine in clinically stable patients with BD as compared to healthy controls, and significantly lower L-serine serum levels in BD ([Hoekstra et al., 2006](#); [Palsson et al., 2015](#)). This pattern was not mirrored in cerebrospinal fluid (CSF) where no statistically significant differences were found ([Palsson et al., 2015](#)). Taken together, the results support the notion of a systemic aberration in Glu signalling. However, the studies do not present a clear picture on changes in blood or CSF amino acid concentrations, with relevance for glutamatergic signalling in BD. The development of the oxidative stress theory of BD has led to identification of potential biomarkers possibly linked to glutamatergic pathways. During manic episodes, nitric oxide (NO) levels were found to be increased in blood serum, accompanied by reduced superoxide dismutase ([Gergerlioglu et al., 2007](#)). Meta-analyses have found increased NO levels in people with BD compared with healthy controls ([Brown et al., 2014](#)). In this context, glutathione has been suggested to be involved in glutamatergic neurotransmission via the positive modulation of NMDAR function, as well as acting as an antioxidant ([Chin et al., 2006](#)). Notably, research has reported that plasma

glutathione levels are reduced in patients with BD (Nucifora et al., 2017; Raffa et al., 2012; Rosa et al., 2014). The role of anti-NMDAR antibodies has received particularly attention, for the potential pathogenic role of Glu-related antineuronal antibodies in neuropsychiatric disorders. NMDAR antibodies are considered to cause a reduction in NMDAR expression and subsequent neuronal dysfunction (Pruss et al., 2012). Dickerson et al., (Dickerson et al., 2012) found that BD patients had elevated anti-NMDAR antibodies during mania, but not after recovery. A meta-analysis of the association between NMDAR antibodies and schizophrenia, schizoaffective disorder, BD, and major depressive disorder (MDD) reported a significantly higher odds ratio for NMDAR antibody seropositivity among all the studied conditions with various combinations of IgG, IgM, and IgA class antibodies against the NR1, NR1/NR2B, and NR2A/NR2B subunits (Pearlman and Najjar, 2014). In line with this, a recent study found that patients with an acute manic episode had significantly higher levels of anti-NMDAR antibodies compared to euthymic patients during long-term lithium treatment, suggesting a role for anti-NMDAR antibodies in the pathogenesis of acute mania (Ferensztajn-Rochowiak et al., 2019). One possible mechanism explaining the normalization of NMDAR antibodies levels during remission could be the possible therapeutic effects of lithium in modulation of the immune system (Rybakowski, 2000).

Studies using both gas chromatography-mass spectroscopy (GC-MS) and nuclear magnetic resonance (NMR) spectroscopy have tried to characterize the urinary profile of patients with BD and healthy controls. In particular, quantitative analysis showed that the urinary level of 2,4-dihydroxypyrimidine is significantly decreased in BD subjects relative to healthy controls and in addition, 2,4-dihydroxypyrimidine has been identified as a promising candidate urinary biomarker for BD (Xu et al., 2014). Given the role of 2,4-dihydroxypyrimidine in Gln formation, the decreased level of 2,4-dihydroxypyrimidine implies a role of the Gln–Glu cycle in the pathogenesis of BD (Hashimoto, 2018). Moreover, 2,4-dihydroxypyrimidine has also been identified as a potential urine metabolite that could distinguish BD from MDD (Chen et al., 2015).

2.3. Post-mortem and CSF

Studies on CSF glutamatergic metabolites in BD are still scarce. One study reported lower CSF Glu and glycine in BD and another reported no difference compared to healthy controls (Frye et al., 2007a; Palsson et al., 2015). Post-hoc analysis of the study of Palsson and colleagues (Palsson et al., 2015) found that CSF Gln and D-serine levels were positively associated with lithium and valproate treatment, confirming previous data showing that treatment with valproate increase the CSF levels of Gln (Perry et al., 1976). There is increasing interest in the excitotoxic and oxidative stress pathways linked to Glu. In particular, the kynurenine (KYN) pathway has gained more and more importance in psychiatry research. On the one hand, it has been linked to the excitotoxic effects of Glu via quinolinic acid (Qa) (product of the kynurenine pathway) as a Glu NMDAR agonist (Stone et al., 2012). On the other hand, it is known that kynurenic acid (KynA) could have neuroprotective potential via NMDA antagonism (Cervenka et al., 2017). Despite theoretical neuroprotection effects of KynA, an increase in KynA has been implicated in BD. Indeed, studies consistently found that KynA is increased in CSF of BD patients with a history of psychotic features (Lavebratt et al., 2014; Olsson et al., 2010; Olsson et al., 2012; Sellgren et al., 2019; Trepci et al., 2021) and this has been confirmed also by a meta-analysis (Wang and Miller, 2018). Induction and exacerbation of psychotic symptoms by other NMDAR antagonists such as ketamine support the hypothesis of the influence of KynA on psychotic features in BD. Another explication is that increase in CSF KynA may be a protective factor associated with recovery from illness rather than a pathogenic marker because studies reporting increased CSF KynA in BD included symptom-free subjects with a history of psychosis.

Post-mortem studies have generally supported the hypothesis of abnormalities in glutamatergic neurotransmitter mechanisms in BD.

Studies using ^1H NMR spectroscopy-based metabolomics have described increased Glu levels in cortical brain areas in BD subjects (Hashimoto et al., 2007; Lan et al., 2009). However, it's worth knowing that tissue concentrations of small molecules, like Glu, in brain samples are significantly affected by post-mortem interval (Perry et al., 1981). For example, Glu concentration decreases with increasing length of post-mortem interval (Hashimoto et al., 2007). Therefore, metabolomics using post-mortem brain samples is not very useful for the identification of biomarkers. Post-mortem studies examining iGluRs from patients with BD have found reduced expression of NMDAR subunits and receptor-associated proteins in the hippocampus (McCullumsmith et al., 2007), dorsolateral prefrontal cortex (DLPFC) (Beneyto and Meador-Woodruff, 2008), while others have noted reduced expression of NMDA, AMPA, and kainite receptor subunits in medial temporal lobe structures (Beneyto et al., 2007). In particular, reduced NMDAR NR1 and NR2a mRNA levels have been found in hippocampus dentate gyrus of BD (Law and Deakin, 2001; McCullumsmith et al., 2007). Interestingly, increased activity in NO synthase, has also been reported in the hippocampus of patients with BD (Oliveira et al., 2008). Nitric oxide synthase (nNOS) is possibly upregulated in response to reduced NMDAR functioning as NO release is activated by NMDAR activation (Doucet et al., 2012). Notably, recruitment by NMDARs of calcium-dependent enzyme nNOS via PSD95 is seen as a key contributor to neuronal excitotoxicity. In this scenario, nNOS adaptor protein (NOS1AP) is viewed as an inhibitor of NMDA function. In line with this, overexpression of NOS1AP has been found in brain tissue from patients with BD and schizophrenia (Xu et al., 2005). Overexpression of NOS1AP could exacerbate NMDARs hypoactivity in BD. Moreover, an in-utero electroporation study in neuronal progenitor cells of embryonic rat neocortex (Carrel et al., 2015) showed that NOS1AP overexpression disrupts neuronal migration, resulting in increased cells in intermediate zone (IZ) and fewer cells in cortical plate (CP), and decreases dendritogenesis, supporting the neuro-development hypothesis of BD (Guglielmo et al., 2021). In line with this, patients diagnosed with BD have been reported to show altered neuronal connectivity and heterotopias (Sanches et al., 2008). Interestingly, the long isoform (L) of NOS1AP mRNA expression is significantly decreased by 40% in post-mortem brain tissue from bipolar patients treated with antipsychotics when compared to untreated patients (Xu et al., 2005). This finding is difficult to interpret, since expression of short-form mRNA does not appear sensitive to treatment with antipsychotic medication. A study found that treatment with D-serine, a full co-agonist at the glycine modulatory site on the NMDAR, reduced expression of three NOS1AP isoforms and rescued in vitro NOS1AP overexpression induced reductions in dendrite branching. The same study did not find any effect for antipsychotics (Svane et al., 2018). This may be due to the primary action of antipsychotics on dopaminergic receptors without direct agonism on NMDARs as in the case of D-serine. As the nitrinergic system comprises a relevant target for pharmacological interventions, further studies are warranted.

mGluRs have received less attention in the research on BD. An in-situ receptor autoradiography post-mortem study found that mGluRs were unaltered in the anterior cingulum of patients with BD (Matosin et al., 2014).

Beyond Glu receptors, post-mortem studies have found a direct involvement of the striatal excitatory amino acid transporters (EAATs), a family of molecules responsible for maintaining appropriate synaptic Glu levels via transport of Glu into neurons or glia. Particularly, an in-situ hybridization study from brain tissues detected decreased expression of EAAT3 and EAAT4 transcripts in the striatum in BD (McCullumsmith and Meador-Woodruff, 2002). A decrease in EAAT3 and/or EAAT4 expression may diminish the capacity of the synapse to clear Glu, resulting in increased levels of Glu and its metabolites.

2.4. Molecular neuroimaging

Neuroimaging studies have provided direct evidence of Glu dysfunction in the pathophysiology of BD. ^1H -MRS can detect N-acetylaspartate (NAA), Glu, Gln, the combined signal of Glu and Gln (Glx), creatine, choline-containing compounds, and several other metabolites in specific brain regions. The information of glutamate derived by MRS does not exactly reflect glutamatergic neurotransmission but rather the total level/concentration in the given region of interest (Li et al., 2018).

To date, ^1H -MRS findings of BD have been mixed, with the most robust findings showed Glx increases and NAA reductions in various brain regions. A meta-analysis of ^1H -MRS studies on brain Glu and Gln in BD showed that patients with BD had widespread increased Glx, including in the PFC, compared with healthy control subjects (Gigante et al., 2012). The finding of increased Glx in the frontal cortex was replicated in a subsequent meta-analysis (Chitty et al., 2013). The most recent systematic review of 26 studies concluded that specific ^1H -MRS findings in patients with BD include NAA reductions and Glu or Gln increases in frontal areas, such as the DLPFC, anterior cingulate cortex (ACC), and hippocampus (Szulc et al., 2018). The same study examined the effects of lithium. The investigators found inconclusive results regarding Glu levels and the influence of lithium treatment, i.e., no correlation was found between decreases in Glx and symptomatic improvement (Szulc et al., 2018). One possible explication of the Glx increase in BD is the post-mortem finding of a reduction in the expression of Glu transporters, EAAT3 and EAAT4, in BD (McCullumsmith and Meador-Woodruff, 2002).

PET/SPECT studies using specific radioligands targeting Glu receptors in BD are still lacking. This is due to the complexity associated with developing radioligands for iGluRs. Tracer development for Glu targets is often hampered by pharmacokinetic factors such as limited blood-brain barrier penetration, rapid clearance, and nonspecific receptor binding (Kassenbrock et al., 2016). Tracer development for iGluRs is relevant given the observation that the non-competitive NMDA antagonist ketamine acts as a rapid antidepressant in treatment resistant depression (TRD) and bipolar depression. In this sense, 18F-(18F-fluorodeoxyglucose FDG)-PET, in combination with glutamatergic agents (i.e. ketamine) has been proposed as an alternative and proxy measure of glutamatergic neurotransmission (Li et al., 2018). An 18F-FDG-PET study, before and after ketamine infusion, found that brain glucose metabolism changes in the right ventral striatum of basal ganglia were significantly correlated with depression improvement (Nugent et al., 2014). In particular, bipolar patients had significantly lower glucose metabolism in the left hippocampus following the ketamine infusion compared to after placebo. In addition, patients with the largest improvement in depression symptoms had the largest regional cerebral glucose metabolic rates increase (rCMRglu increase) in the right ventral striatum post-ketamine compared to placebo. In addition, metabolism of the sgACC was positively correlated with improvements in depression scores following ketamine (Nugent et al., 2014). These findings suggest that ketamine improved BD depression by promoting glutamatergic neurotransmission in brain firegions involved in reward processing and emotion regulation.

In line with the aforementioned findings of glutamatergic dysmodulation in BD, a transcranial magnetic stimulation study has reported impaired cortical inhibition in patients with BD (Levinson et al., 2007). Unfortunately, paired-pulse transcranial magnetic stimulation (ppTMS) research that specifically examines intracortical facilitation (ICF) is still lacking, despite research demonstrating cortical inhibitory deficits in patients with BD (Levinson et al., 2007).

3. Mood stabilizers, antipsychotics, riluzole and glutamatergic transmission

3.1. Neuroprotection and neuroplasticity

Neuroprotection is a mechanism to preserve neurons so that neurons cannot be hurt by different risk factors like stress. This mechanism may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function (Vajda, 2002). It is thought that there are many neurochemical modulators of nervous system damage. On the other hand, neuroplasticity is the brain's ability to change throughout life and consists of changes in cell structure, structural plasticity, and changes in the efficacy of synaptic transmission, also called functional plasticity (Fuchs and Flugge, 2014). Neuroplasticity includes structural and functional mechanism leading to neurogenesis, dendritogenesis and synaptogenesis (de Vos et al., 2021). Both neuroprotection and neuroplasticity include molecular changes (i.e. gene transcription, protein synthesis and signalling pathway) and cellular changes (i.e. survival and differentiation).

There is plenty of evidence to support the neuroprotective role exerted by mood stabilizers in BD but direct data on neuroplastic mechanisms mediated by mood stabilizers via the glutamatergic synapse are still scarce (Table 3). This is quite surprising because dysfunctions in plasticity cascades have been found in BD pathophysiology and the actions of mood stabilizers on cell proliferation and synaptic structuring may be involved in the processes of long-term potentiation (LTP) or long-term depression (LTD) at cellular level. The cellular mechanisms that contribute to neuroprotection are also involved in neuroplasticity and may give us an indication of the neuroplastic potential of classical mood stabilizers, particularly lithium and valproate.

The putative neuroprotective effects of mood stabilizers rely on the modulation of several homeostatic mechanisms involved in autophagy, oxidative stress, neurotrophic response, inflammation, and mitochondrial function.

From a clinical perspective, neuroplasticity increase is mostly helpful in depression, but could be potentially harmful in mania because it is associated with increased openness toward new experiences which is thought to be a clinical correlate of enhanced neuroplasticity (Jackson et al., 2012). As a result, such therapy may be more likely effective for patients with predominantly depressive polarity. Regarding bipolar phase, it might be that such therapy are particularly well-suited for patients in later stages of the illness because neuroplasticity decreases with illness duration and with age. This is in line with the glutamate dysfunction across the lifespan (Roalf D et al., 2021). In fact, age-related changes in Glu neurometabolites result in global lower levels of Glu and Glx in healthy aging (Roalf et al., 2020). At the cellular level, age-related changes in the brain include reductions in neuron size, neuron density, dendritic arborization, and axonal length (Drachman, 2006). Finally, age-related reductions in Glu metabolites likely affect the balance of neural transmission, ultimately affecting cognitive functioning and behavior.

In this section we will focus specifically on neuroprotective and neuroplastic effects of mood stabilizers involving the glutamatergic system.

3.2. Neuroprotection preclinical evidence

Long-term lithium use exerts neuroprotective activity, probably by increasing Glu reuptake and downregulating NMDAR and inositol 1, 4, 5- phosphates receptors (Nonaka et al., 1998). In the short term it inhibits the inositol-mono phosphatase enzyme, resulting in inositol depletion and disruption of the inositol cycle (Malhi et al., 2013). Several molecular mechanisms could account for his neuroprotective action. Chronic treatment with lithium or valproate has been reported to decrease hippocampal GluR1 gene expression in rats (Du et al., 2004). Lithium treatment has also been found to suppress NR2B

Table 3

Neuroprotective and neuroplastic power of glutamatergic therapeutic drugs in bipolar disorder.

Drug	Glutamatergic neurotransmission	Signaling pathways	Structural and functional changes
Lithium	Block of pre-synaptic NMDA ↑ Post-synaptic AMPA ↓mGluR 1/5 IP3Rs coupling	↓GSK3β, ↑BDNF, ↓HOMER 1b/c, ↑Bcl2, ↑EAAT3, ↑AKT kinase, ↑wnt/β-catenin pathway, ↓neuroinflammation, ↓IP3, ↓Glu induced increase in [Ca2+], ↓Glu induced reactive oxygen accumulation	↑Global GM volume ↑PFC, amygdala and hippocampus volumes ↓WM volume reduction ↑DTI AD
Valproate	↓NMDA transmission involving AA signaling ↓mGluR 1/5 IP3Rs coupling ↑GABA transmission	↑Bcl2, ↑BDNF, ↓GSK3β, ↓HOMER 1b/c, ↓inositol uptake, ↓Glu induced increase in [Ca2+], ↓Glu induced reactive oxygen accumulation, ↓inflammation (HDAC inhibition)	↑Global GM volume
Lamotrigine	Inhibition of voltage-dependent Na+, Ca++ , K+ , channels ↓ Glu release ↑ Post-synaptic AMPA	↑Bcl2, HDAC inhibition, ↑PPI in both the mGluR1 knockout and wild type mice, ↑BDNF?	↓amygdala, cerebellum, and nucleus accumbens volumes ↓amygdala activation (fMRI)
Riluzole	Inhibition of voltage-dependent Na+ channels ↓Glu release ↑astrocyte Glu reuptake ↑cortical Glu metabolism ↑AMPA trafficking	↓neuroinflammation (via modulation of PKC and MAPK pathways), ↓GFAP, ↑BDNF, ↓caspase3?, ↓JNK?, ↑Bcl2?	↑Acc Gln/Glu ratio ↓Acc Glx ↑Acc-frontal functional connectivity
Ketamine	Block of NMDA ↑Post-synaptic AMPA ↓GABAergic interneurons	↑kynurenine, ↑kynurenic acid, ↓QA/KYN ratio, ↓IL-1β, ↓IL-6, ↓TNF-α, ↑BDNF, ↑mTOR, ↑Trkβ	↑functional connectivity ↑dMRI FA ↑spine formation rate
Psychedelics	5-HT2ARs agonists 5-HT2A-mGlu2 receptors modulators ↑Glu in PFC ↑AMPA ↓mGluR5	↑mTOR, ↑BDNF, ↑Trkβ, ↑cFOS, ↓inflammation, ↓IL-2, ↓IL-4, IL-6, ↓TNF-α, ↓IDO	↑Adult neurogenesis, spinogenesis and synaptogenesis Global network disintegration and connectivity reset ↓REM ↑SWS

5-HT2ARs 5-Hydroxytryptamine Receptor 2A, AA arachidonic acid, ACC anterior cingulate cortex, AD axial diffusivity, AKT protein kinase B, AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, Bcl2 B-cell lymphoma 2, BDNF brain-derived neurotrophic factor, Ca2+ calcium ions, cFOS fos proto-oncogene, dMRI diffusion magnetic resonance imaging, DTI diffusion tensor imaging, EAAT3 Excitatory amino acid transporter 3, FA fractional anisotropy, fMRI functional magnetic resonance imaging, GABA gamma-aminobutyric acid, GFAP glial fibrillary acidic protein, GLN glutamine, GLU glutamate, GLX glutamine and glutamate, GM grey matter, GSK3β glycogen synthase kinase-3 beta, HDAC histone deacetylase, HOMER 1b/c homer protein homolog 1b and c, IDO indoleamine 2,3-dioxygenase, IL-1β interleukin-1 beta, IL-2/4/6 interleukin 2–4–6-, IP3Rs inositol triphosphates receptors, JNK c-Jun N-terminal kinase, K+ potassium, KYN kynurenic acid, MAPK Mitogen-activated protein kinase, mGluR 1/5 metabotropic glutamate receptors 1 and 5, mTOR mammalian target of rapamycin, Na+ sodium, NMDA N-methyl-D-aspartate receptors, PFC prefrontal cortex, PKC protein kinase C, PPI prepulse inhibition, QA quinolinic acid, REM rapid eye movement, SWS Slow-wave sleep, TNF-α tumor necrosis factor alpha, Trkβ tropomyosin kinase B, WM white matter

phosphorylation in cultured cerebral cortical neurons, a mechanism that has been suggested to inactivate NMDARs (Hashimoto et al., 2002), and to alter NMDAR NR1 subunit mRNA expression in primary cultures (Valdes and Weeks, 2009). In cultured hippocampal cells of rat embryos, lithium pre-treatment for seven days significantly decreased the maximum amplitude of [Ca2+]_i for both sustained NMDA-induced and transient mGluR5-induced responses. Moreover, lithium significantly decreased basal [Ca2+]_i and endoplasmic reticulum calcium stores, and significantly reduced cell surface expression of mGluR5 in hippocampal neurons without significantly altering intracellular levels of mGluR5 (Sourial-Bassillious et al., 2009).

Among the various mechanisms of action studied for lithium is that of inhibiting the glycogen synthase kinase 3-β (GSK3-β). GSK3-β is a regulator of several pathways such as inflammation, neuronal polarity, or either cell membrane signalling. Mounting evidence indicates a pivotal role in the glutamatergic synthesis. Of note, GSK3-β acts as a powerful regulator of EAAT3/4 activity and thus of the regulation of NMDARs and glutamatergic currents (Abousaab and Lang, 2016). EAATs 1–5 superfamily's specific alleles have been linked to BD and particularly with the risk to develop a rapid cycle phenotype (Veldic et al., 2019). Lithium treatment has been found to affect GSK-3 protein levels and phosphorylation status in an animal model of mania (Cechinel-Recco et al., 2012) and to inhibit GSK-3, either via competition with magnesium for the active site of the enzyme (Ryves and Harwood, 2001) or via increased phosphorylation at the GSK-3β Ser-9 site and GSK-3α Ser-21 site (De Sarno et al., 2002), putatively via PI-3K/Akt dependent mechanisms (Pan et al., 2011). This has been confirmed in a recent study showed that low-therapeutic dose (0.5 mM) of lithium in the form of LiCl is sufficient to increase GSK3B (ser9) and GSK3α (ser21) phosphorylation with consequent inhibition of GSK 3 activity (Kurgan et al., 2019). These mechanisms are likely to have a key role in the neuroprotective effects of lithium (Quiroz et al., 2010) and could be an essential part of the mechanism of its therapeutics action in BD by correcting impairment of cellular plasticity and resilience (Bachmann et al., 2005).

Chronic treatment with lithium or valproate has been demonstrated to decrease Homer1b/c transcription in brain regions that have specifically been implicated in the pathophysiology of BD (de Bartolomeis et al., 2012). Both lithium and valproate reduce Homer1b/c gene expression in the dorsolateral caudate-putamen, whereas valproate only reduces the expression of the gene also in other striatal subregions. Modulation of the amount of Homer1b/c induces sustained neuroplastic changes by affecting mGluRs1/5 coupling to inositol 1,4,5-trisphosphate receptors (IP3Rs) (Sala et al., 2005). Homer isoforms modulate both, the phosphoinositide (PI) signalling pathway (Mao et al., 2008), and the phosphatidylinositol-3-kinase–Akt (PI3K–Akt) pathway (Ronesi and Huber, 2008), which regulates the function of GSK-3β. Both PI and GSK-3β are targets for lithium and GSK-3β has been implicated in the lithium's effects on GM and WM in BD (Benedetti et al., 2013).

Bipolar mania is associated with a decreased prepulse inhibition (PPI) (Perry et al., 2001), and it is hypothesized that mGluRs mediate PPI. This observation is based on mGluR1/5 knockout mice displaying decreased PPI (Brody et al., 2003). Administration of lamotrigine caused an increase in PPI in both the mGluR1 knockout and wild type mice, perhaps by virtue of its ability to reduce Glu release (Brody et al., 2003). On the other hand, dopamine antagonists, including typical antipsychotic drugs, appear to be ineffective in reversing PPI deficits associated with manipulations of glutamatergic system. These data may suggest that mGluR1 receptors play a role in effective treatment of BD but not in schizophrenia. Moreover, lamotrigine has remarkable neuroprotective effects against Glu excitotoxicity in vitro, where it both induced chromatin remodelling via histone deacetylase inhibition and robustly increased the anti-apoptotic Bcl-2 protein expression (Leng et al., 2013). This is in line with the effects of other mood stabilizers including lithium, valproate, and carbamazepine that have been reported to induce Bcl-2 mRNA and protein levels increase (Leng et al., 2013). Thus,

the effect of mood stabilizers on the regulation of BCL-2 appears to be a key aspect of their neuroprotective mechanism against Glu excitotoxicity.

There is also evidence that antipsychotic drugs with anti-manic properties have neuroprotective effects. Chronic treatment with asenapine decreases the binding of [3H] MK-801 to NMDARs in nucleus accumbens and caudate-putamen, and elevates the binding of [3H] AMPA to AMPARs in hippocampal CA1 and CA3 regions (Tarazi et al., 2009). Thus, asenapine appears to exert a region-specific and dose-dependent effect on NMDARs and AMPARs in rat forebrain (Tarazi et al., 2009). Moreover, asenapine potentiates the NMDAR-dependent currents via activation of D1 receptors (Jardemark et al., 2010).

3.3. Neuroprotection clinical evidence

The class of mood stabilizers incorporates several categories of substances including: lithium, anti-epileptics and antipsychotics among others. It is known that mood stabilizers exert neuroprotective effects in conditions of Glu excess, a finding that has been reported in distinct brain areas of patients with BD, such as the cortex and the hippocampus (van Erp et al., 2012). Subchronic lithium treatment decreases Glx levels bilaterally in basal ganglia of healthy individuals, a feature that has been associated with the pharmacological action of this drug (Shibuya-Tayoshi et al., 2008). In addition, the degree of symptoms improvement in BD remitters has been related to the change in Glu concentrations in the left ventrolateral PFC of young BD subjects experiencing a manic or mixed episode (Strawn et al., 2012), thereby suggesting that lithium and valproate may modulate the prefrontal glutamatergic system.

Discrete GSK-3 gene SNPs have been reported to predict the efficacy of lithium treatment in patients with BD (Benedetti et al., 2005; Mitjans et al., 2015), and GSK-3 has been considered a candidate gene for lithium prophylactic efficacy (Rybakowski et al., 2012). In line with this, Benedetti et al. (Benedetti et al., 2013) found that the less active GSK3- β rs334558 *C gene-promoter variants, and the long-term administration of lithium, were associated with increases of DTI measures of axial diffusivity (AD) in several WM fibre tracts, including interhemispheric, limbic, and large frontal, parietal, and fronto-occipital connections, suggesting that GSK3- β inhibition and lithium could counteract the detrimental influences of BD on WM structure, contributing to the functional integrity of the brain (Benedetti et al., 2013). Moreover, there are preliminary data suggesting that, after a first episode of mania, lithium might be superior to quetiapine in preventing reductions of GM volume. Indeed, a longitudinal study comparing the putative protective effects of lithium and quetiapine on GM and WM volume showed that, compared with baseline, lithium was more effective than quetiapine in slowing the progression of WM volume reduction in the left internal capsule after 12 months. No protective effects were noted on GM (Berk et al., 2017). Although these data support the use of lithium from the earliest stages of the disorder, these results were limited by the high prevalence of psychotic features, schizoaffective diagnoses and substance use in the sample.

It has been proposed that lithium and valproate induced down regulation of Homer1b/c gene expression may represent a neuroprotective mechanism leading to lowered activation of pathways involved in the response to postsynaptic excitatory stimuli (de Bartolomeis et al., 2014). In support of this, a recent clinical study found the best effects of lithium on AD in Homer 1 rs7713917 AA bipolar patients, who showed the worse FA in a sample of 199 subjects. The authors suggested that lithium could counteract the detrimental effect of rs7713917 AA on WM, and that the effects of lithium on Homer could be essential for its effects on WM (Benedetti et al., 2018).

One important therapeutic effects of lithium is modulation of the immune system (Rybakowski, 2000), which involves normalization of increased levels of proinflammatory cytokines in affective episodes, resulting in a state of clinical and neurobiological remission (van den Aamele et al., 2016). A study found that the inflammatory cytokine

concentrations in lithium treated patients experiencing a long-term euthymic status did not differ from those observed in healthy persons (Remlinger-Molenda et al., 2012). Moreover, a study on embryonic-like stem cells and mRNA expression of pluripotency and glial markers in peripheral blood of patients with BD found that patients not treated with lithium had a higher number of very small embryonic-like stem cells, paralleling the illness duration, and an increased expression of inflammatory markers, compared to matched healthy subjects, whereas patients treated with lithium had a lower number of very small embryonic-like stem cells and a lower expression of some inflammatory markers. This may suggest that lithium can alleviate excessive regenerative and inflammatory processes in BD (Ferenstajn-Rochowiak et al., 2018).

About antipsychotics, olanzapine has been reported to modulate Glu neurotransmission as reflected by an increase in serum Glu levels and Glx/creatinine ratio in the ACC of subjects with schizophrenia (Goff et al., 2002). In addition, a 1H-MRS study has shown that medication-naïve children with mania exhibit lower Glx/creatinine levels in the ACC than children with BD in treatment with risperidone (Moore et al., 2007). These findings suggest an involvement of the glutamatergic system in the antimanic mechanism of action of antipsychotic in BD.

Finally, riluzole, a glutamatergic modulator approved for the treatment of amyotrophic lateral sclerosis (ALS), has shown promise as monotherapy or augmentation therapy in TRD (Sakurai et al., 2019). Open-label studies suggested that riluzole in combination with lithium may be effective in treating bipolar depression (Zarate et al., 2005) but it was not more effective than placebo for the treatment of bipolar depression in double-blind studies as monotherapy (Park et al., 2017). Notably, riluzole shows neuroprotective properties. It has been shown to increase Glu uptake and AMPAR trafficking by enhancing membrane insertion of GluR1 and GluR2 subunits (Du et al., 2007; Frizzo et al., 2004). Administration of riluzole in preclinical paradigms has the potential to induce antidepressant-like behaviours (Gourley et al., 2012). In clinical studies, riluzole rapidly increases Gln/Glu ratio and exerts antidepressant effects in patients with bipolar depression (Brennan et al., 2010). Altogether, these findings may further highlight the key role of glutamatergic system modulation in the treatment of patients with BD.

3.4. Neuroplasticity preclinical evidence

Glu, also act through G protein coupled receptors. Thus, the effects of lithium and valproate on the inositol cycle may translate into altered receptor activity following mGluRs stimulation, which in turn dampen the calcium signal, inducing synaptic stabilization (Puglisi-Allegra et al., 2021). By reducing calcium signals, lithium and valproate stabilize the balance between Akt and GSK3 β in favour of Akt (Pisano et al., 2019). In addition, the increase in BDNF due to lithium and valproate administration further increases the action of Akt with consequent further inhibition of GSK3 β (Bramham and Messaoudi, 2005). Akt influence memory consolidation by acting on the Ras-Related C3 Botulinum Toxin Substrate 1 (Rac-1) pathway (Zimmermann and Moelling, 1999) that is required for learning-evoked neurogenesis. Rac-1 enhances the survival of young post mitotic neurons and stimulates the proliferative production and retention of new neurons generated during learning itself (Haditsch et al., 2013). Moreover, another target of Akt is NF- κ B (Listwak et al., 2013), which is involved in potentiation mechanisms as NF- κ B modulates some aspects of postsynaptic membrane density, by clustering together with Glu receptors and increasing their membrane density (Voytyvych et al., 2012).

GSK3 β has also been implicated in the regulation of the direction and magnitude of NMDAR dependent plasticity. In rat hippocampus, induction of NMDAR dependent LTD by electrical stimulation resulted in further activation of GSK3 β through dephosphorylation, while induction of LTP resulted in deactivation of GSK3 β through phosphorylation (Peineau et al., 2007). Therefore, the inhibitory action of lithium and

valproate on GSK3 β modulates NMDAR dependent synaptic plasticity favouring LTP over LTD.

Indeed, the neurogenic properties of lithium have been reported in animal studies, whereby lithium either increases the number of proliferating (Fiorentini et al., 2010) or differentiating neural cells (Kim et al., 2004). To date, there is just one study reporting the relationship between lithium, human hippocampal neurogenesis, and hippocampal volume (Palmos et al., 2021). The authors found that high lithium dose treatment in human hippocampal progenitors increased the generation of neuroblasts, neurons, and glia, alongside the expression of genes which regulate the volume of the molecular layer of the dentate gyrus, particularly genes responsible for cell adhesion and the extracellular matrix (i.e. Laminin Subunit Gamma 1 [LAMC1]) (Palmos et al., 2021). Notably, studies revealed that laminin regulates neurite growth and neuronal migration via integrin signalling through the AKT/GSK-3 β pathway (Chen et al., 2009).

3.5. Neuroplasticity clinical evidence

Clinical research regarding the neuroplastic effects of mood stabilizers is still in its infancy. There are only very few studies that have linked the mechanism of action of mood stabilizers to neuroplasticity.

There is preliminary human evidence that lithium significantly modulates brain stimulation induced plasticity in human cortex. The effect of a single oral dose of 900 mg of lithium on LTP-/LTD-like plasticity in human motor cortex induced by established paired associative transcranial magnetic stimulation (PAS_{LTP}, PAS_{LTD}) has been studied in 10 healthy individuals (Voytovych et al., 2012). It was found that lithium switched the paired associative stimulation (PAS)_{LTP}-induced LTD-like response into an LTP-like response. The authors explained the switch from LTD- to LTP-like plasticity by the inhibitory action of lithium on GSK3 β but GSK3 β activity was not directly measured in that study (Voytovych et al., 2012).

It is known that chronic lithium users exhibit larger hippocampal volumes relative to BD patients who are either unmedicated or undergoing other forms of treatment (Hajek et al., 2012). This suggests that lithium treatment may act on hippocampal volume, either by protecting existing neurons or by promoting neurogenesis.

4. Ketamine

The discovery of ketamine as a rapid antidepressant has caused a paradigm shift in depression research and treatment. Ketamine effects in bipolar depression have been studied in several studies (Diazgranados et al., 2010; Ionescu et al., 2015; Lally et al., 2014; Nugent et al., 2014; Permoda-Osip et al., 2013; Permoda-Osip et al., 2014; Rybakowski et al., 2017; Rybakowski et al., 2013; Zarate et al., 2012) (Table 2). Overall, ketamine improved depressed mood, negative cognition, anhedonia, and suicidal thoughts, reduced appetite, and impaired sleep (Hasler et al., 2020). A recent meta-analysis of 20 randomized and controlled studies evaluated the efficacy of a single or repeated ketamine dose in different subgroups of patients with MDD and bipolar depression (Kryst et al., 2020). A single dose of ketamine reduced depressive symptoms, producing a peak antidepressant effect at 24 h, followed by a significant antidepressant effect lasting up to 7 days after ketamine administration. In addition, ketamine's effect could be observed in TRD patients, who received ketamine in monotherapy, and also when ketamine was used as adjunctive to the current antidepressant therapy, in both unipolar and bipolar depression. Several studies evaluated the efficacy of ketamine repeated treatments; importantly, serial ketamine administration (twice or thrice a week for three weeks) produced a significant and sustained antidepressant effect over placebo at three weeks, both in terms of depression symptoms and in terms of remission (Kryst et al., 2020). Some studies have also been carried out on psychotic depression. However, the safety of ketamine in these patients is controversial since ketamine is known to induce psychotomimetic and dissociative effects.

Additionally, the efficacy and safety of ketamine in patients with psychotic depression has not been established as most clinical trials have excluded these persons due to the theorized risk of aggravating psychotic symptoms (Le et al., 2021).

4.1. Ketamine mechanism of action

While ketamine also appears to be clinically effective in bipolar depression, its mechanism of action remains unclear. To date, the most robust findings about glutamatergic dysfunction in BD subjects include higher levels of Glx in frontal brain regions and reduced expression of iGluRs. Moreover, genetic studies have substantially reported reduced gene expression of Glu receptors in BD. Taken together, these data would primarily indicate an underlying Glu excess that is accompanied by downregulation of glutamatergic receptors in BD. This would seem to be partially opposite to MDD where a reduced Glu concentration along with reduction of glutamatergic receptors has primarily been reported (Amidfar et al., 2019). Glu transmission is mainly known to mediate excitatory synaptic transmission, plasticity and neurotoxicity. In line with this, both BD and MDD are now seen as neuroplasticity disorders. Particularly, synaptic dysconnectivity is a central feature of mood disorders, and this has been linked to an altered glutamatergic function (Abdallah et al., 2015). However, the mechanisms leading to synaptic disconnection, in MDD and BD may be dissimilar in light of data on different Glu levels. This complicates the discovery of ketamine's mechanisms of action considerably.

Ketamine is a non-selective NMDAR antagonist and low sub-anaesthetic dose of ketamine can generate rapid anti-depressant effects on TRD patients. However, whether ketamine's rapid antidepressant effect depends on NMDARs remains controversial. NMDARs are Glu receptors mediating excitatory synaptic transmission. Intuitively, NMDAR antagonism should inhibit neural circuit activity in the brain. However, low doses of NMDAR inhibitors, like ketamine, cause excitation instead of inhibition in the brain. Animal studies have reported that ketamine at sub-anaesthetic doses significantly increases extracellular level of Glu in the PFC in rats (Homayoun and Moghaddam, 2007), and human studies showed that it can increase focal prefrontal activity in healthy volunteers (Breier et al., 1997). Normally, one would expect that NMDAR antagonism should decrease excitability. Different mechanisms have been proposed to explain this paradox. One possibility is that NMDAR inhibitors at low doses preferentially act on GABAergic interneurons (Widman and McMahon, 2018), therefore they decrease interneuron activity and result in disinhibition of the overall neuronal network activity. In contrast, the basal activity of pyramidal neurons, is not directly regulated by NMDARs (Homayoun and Moghaddam, 2007). Thus, it is estimated that ketamine blockage of NMDARs leads to the subsequent suppression of tonic Glu input to GABAergic interneurons and this results in the disinhibition of glutamatergic transmission to pyramidal neurons in the PFC (Yamamoto et al., 2015).

An alternative explanation is that basal NMDAR activity suppresses neuronal activity in excitatory neurons. In this case, NMDAR antagonism leads to attenuation of suppression on excitatory synaptic transmission, therefore promoting excitation and global neuronal activity (Sutton et al., 2006). In fact, it has been reported that basal NMDAR activity suppresses AMPAR-mediated synaptic transmission, and a brief blockade of NMDAR is sufficient to boost synaptic transmission by increasing surface AMPAR insertion, depending on local protein synthesis (Sutton et al., 2006). In line with this, studies have found that blockade of NMDARs rapidly potentiates AMPAR-mediated synaptic transmission (Nosyreva et al., 2013). Specifically, animal studies found that 30 min ketamine antagonism elicits rapid potentiation of synaptic responses recorded in the CA1 region of hippocampus, a key brain region involved in antidepressant action. This potentiation requires eEF2 kinase to trigger rapid protein synthesis of BDNF and increases surface expression of AMPAR (Nosyreva et al., 2013). Interestingly, it seems that NMDAR subunit epsilon-2 (GluN2B) could play a pivotal role for

ketamine antidepressant effect. Indeed, under non-stimulated conditions, ambient Glu activates GluN2B containing NMDARs and suppresses excitatory transmission (Miller et al., 2014). GluN2B inhibition promotes protein synthesis and trigger antidepressant actions via mTOR expression. Notably, ketamine loses its efficacy in inducing antidepressant-like behaviors in mice with GluN2B knockout in cortical neurons (Miller et al., 2014).

Together, these data could partly explain the antidepressant action of ketamine in depressed subjects where reduction in Glu levels has been reported. Thus, NMDAR antagonism would compensate for the reduction in Glu concentration through the mechanisms just described. In contrast, as seen earlier, in bipolar subjects there is rather a Glu excess at baseline. Thus, the antidepressant action of ketamine in bipolar depressed subjects does not depend only on action on NMDARs, but other mechanisms could be considered.

It would be possible to hypothesize a shift in Glu levels between the manic phase (Glu excess) and the depressive phase (Glu reduction). Unfortunately, there are only a few studies that have addressed this hypothesis. One study has shown elevated Glx level in the ACC and PFC during acute mania of people with BD (Ongur et al., 2008). Another study reported an increased anterior cingulate/medial prefrontal cortical Glu (quantified as [Glx] and as [Glu] itself) during a depressed state in people with BD (Frye et al., 2007b). Overall, there is no evidence for phase-specific alterations of cortical Glu concentration in BD patients.

Another hypothesis is that Glu is elevated only in certain areas of the brain of BD. Specifically, neuroimaging studies report high Glu levels, particularly in the frontal areas (Chitty et al., 2013). In this case, the excess Glu precipitates excitotoxicity, altered synaptic strength, reduced dendritic spine density, dendritic retraction, and reduced dendritic branching in the PFC. This may contribute to prefrontal synaptic deficits and the subsequent fronto-limbic disconnection that, as known, is a consistent endophenotype of BD (Guglielmo et al., 2021). It has been found that synaptic deficits are precipitated by reduction in neurotrophic factors such as BDNF and by inhibition of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. Together, these data posit that enhancement of BDNF and mTORC1 signaling leading to prefrontal synaptic formation (synaptogenesis), and reversal of stress- and depression-induced neuronal atrophy and synaptic dysconnectivity, are required for efficacious antidepressant treatment (Abdallah et al., 2015).

However, this hypothesis, although it could explain in part the neuroplastic action of ketamine in conditions of excitotoxicity, cannot solve the enigma of its effects in BD, because, to the best of the actual evidence, it is assumed that bipolar subjects already have an excess of Glu in PFC (Shen and Tomar, 2021). To better explain the mechanism of action of ketamine in BD, we need to consider its anti-inflammatory properties and its action on the KYN cycle. KYN is a metabolite of the amino acid tryptophan (TRP) synthesized by the enzyme tryptophan dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). In the brain, KYN can be differentially processed by either astrocytes in KynA or microglia in Qa. KynA is an antagonist of the NMDAR and through which it exerts neuroprotection, enhances synaptic plasticity, and clears excess Glu in the brain (Cervenka et al., 2017). On the other hand, Qa agonizes NMDARs inducing Glu excitotoxicity and contributing to a signalling cascade that leads to reduced BDNF, protein synthesis, and synaptogenesis (Stone et al., 2012). It is known that a pro-inflammatory state could lead to a switch in the KYN pathway as pro-inflammatory cytokines activate the enzyme IDO, which metabolizes TRP into KYN instead of serotonin (Maes et al., 2007). In addition, pro-inflammatory cytokines activates the enzyme 3-monooxygenase (KMO) (Zunszain et al., 2012), which converts KYN into its neurotoxic microglial products, such as 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA) and Qa (Ogyu et al., 2018), contributing to neurotoxicity. Evidence suggests that alterations of the KYN pathway may contribute to pathophysiology of BD. Studies consistently found that KynA is

increased in CSF of BD patients (Lavebratt et al., 2014; Olsson et al., 2010; Olsson et al., 2012; Sellgren et al., 2019; Trepci et al., 2021) and this has been confirmed also by a meta-analysis (Wang and Miller, 2018). Notably, ketamine has been found to increase the level of KYN, KynA and decreases the level of QA/KYN ratio, in patients with bipolar depression (Kadriu et al., 2019). Moreover, ketamine infusions induce reductions of inflammatory markers principally, IL-1 β , IL-6, and TNF- α , showing rapid anti-inflammatory properties (Wilkowska et al., 2020). The overall evidence seems to support reduction in inflammation and activation of the neuroprotective branch of the KYN pathway, after ketamine treatment. At molecular level, some data postulated that ketamine induces down regulation of proinflammatory cytokine gene expressions by down regulation of endotoxin-induced macrophage activation through toll-like receptor-dependent activation of mitogen activated protein kinases and the transcription factors nuclear factor-kappa B and activator protein-1 (Liu et al., 2012).

The combined direct and indirect action of ketamine on NMDAR may, perhaps better explain its mechanism of action in BD. Indeed, if one assumes a baseline Glu excess, this results in over activation of NMDARs with consequent downregulation in their expression as a homeostatic mechanism to counteract excitotoxicity. In addition, the elevated levels of KynA found in the CSF of euthymic bipolar subjects could indicate another homeostatic mechanism to counterbalance neurotoxicity and promote recovery. As known, basal NMDAR activity suppresses AMPAR-mediated synaptic transmission, and a brief blockade of NMDAR is sufficient to boost synaptic transmission by increasing surface AMPAR insertion (Sutton et al., 2006). Thus, it is possible that the ultimate result of ketamine action in BD is the increased expression of AMPARs through direct antagonism of ketamine on NMDARs and indirectly through reduction of the pro-inflammatory state and subsequent increase in KynA, another NMDA antagonist.

As described, preclinical research has shown that ketamine induces synaptogenesis and this synaptogenesis is necessary for ketamine effects on depressive behaviors. Rapid modulation of synaptic function and neural connectivity are thought to contribute to ketamine's antidepressant actions. Moreover, changes in astrocyte activation and morphology have been implicated in ketamine's antidepressant mechanisms (Ardalan et al., 2017). The extent to which these preclinical findings translate to humans neuroplasticity processes is not clear. Synaptic plasticity and network organization are highly interconnected. According to the graph theory, a complex network can be represented as a set of nodes and edges, respectively indicating the basic elements of the network and the relationships between them. This approach can be used to describe complex networks with different spatial resolution, from microscale to large-scale networks. Studies combining neurophysiological investigations and fMRI measures could help to define the relationship between synaptic plasticity and brain network topology (Bullmore and Sporns, 2009).

In this scenario, there is preliminary, though still speculative, evidence originating from imaging studies on MDD that ketamine produces its antidepressant effects by increasing the number and the strength of synapses, effectively increasing global brain connectivity. A resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) study of global brain connectivity with global signal regression (GBCr) measure, reported that ketamine increases functional connectivity of several regions of GM with the rest of the brain, reflecting increases in regional synaptic strength (Abdallah et al., 2017). The working hypothesis of the authors was that GBCr may reflect overall synaptic strength in a brain region because GBCr has been found to positively correlate with regional cerebral blood flow (rCBF) (Abdallah et al., 2017). Moreover, a recent diffusion magnetic resonance imaging (dMRI) study showed that FA rapidly increased in numerous WM bundles in the brain four hours after intravenous administration of ketamine and this increase was significantly associated with 24 h symptom improvement in select bundles (Sydnor et al., 2020). The authors of this study speculated that the FA changes observed following ketamine are likely the result of astrocyte

plasticity, as 4 h time frame is too short for substantial changes in myelination or axonal organization to occur. Taken together, this preliminary data showed a possible protective effect of ketamine like lithium. Indeed, it has been shown that lithium could counteract the detrimental influences of BD on WM structure, contributing to the functional integrity of the brain, which is a precondition for neuroplastic adaptations of the brain to a changing environment (Benedetti et al., 2013). Moreover, lithium potentiates the electrophysiological, synaptogenic, and antidepressant-like behavioural effects of ketamine in rats (Liu et al., 2013). This supports a pharmacological association of lithium and ketamine in BD treatment, even if recent findings on TRD patients showed that lithium was not superior to placebo in continuing the antidepressant response to ketamine at 2 weeks following the cessation of the ketamine infusions (Costi et al., 2019).

5. Psychedelics

The class of serotonergic psychedelics includes psilocybin, mescaline, ayahuasca (a plant brew containing dimethyltryptamine [DMT] and harmine), 2,5-Dimethoxy-4-iodoamphetamine (DOI), 5-methoxy-DMT (5-MeO-DMT) and lysergic acid diethylamide (LSD). They have been used in psychiatry before they were placed in Schedule I of the UN Convention on Drugs in 1967. Nowadays, there is a resurgence of research investigating the use of psychedelic in psychiatry and psilocybin has recently received the designation of breakthrough therapy for depression by the Food and Drug Administration (FDA). However, modern clinical trials with psychedelics have excluded individuals with BD out of a concern for worsening the course of the condition, so very little is known about the safety and efficacy of psychedelics therapy for people with BD. Modern research began in the early 2000s and has focused on the use of psychedelics in obsessive disorder, alcohol and tobacco addiction, end-of-life depression and anxiety associated with lifethreatening illness and resistant depression in MDD (Rucker et al., 2018). A recent meta-analysis of randomized controlled trials involving 133 patients with mood disorders (particularly end-of-life depression) found significant effect sizes on the acute, medium (2–7 days after treatment), and longer-term outcomes favouring psychedelics (psilocybin, LSD, and ayahuasca) on the reduction of depressive symptoms compared to placebo (Galvão-Coelho et al., 2021). This supports the results of a previous meta-analysis finding that psychedelic-assisted therapy, significantly outperformed placebo, with large effect sizes across a range of mental disorders such as unipolar depression, anxiety/depression associated with a life-threatening illness, social anxiety in autistic subjects, and post-traumatic stress disorder (Luoma et al., 2020). Regarding BD, research is absent. To date, two clinical trials are underway, exploring the safety and efficacy of psilocybin in BDII depression (Table 4).

5.1. Why might psychedelics also be useful in BD?

Like ketamine, serotonergic psychedelics have demonstrated rapid and long-lasting antidepressant and anxiolytic effects in the clinic after a single dose. Several lines of evidence suggest that therapeutically effects of psychedelics arise from biological changes leading to neuroplasticity via activation of Glu networks (Table 3). Briefly, psychedelics act as serotonin 5-HT_{2A} receptors (5-HT_{2A}Rs) agonists. However, accumulating evidence emphasizes the role of the Glu system in psychedelics mediated effects on brain function (Nichols, 2016). Specifically, activation of 5-HT_{2A} receptors leads to a Glu-dependent increase in activity of pyramidal neurons in the PFC (Beique et al., 2007), subsequently modulating prefrontal network activity (Vollenweider and Kometer, 2010). The increase in extracellular Glu has been suggested to activate AMPARs located on the same neurons, increasing expression of BDNF (Vollenweider and Kometer, 2010). Moreover, recent findings demonstrate that mGluR2/3 modulate the responses induced by activation of 5-HT_{2A}Rs. In particular, these findings suggest that the

5-HT_{2A}-mGluR2 complex is critical for the hallucinogen-like behaviors induced by 5-HT_{2A}R agonists. Notably, head-twitch behavior induced by hallucinogenic 5HT_{2A} agonists is abolished in mGlu2-KO mice as well as the cellular response (Moreno et al., 2011). The translational potential of these findings is suggested by the significant involvement of mGluR signalling in BD (Nurnberger et al., 2014).

Preclinical and clinical studies have consistently shown that psychedelics have neuroplastic and neuroprotective properties. It has been demonstrated that administration of 5-methoxy-N,N-dimethyltryptamine (5-MeO-)DMT or LSD resulted in increased dendritic complexity, expressed by an increased number and total length of dendrites in cortical rat neurons (Ly et al., 2018). Psychedelics are significantly more potent and effective than ketamine in promoting neurogenesis probably explaining why psychedelics have a longer duration of antidepressant effects versus ketamine (Ly et al., 2018). In human cerebral organoids, 5-MeO-DMT modulates the anti-inflammatory response, as well as the formation and maturation of new dendritic spines, by modulating specific signaling molecules of LTP such as NMDAR, AMPAR, and Ephrin B2 (Dakic et al., 2017; Kayser et al., 2006). Additionally, 5-MeO-DMT administration has been linked to downregulation of mGluR5 (Dakic et al., 2017). Given mGluR5's role in addiction disorders (Terbeck et al., 2015), these effects of 5-MeO-DMT can possibly explain the therapeutic effect of dimethyltryptamines from ayahuasca on substance dependence (Thomas et al., 2013). Moreover, ayahuasca administration to healthy subjects reduces rapid-eye-movement sleep (REM) and increases slow-wave sleep (SWS) (Barbanoj et al., 2008), two sleep stages respectively associated with increased and decreased LTP (Blanco et al., 2015), further demonstrating the role of psychedelics in neuroplasticity. In line with this, alkaloids from ayahuasca stimulate adult neurogenesis in vitro and in vivo. Indeed, DMT administration activates the main adult neurogenic niche, the mice's subgranular zone of the dentate gyrus of the hippocampus, promoting newly generated neurons in the granular zone, therefore enhancing adult neurogenesis and improving spatial learning and memory tasks (Morales-Garcia et al., 2020). These data further suggest that psychedelics' activity is linked to hippocampal neurogenesis. Some preliminary clinical studies also suggested that psychedelics can increase peripheral BDNF in healthy volunteers and depressed patients (de Vos et al., 2021). However, to date, there are no studies investigating BDNF changes in CSF to directly assess BDNF activity in the brain.

Neuroimaging studies suggested that psychedelics could strengthen specific connections between the thalamus and specific cortical areas. Indeed, in healthy human participants, neuroimaging studies confirmed that LSD induces increases in functional connectivity between the thalamus and sensory-somatomotor cortical regions, including the posterior cingulate cortex (Muller et al., 2017; Preller et al., 2018; Preller et al., 2019). Moreover, changes in positive mood after a low dose of LSD were associated with increased amygdala connectivity with the right angular gyrus, right middle frontal gyrus, and the cerebellum, and decreased amygdala connectivity with the left and right post central gyrus and the superior temporal gyrus confirming that LSD could alter brain connectivity in fronto-limbic circuits (Bershad et al., 2020). In depressed patients it has been shown that treatment response measured 5 weeks after psilocybin treatment was predicted by increased ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex resting-state functional connectivity (RSFC) as was decreased parahippocampal-prefrontal cortex RSFC. Furthermore, decreased amygdala cerebral blood flow correlated with reduced symptoms in the same study (Carhart-Harris et al., 2017). The authors found that psychedelics alter connectivity between brain regions, especially with regard to the Default Mode Network (DMN), to produce a transient hyperconnected state. They postulated that, as the drug's effects disappear, the brain may reset into a pattern of connectivity that is less associated with previous depressive states (Carhart-Harris et al., 2017).

Finally, as for ketamine, the anti-inflammatory action of psychedelics must also be taken into account. Indeed, in vivo and in vitro

Table 4
Ongoing clinical trials of ketamine and psilocybin in bipolar disorder.

Drug	NCT Number	Title	Intervention model	Population	Sponsor/ collaborators	Estimated completion date
etamine	NCT05004896	Repeated Ketamine Infusions for Treatment-Resistant Bipolar Disorder: A Randomized, Double-blind, Midazolam-controlled, Phase II Clinical Trial	•Randomized •Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Enrollment: 100 Age: 21 Years to 65 Sex: All	University Health Network, Toronto	December 31, 2024
	NCT05209217	Open Study of the Neurobiological Effects of Intranasal Ketamine in Children and Adults With Bipolar Disorder - Fear of Harm Phenotype	•Observational Model: Cohort •Time Perspective: Prospective •Primary Purpose: Neuroimaging study	Enrollment: 20 Age: 14 Years to 40 Sex: All	•McLean Hospital •Juvenile Bipolar Research Foundation	January 15, 2023
	NCT05177146	Neural Correlates of Anti-suicidal rEsponse to kEtamine in Treatment Resistant biPolar dePression (DEEPP-Study)	•Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Enrollment: 30 Age: 24 Years to 65 Sex: All	Centre for Addiction and Mental Health, Toronto	August 19, 2024
	NCT03367533	Alpha-Amino-3-Hydroxy-5-Methyl-4- Isoxazole Propionic Acid Receptor Components of the Anti-Depressant Ketamine Response	• Randomized • Model: Crossover Assignment •Masking: Double (Participant, Investigator) •Primary Purpose: Basic Science	Enrollment: 50 Age: 18 Years to 65 Sex: All	Yale University	December 2032
	NCT05339074	Maintenance Ketamine Infusions for Treatment-Resistant Bipolar Depression: An Open-Label Extension Trial	• Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Enrollment: 60 Age: 21 Years to 65 Sex: All	University Health Network, Toronto	August 31, 2024
	NCT05249309	Naturalistic Study of Ketamine in the Treatment of Depression: Suicide Risk Assessment and Serum Measurements of SIRT3, suPAR, hsCRP, Interleukin 6, Complete Blood Count, Leptin, Lipid Profile and Blood Glucose	• Randomized •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Enrollment: 90 Age: 18 Years and older Sex: All	•Hospital de Clinicas de Porto Alegre •Federal University of Rio Grande do Sul •Hospital Moinhos de Vento	March 10, 2023
	NCT04939649	Ketamine as an Adjunctive Therapy for Major Depression - A Randomised Controlled Trial: [KARMA-Dep (2)]	• Randomized • Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Enrollment: 104 Age: 18 Years and older Sex: All	University of Dublin, Trinity College	April 1, 2024
	NCT03674671	Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy	• Randomized • Model: Crossover Assignment •Masking: Single (Outcomes Assessor) •Primary Purpose: Treatment	Enrollment: 240 Age: 18 Years to 70 Sex: Al	•University of Ottawa •McGill University •Queen's University •University Health Network, Toronto	March 2023
	NCT04640636	IM Ketamine vs Midazolam for Suicidal ER Patients	• Randomized • Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Enrollment: 90 Age: 18 Years to 65 Sex: All	•New York State Psychiatric Institute •National Institute of Mental Health (NIMH)	March 2025
	NCT03396601					April 30, 2022

(continued on next page)

Table 4 (continued)

Drug	NCT Number	Title	Intervention model	Population	Sponsor/ collaborators	Estimated completion date
		Administration of Intravenous NRX100 (Ketamine) vs Placebo Infusion for Rapid Stabilization of Acute Suicidal Ideation and Behavior in Patients with Bipolar Depression	• Randomized • Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Treatment	Enrollment: 150 Age: 18 Years to 65 Years Sex: All	• NeuroRx, Inc. • Target Health Inc.	
	NCT04480918	University of Iowa Interventional Psychiatry Service Patient Registry	• Observational [Patient Registry] • Model: Cohort • Time Perspective: Prospective	Enrollment: 1000 Age: 18 Years to 99 Years Sex: All	Mark Niciu, University of Iowa	August 2050
	NCT04701866	Music as a Potential Intervention to Improve Hemodynamic Tolerability of Repetitive Sub-Anesthetic IV Ketamine Infusions in Bipolar and Unipolar Depression: A Pilot Study	• Randomized • Model: Parallel Assignment • Masking: Double (Investigator, Outcomes Assessor) • Primary Purpose: Treatment	Enrollment: 20 Age: 18 Years to 75 Years Sex: All	• Douglas Mental Health University Institute • Réseau québécois sur le suicide, les troubles de l'humeur et les troubles associés	November 2022
	NCT04226963	A Naturalistic Study of Ketamine for Treatment Resistant Mood Disorders: Gdansk Depression Ketamine Project	• Observational • Model: Cohort • Time Perspective: Prospective	Enrollment: 120 Age: 18 Years to 90 Years Sex: All	Medical University of Gdansk	December 31, 2022
Psilocybin	NCT04433845	The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression.	• Open-Label - Single Group Assignment • Masking: None • Primary Purpose: Treatment	Enrollment: 12 Age: 18 Years to 65 Years Sex: All	• Sheppard Pratt Health System • COMPASS Pathways	August 2022
	NCT05065294	An Open-Label Pilot Study Examining the Feasibility, Safety, and Effectiveness of Psilocybin Therapy for Depression in Bipolar II Disorder	• Open-Label - Single Group Assignment • Masking: None • Primary Purpose: Other	Enrollment: 14 Age: 30 Years to 65 Years Sex: All	University of California, San Francisco	December 2023

studies have shown that psychedelics produce a potent anti-inflammatory effect. Although multiple psychedelics tested were shown to have potent anti-inflammatory effects (including LSD) this is particularly true for (R)-2,4-dimethoxy-4-iodoamphetamine [(R)-DOI] (Flanagan and Nichols, 2018). In fact, it has been reported to be particularly potent in repressing TNF- α -induced inflammation and inhibiting, among others, the inflammatory cytokine IL-6 (Yu et al., 2008). Unfortunately, there are no studies that have evaluated the role of psychedelics on the KYN cycle. It is known that a pro-inflammatory state could lead to a switch in the kynurenine pathway, as pro-inflammatory cytokines activate the enzyme IDO, which metabolizes TRP into KYN instead of serotonin (Maes et al., 2007). So, it would be interesting to see if, like ketamine, psychedelics could also act on the KYN pathway via an anti-inflammatory state and consequently act on NMDARs.

6. Summary

In summary, there is evidence from genetic, peripheral neurochemical studies, post-mortem studies and human neuroimaging studies that glutamatergic abnormalities occur in BD (Table 1). Specifically, meta-analyses have confirmed the involvement of Glu receptors signalling in genetic studies and increased Glx levels in neuroimaging studies. At

the same time, a close relationship between immune system and the Glu system has been found. Elevated levels of KynA have been consistently found in the CSF of BD suggesting it as a possible marker of recovery from illness rather than a pathogenic marker, because studies that reported increased CSF KynA in BD included symptom-free subjects. Moreover, KynA is implicated in ketamine efficacy in BD, as ketamine has been found able to increase the neuroprotective branch of the KYN pathway. In this sense, it is possible that the ultimate result of ketamine action in BD is the increased expression of AMPARs through direct antagonism of ketamine on NMDARs and indirectly through reduction of the pro-inflammatory state and subsequent increase in KynA, another NMDA antagonist.

Accumulating evidence strongly supports the notion that classical mood stabilizers exert multiple neuroplasticity and neuroprotective effects in BD via glutamatergic pathways. Indeed, these drugs act on pre- and post-synaptic glutamatergic neurons by reducing Glu excess, blocking exaggerated NMDA transmission and increasing post-synaptic AMPA trafficking, among others (Fig. 1, Table3). These effects initiate transcriptional activation of downstream molecules, including neuroprotective and neurotrophic products, comprising BDNF and Bcl-2. There is growing evidence for AKT/GSK-3 β pathway to be a key mechanism of the neuroplastic action of lithium and valproate. This leads to structural and functional changes like protection of WM and cerebral

functional connectivity. This ultimately helps counteract the neuroprogression of BD. Research suggests that adult neurogenesis and gliogenesis could be mechanisms contributing to lithium's effect. More research into the neuroplastic mechanisms of lithium is desirable. Some recent data seem to indicate that the effects of lithium on neuroprotection or neuroplasticity may be related in some way to its dosage. This could contribute even more to personalized and precision medicine.

The mechanism of action underlying ketamine's rapid antidepressant effects in patients with MDD and TRD remains unclear. Here we postulated that, the direct action of ketamine on NMDAR on the one hand and on the immune system on the other may perhaps better explain its mechanism of action in BD. As known, basal NMDAR activity suppresses AMPAR-mediated synaptic transmission, and a brief blockade of NMDAR is sufficient to boost synaptic transmission by increasing surface AMPAR insertion (Sutton et al., 2006). Ketamine could increase AMPA expression through direct antagonism on NMDARs and indirectly through reduction of the pro-inflammatory state and subsequent increase in KynA, another NMDA antagonist. In this way, by increasing AMPAR trafficking, ketamine could modulate BD neuroplastic shortcomings.

Several lines of evidence suggest that therapeutically effects of serotonergic psychedelics arise from biological changes leading to neuroplasticity via activation of Glu networks (Table 3). Specifically, psychedelics drive an increase in adult neurogenesis, spinogenesis and synaptogenesis via modulation of the 5-HT_{2A}-mGlu₂ heterodimer and AMPA trafficking. This leads to transcriptional activation of neuroplastic downstream molecules, as for classical mood stabilizers and ketamine. Psychedelics are also potent anti-inflammatories and this contributes to their neuroprotective effect in BD. Future studies will be needed to evaluate the effects of psychedelics on the KYN cycle, like ketamine.

7. Conclusions

There might be important differences in the kind of strength of neuroprotective and neuroplastic effects among therapeutic substances. Human and animal research provides substantial evidence for neuroprotective and neurotrophic effects of lithium. Regarding neuroplasticity, there is preclinical evidence for ketamine and psychedelics to have stronger neuroplastic properties than classical antidepressants, mood stabilizers and antipsychotics.

The enhancement of neuroplasticity may not represent by itself a therapeutic effect. Shutdown of neuroplasticity in animals and humans may be a protective mechanism to survive in chronically adverse conditions. To use the full potential of enhanced neuroplasticity, a positive therapeutic and social environment may be needed. As a result, substance with high neuroplastic potential should be combined with psychotherapy to enable their full therapeutic potential.

Taken together, our review indicates that increased trafficking of AMPARs, is a common final pathway for the neuroprotective action of these drugs. It is essential for the neuroprotective and neuroplastic potential of glutamatergic therapeutic drugs in BD. Such findings encourage the investigation of drugs that enhance AMPAR function to increase personalized treatment in BD and to test them in combination with psychotherapy.

Declarations of interest

None.

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