

# The role of NMDA receptors in bipolar disorder: A systematic review

Francesco Weiss<sup>1</sup>  | Valerio Caruso<sup>1</sup> | Ugo De Rosa<sup>1</sup> | Maria Francesca Beatino<sup>1</sup> | Margherita Barbuti<sup>1</sup>  | Ferdinando Nicoletti<sup>2,3</sup> | Giulio Perugi<sup>1</sup> 

<sup>1</sup>Psychiatry 2 Unit, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa, Italy

<sup>2</sup>Department of Physiology and Pharmacology, University Sapienza of Rome, Rome, Italy

<sup>3</sup>IRCCS Neuromed, Pozzilli, Italy

## Correspondence

Giulio Perugi, Department of Clinical and Experimental Medicine, University of Pisa, Via Savi 10, 56126, Pisa, Italy.  
Email: [giulio.perugi@med.unipi.it](mailto:giulio.perugi@med.unipi.it)

## Abstract

**Objectives:** Glutamatergic transmission and N-methyl-D-aspartate receptors (NMDARs) have been implicated in the pathophysiology schizophrenic spectrum and major depressive disorders. Less is known about the role of NMDARs in bipolar disorder (BD). The present systematic review aimed to investigate the role of NMDARs in BD, along with its possible neurobiological and clinical implications.

**Methods:** We performed a computerized literature research on PubMed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, using the following string: (("Bipolar Disorder"[Mesh]) OR (manic-depressive disorder[Mesh]) OR ("BD") OR ("MDD")) AND ((NMDA [Mesh]) OR (N-methyl-D-aspartate) OR (NMDAR[Mesh]) OR (N-methyl-D-aspartate receptor)).

**Results:** Genetic studies yield conflicting results, and the most studied candidate for an association with BD is the GRIN2B gene. Postmortem expression studies (in situ hybridization and autoradiographic and immunological studies) are also contradictory but suggest a reduced activity of NMDARs in the prefrontal, superior temporal cortex, anterior cingulate cortex, and hippocampus.

**Conclusions:** Glutamatergic transmission and NMDARs do not appear to be primarily involved in the pathophysiology of BD, but they might be linked to the severity and chronicity of the disorder. Disease progression could be associated with a long phase of enhanced glutamatergic transmission, with ensuing excitotoxicity and neuronal damage, resulting into a reduced density of functional NMDARs.

## KEYWORDS

bipolar disorder, glutamate, NMDA

## 1 | INTRODUCTION

The conceptual framework of the biological basis of mood disorders has been largely hijacked by the catecholaminergic<sup>1</sup> and serotonergic models.<sup>2,3</sup> Such theoretical reading frame appears today as a

simplistic and circular perspective, which may hinder further progress in biological and pharmacological research.

The history of an alternative physiological/therapeutic pathway in mood disorders starts with cycloserine-D, the first "non-monoaminergic" agent showing anti-depressant activity.<sup>4</sup> The

Francesco Weiss and Valerio Caruso should be considered joint first author.

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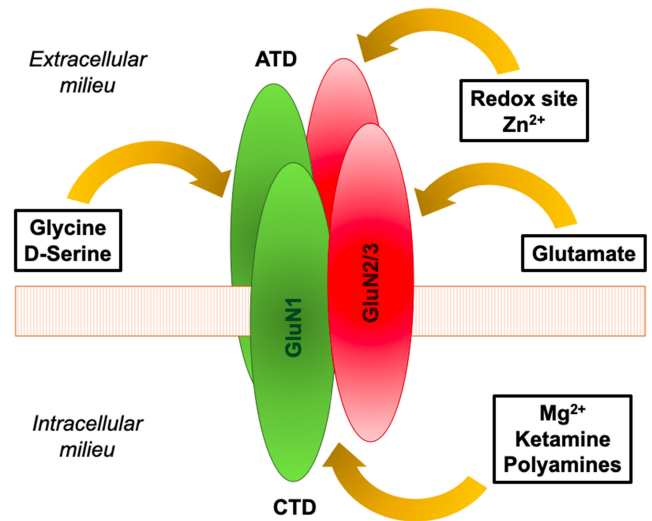
mechanism of action of cycloserine-D remained unknown until the early nineties, when it has been shown to act as a partial agonist at the glycine site of N-methyl-D-aspartate receptor (NMDAR).<sup>5</sup> These observations remained unfollowed by clinical implications until the beginning of the twenty-first century, when the glutamatergic system started to emerge as a main new investigational target, notably following the successful outcomes of clinical trials in treatment-resistant depression with the slow NMDAR channel blockers, ketamine and its two enantiomers, R-ketamine, and S-ketamine.<sup>6,7</sup> The latter is currently the first and only “rapid-acting antidepressant” authorized and traded both in the United States and Europe.<sup>8</sup>

Glutamate represents the main excitatory neurotransmitter in the mammalian central nervous system (CNS).<sup>9</sup> Glutamate signal transduction occurs through two different types of receptors: ionotropic glutamate (iGlu) receptors, which are ligand-gated cation channels, mediating depolarizing currents; and metabotropic glutamate (mGlu) receptors, which are coupled to G proteins and modulate synaptic transmission.<sup>10</sup> There are three types of iGlu receptors:  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, kainate receptors and NMDARs,<sup>11</sup> whereas mGlu receptors form a family of eight subtypes, of which mGlu1 and mGlu5 are coupled to  $G_{q/11}$  proteins, and all other subtypes are coupled to  $G_{i/o}$  proteins.<sup>10,12</sup>

NMDARs form high conductance ion channels permeable to  $Ca^{2+}$ .<sup>13</sup> They are obligate heterotetramers composed of two GluN1 subunits (encoded by the GRIN1 gene and subject to eight splicing variants) and diverse combinations of either two GluN2A-D subunits (encoded by GRIN2A, GRIN2B, GRIN2C, and GRIN2D genes) or one GluN2A-D and one GluN3A-B subunit (encoded by GRIN3A and GRIN3B genes).<sup>14,15</sup> For a deeper insight into the molecular structure and functioning of NMDARs, see Figure 1 and references.<sup>16–18</sup>

Overstimulation of NMDARs causes excitotoxic neuronal death as a result of an excessive influx of extracellular  $Ca^{2+}$ .<sup>19</sup> Increasing evidence suggests a possible involvement of NMDARs and NMDAR-mediated excitotoxicity in the pathophysiology of major psychiatric disorders such as schizophrenia and mood disorders, including bipolar disorder (BD).<sup>20,21</sup> NMDAR-mediated glutamatergic transmission seems to have a role in the pathogenesis of BD. Mood-stabilizing agents, such as lithium and valproic acid, can modulate NMDAR activation, although this is not considered as a primary mechanism of action of the two drugs.<sup>22,23</sup> For instance, lithium has biphasic effects on glutamatergic transmission: acutely, lithium stimulates glutamate release and inhibits glutamate reuptake, while, chronically, it reduces synaptic glutamate levels, stabilizes glutamate reuptake, and decreases NMDAR-mediated  $Ca^{2+}$  influx, thus restraining excitotoxicity and exerting a neuroprotective effect.<sup>24</sup> Similarly, valproic acid has biphasic effects on NMDAR activation, causing an initial increase in glutamate release followed by an antagonistic action on NMDAR-dependent synaptic transmission, which predominates in response to a prolonged administration of the drug.<sup>25,26</sup>

While the relationship between NMDARs and schizophrenia or major depression has been the focus of extensive research, and data have been translated into drug development (e.g., the development



**FIGURE 1** Molecular structure and pharmacology of NMDARs has been extensively characterized in the last three decades. L-glutamate and glutamate-like endogenous agonists (e.g., L-aspartate, cysteinylsulphonic acid, homocysteic acid, and quinolinic acid) bind to the GluN2 subunits, whereas the co-agonists, glycine, and D-serine, bind to the GluN1 subunit (see references 16 and 17). An increasing number of ions and molecules interact with different recognition sites localized in the extracellular portions or the transmembrane domains of NMDAs. Micromolar concentrations of  $Mg^{2+}$  inhibit the NMDA-gated ion channel in a voltage-dependent manner, and other channel blockers, i.e., memantine, amantadine, dextrometorphane, MK-801, phencyclidine, and ketamine, bind inside the NMDAR channel, similarly to  $Mg^{2+}$ . The structural bases of ketamine's action on human NMDARs have been recently identified.<sup>20</sup>  $Zn^{2+}$ , polyamines, nitrosylating and phosphorylating agents, and the redox potential are additional endogenous regulators of NMDA receptor function (see references 13 and 16). In most CNS synapses, NMDARs are silent under resting conditions because of the  $Mg^{2+}$  blockade of the ion channels. Membrane depolarization removes the  $Mg^{2+}$  blockade allowing NMDAR activation with ensuing influx of extracellular  $Ca^{2+}$ . Depending on the amount of  $Ca^{2+}$  entering the cell,  $Ca^{2+}$ -dependent protein kinases or protein phosphatases are predominantly activated, resulting into the induction of long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission. LTP and LTD are the two major paradigms of activity-dependent synaptic plasticity underlying associative memory (see reference 18).

of (S)-ketamine in the treatment of drug-resistant depression), much less is known on the relationship between NMDARs and BD. Hence, we systematically review the available literature regarding the role of NMDAR in the pathophysiology of BD and discuss any possible clinical implication.

## 2 | METHODS

This review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) statement.<sup>27-29</sup> Search methods and results are highlighted in Figure 2.

## 2.1 | Search strategy

First, a comprehensive computerized literature search on PubMed was performed from inception to July 1, 2021, cross-checking the obtained references. The systematic search was conducted using the following string: ("Bipolar Disorder"[Mesh]) OR (manic-depressive disorder[Mesh]) OR ("BD") OR ("MDD") AND ((NMDA [Mesh]) OR (N-methyl-d-aspartate) OR (NMDAR[Mesh]) OR (N-methyl-d-aspartate receptor)).

Two independent investigators (U.D.R. and V.C.) screened title/abstracts of retrieved references for eligibility, evaluated the full text of potentially eligible articles, and extracted pre-established relevant information. Disagreements were resolved through consensus, and a third investigator was consulted whenever a consensus could not be achieved (M.B.).

## 2.2 | Eligibility criteria

We included all studies exploring the involvement of NMDA glutamate receptors in the pathogenesis of BD, meeting the following inclusion criteria: peer-reviewed original reports published in any language; observational studies (cross-sectional, case-control, and

cohort studies). Articles were excluded in the following cases: studies that enrolled youths (<18 years old) to an extent superior to 5% of the study population without distinguishing between adults and children/adolescents in data processing; studies with no comparison population (case reports, case series); review and meta-analysis; animal studies; randomized clinical trials.

## 2.3 | Data extraction

A structured, pre-piloted Excel form has been used to extract data from the included studies on the following characteristics: first author, publication year, setting, country, study design, sample size, age, gender, diagnostic criteria for BD, study methods, and main results.

## 2.4 | Synthesis of results

Because of the expected heterogeneity in terms of study design, participants, and outcomes, a meta-analysis was not feasible; two authors (FW and VC) conducted a narrative synthesis of the included studies.

## 3 | RESULTS

The literature search initially yielded 411 records. After performing the abstract/title screening, 337 papers were excluded. Among the

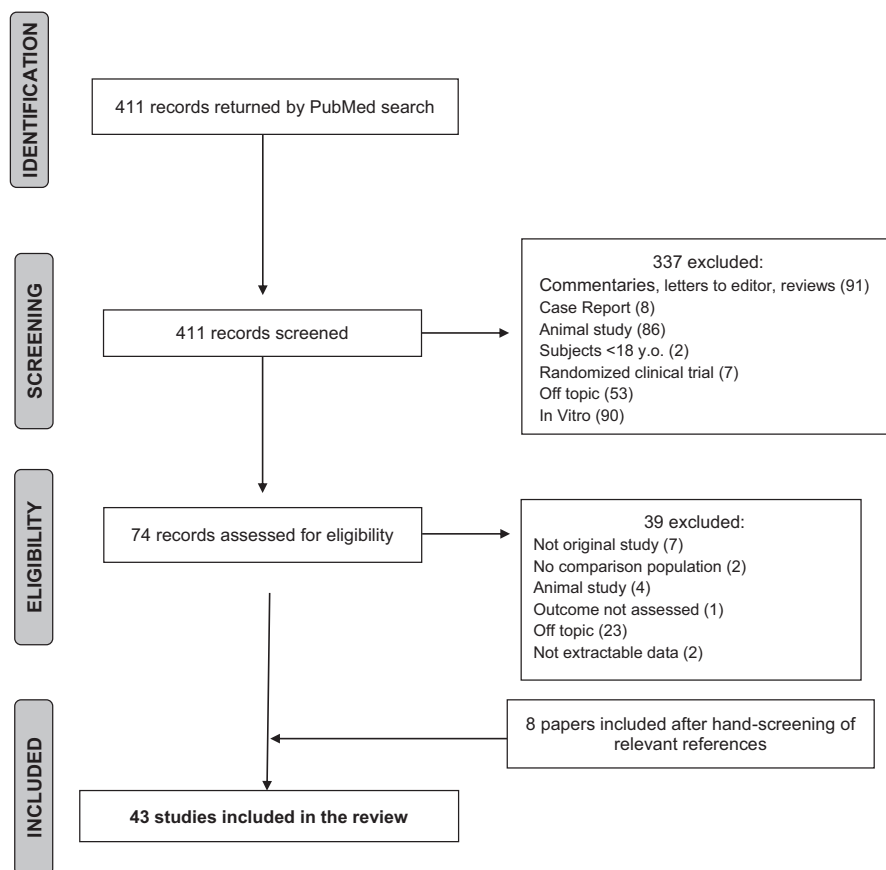


FIGURE 2 PRISMA flowchart.

74 papers that underwent full-text screening, 39 were excluded, and 35 were deemed eligible for inclusion. The hand-screening of relevant references led to the further inclusion of eight articles. Subsequently, a total of 43 papers were considered for the present systematic review.

There is evidence that either acquired or inborn variations in glutamatergic transmission and NMDAR-mediated transduction are variably associated with psychiatric disorders, such as schizophrenic spectrum disorders and mood disorders, including BD. However, the role of these variants in the pathophysiology of BD remains still largely elusive. First, we will systematically review relevant genetic studies; then, we will move to the available literature concerning functional alterations in NMDAR-mediated synaptic transmission, including transcriptional/translational studies and spectroscopy/electrophysiological studies. Among acquired disturbances in glutamatergic transmission, we will also recall autoimmune disorders linked to IgG autoantibodies targeting NMDARs and other transduction-related antigens. Finally, we will discuss the available evidence pertaining to the therapeutic significance of NMDAR modulators in BD.

### 3.1 | The genetics of NMDARs in BD

Variants in NMDARs genes have been linked to psychiatric disorders, with some polymorphisms associated more tightly to schizophrenic spectrum disorders and others to BD.<sup>30</sup> (Table 1).

A molecular genetics study found that two haplotypes of the GRIN1 gene (1001G-1970A-6608A and 1001G-1970A-6608G) are strongly associated with BD (including BD type 1, type 2, and schizoaffective disorder),<sup>31</sup> although another study in a German population failed to find any association between GRIN1 alleles/haplotypes and BD.<sup>32</sup> A Japanese study reported a significant association between an increased number of non-coding GT repeats in the GRIN2A gene promoter and BD. As a longer GT repeats segment is related to a lower transcriptional activity, the authors hypothesized that a hypoglutamatergic state is implicated in the pathogenesis of BD.<sup>33</sup> Subsequently, a Canadian study found the association of a specific haplotype of GRIN2B gene and BD,<sup>30</sup> and a Chinese study found a significant positive association between a GRIN2B gene haplotype and BD. Another haplotype had a protective effect, being negatively associated with BD.<sup>34</sup> Consistently, results of two studies support an association between GRIN2B variants and BD in subjects of Ashkenazi descent.<sup>35,36</sup> However, other studies found no significant association between polymorphisms in the genes encoding NMDAR subunits and BD.<sup>37,38</sup>

Some authors have found that specific single nucleotide polymorphisms (SNPs) in NMDAR-encoding genes are associated with severity markers, such as the number of hospitalizations for mania. Curiously, more evolutionarily ancient SNPs would be protective, while more recent polymorphisms (so-called “derived SNPs”) would predispose to more severe forms of BD.<sup>37</sup> A specific polymorphism of GRIN2B gene has been related to a diffuse fronto-parieto-occipital

reduction in subcortical white matter in BD subjects, but not in healthy controls. The authors of the study coherently propose a correlation between the different alleles of GRIN2B and other NMDAR-related genes and the possible neuroimaging endophenotypes of BD.<sup>39</sup>

The correlation of specific endophenotypes and polymorphisms in NMDARs-encoding genes could be of some interest in the clinical practice. In fact, it has been hypothesized that GRIN2B polymorphisms could affect treatment response, particularly to lithium, but the available evidence does not support this hypothesis.<sup>40</sup> More recently, a study failed to find any correlation between NMDARs-encoding genes and suicidal behavior in individuals affected by BD.<sup>41</sup>

In summary, the current information on the genetic relationship between NMDARs and BD appears still preliminary, warranting further studies. Future investigations should involve not exclusively NMDARs-encoding genes, but also other genes encoding for proteins that indirectly modulate glutamatergic transmission through NMDARs. For example, synaptotagmin-7 deficiency has been related to a reduced glutamatergic transmission mediated by GluB2B-containing NMDARs in human cells, and this has been associated with manic-like behaviors in rodents.<sup>42</sup>

### 3.2 | Functional alterations in NMDARs-mediated synaptic transmission in BD

Several studies have focused on the expression and distribution of NMDARs in the brain of subjects with BD, although results are not conclusive. The nature of the associations between BD and variations in NMDARs might be at epigenetic/transcriptional or translational level, or may involve immune alterations, targeting NMDARs and/or associated proteins.

Postmortem studies include transcriptional studies, performed by *in situ* hybridization (Table 2) and translational studies carried out with autoradiographic methods (Table 3) or immunolabeling techniques (Table 4). An early autoradiographic study failed to find any difference in [<sup>3</sup>H]MK-801 binding between BD and controls.<sup>43</sup> An *in situ* hybridization study reported a 12% reduction in the transcript of the GluN3A subunit in the dorsolateral prefrontal cortex of subjects with BD compared to controls. Interestingly, opposite results were obtained in the dorsolateral prefrontal cortex of individuals affected by schizophrenia, where the authors observed a 32% increase in the transcript encoding the GluN3A subunit.<sup>44</sup> Similar results were obtained measuring GluN1 subunit expression in the superior temporal gyrus of subjects with schizophrenia, BD, and major depression by means of semiquantitative autoradiography using a glycine site radio-ligand: a significant increase in GluN1 expression was found in schizophrenia, whereas a reduced GluN1 expression was found in BD and major depression.<sup>45</sup>

Two studies by the same research group showed a reduced expression of GluN1 and GluN2A subunits in the hippocampus of subjects with BD.<sup>46,47</sup> These changes were specific for NMDARs and occurred exclusively in the hippocampus.<sup>47</sup> The same group,

TABLE 1 Summary of the included genetic studies.

Gene	Results	Reference
GRIN1	<ul style="list-style-type: none"> <li>The 1001G-1970A-6608A and the 1001G-1970A-6608G haplotypes were associated with BD.</li> <li>Preferential transmission of the G allele in the 1001-G/C and the 6608-G/C polymorphisms.</li> </ul>	Mundo et al. (2003)
	No association between GRIN1 alleles and haplotypes with BD.	Georgi et al. (2006)
	No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)
GRIN2A	<ul style="list-style-type: none"> <li>Preferential transmission of longer GT repeats in the gene promoter in patients with BD.</li> <li>No association with suicidal behavior in patients with BD.</li> </ul>	Itokawa et al. (2003) Gaynor et al. (2016)
GRIN2B	Significant association between SNPs/haplotypes of GRIN2B and BD type I.	Fallin et al. (2005)
	<ul style="list-style-type: none"> <li>The T-C-C haplotype was more frequent in BD bipolar disorder, while the G-C-T haplotype was more frequent in schizophrenia.</li> <li>The 5988C allele was associated with BD</li> <li>The 5806C allele was associated with BD with psychotic symptoms.</li> </ul>	Martucci et al. (2006)
	The genomic region containing GRIN2B (chromosome 12p13.1-p12.3) was significantly associated with BD.	Avramopoulos et al. (2007)
	<ul style="list-style-type: none"> <li>SNP rs1805247 was associated with BD (<math>p=0.018</math>)</li> <li>The rs1805502-rs1805247 haplotype was positively associated with BD.</li> </ul>	Zhao et al. (2009)
	No association between three GRIN2B polymorphisms (rs7301328, rs890G/T and rs1019358) and BD.	Szczepankiewicz et al. (2009)
	No association between three GRIN2B polymorphisms (rs7301328, rs890G/T and rs1019358) and lithium response in patients with BD.	Szczepankiewicz et al. (2009)
	Significant gene-gene interaction between DAOA rs701567 and GRIN2B rs1019385 on number of hospitalizations for mania ( $p=0.0108$ ).	Dalvie et al. (2010)
No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)	
GRIN2C	No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)
GRIN2D	No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)
GRIN3A	No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)
GRIN3B	No association with suicidal behavior in patients with BD.	Gaynor et al. (2016)

Abbreviations: BD, bipolar disorder; DAOA, A-amino acid oxidase activator; GRIN1, glutamate receptor ionotropic NMDA type, subunit 1; GRIN2A-D, glutamate receptor ionotropic NMDA type, subunit 2A-D; GRIN3A-B, glutamate receptor ionotropic NMDA type, subunit 3A-B; SNP, single nucleotide polymorphism.

using a mixed autoradiography/hybridization method, reported an altered pattern of NMDARs subunits expression in the medial temporal regions (hippocampal, entorhinal, and perirhinal cortices), although results appear puzzling and somewhat contradictory, especially comparing data obtained with the autoradiographic approach to those obtained with the riboprobe hybridization approach.<sup>48</sup> Another study found a decreased expression of the obligate GluN1 subunit in the dorsolateral prefrontal cortex of BD subjects, but the same was found in schizophrenia and major depression.<sup>49</sup> A more recent study, using a mixed autoradiographic/riboprobe in situ hybridization technique, confirmed a reduced expression of NMDARs in anterior cingulate cortex (Brodmann area 24) and dorsolateral prefrontal cortex (Brodmann area 46) in subjects with BD.<sup>50</sup>

Some authors hypothesized that the glutamatergic regulation of cortical inhibitory interneurons might have a role in the neurobiology of major mental disorders, including BD. A "labeled-riboprobe" study comparing 17 brain specimens of subjects with a diagnosis of BD with 17 control specimens, showed a reduced expression of the GluN2A subunit in GABAergic interneurons of layer 2 of Brodmann

area 24 (anterior cingulate cortex).<sup>51</sup> However, a similar study examining the expression of the GluN2A subunit in parvalbumin-containing interneurons of the prefrontal cortex, failed to find any difference between BD and control subjects.<sup>52</sup> Other studies explored the NMDAR distribution and function in subcortical regions, reporting a reduced expression of NMDARs-associated postsynaptic density proteins in the thalamus of BD subjects.<sup>53</sup> No reduction in NMDARs expression was found in the corpus striatum of BD subjects.<sup>54</sup> Overall, these findings suggest an association between a reduced/altered expression of NMDAR subunits in some brain regions (especially dorsolateral prefrontal, anterior cingulate, and hippocampal cortices) and BD.

Other studies that employed immunostaining methods either failed to find any difference in NMDARs expression between BD and controls or found a partial reduction in only some splice-variants of the Glu1 subunit.<sup>45,55,56</sup> Interestingly, in one study, a reduced expression of NMDAR subunits in BD was associated with an increased expression of markers of neuroinflammation and cell death, such as interleukin-1 $\beta$ , interleukin-1 receptor, and myeloid differentiation

TABLE 2 Summary of the included in situ hybridization studies.

Author (year)	Method	Results
Meador-Woodruff et al. (2001)	Radioprobes for transcripts encoding NDMAR subunits NR1, 2A, 2B, 2C and 2D.	No difference in the expression of NMDARs in the striatum of subjects with BD and controls.
Mueller and Meador-Woodruff (2004)	Radioprobes for transcripts encoding NDMAR NR3A subunit.	Significant decrease in the expression of NR3A (12%) in BD relative to the control group in dorsolateral prefrontal cortex. No difference in the inferior temporal cortex.
Clinton and Meador-Woodruff (2004)	Radioprobes for transcripts encoding NDMAR subunits NR1, 2A, 2B, 2C and 2D.	No changes in NMDARs subunits expression. (Reduced expression of NMDARs-associated postsynaptic density proteins in the thalamus of bipolar subjects).
Woo et al. (2004)	Radioprobes for transcripts encoding NDMAR NR2A subunit.	Reduced density of GAD-67+ interneurons (60%) expressing the NR2A subunit in the anterior cingulate cortex of subjects with BD.
Benevento et al. (2007)	Riboprobes for the NMDAR subunits NR1, NR2A, NR2B, NR2C, NR2D and NR3A.	No changes in transcript expression in the hippocampus. Reduced expression of NR1 in the entorhinal cortex of subjects with BD.
McCullumsmith et al. (2007)	Radioprobes for transcripts encoding NDMAR subunits NR1, 2A, 2B, 2C and 2D.	Significant decrease in the expression of transcripts for NR1 and NR2A subunits in the hippocampus of subjects with BD.
Benevento and Meador-Woodruff (2008)	Radioprobes for transcripts encoding NDMAR subunits NR1, 2A, 2B, 2C and 2D.	Significant decrease in the expression of transcripts for NR1 subunit in the dorsolateral prefrontal cortex of subjects with BD.
Bitanirwe et al. (2010)	Radioprobes for transcripts encoding NDMAR NR2A subunit.	No difference in the expression of NR2A-containing NMDARs in PV+ inhibitory interneurons of the dorsolateral prefrontal cortex of subjects with BD and controls.
Dean et al. (2015)	Riboprobes for the NMDAR subunits NR1, NR2A, NR2B, NR2C, NR2D and NR3A.	Reduced level of hybridization for NR2C mRNA (27%, $p < 0.05$ ) in anterior cingulate cortex from people with BD. No other significant changes.

Abbreviations: BD, bipolar disorder; GAD67, glutamic acid decarboxylase 67 kDa isoform; mRNA, messenger RNA; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; NR1, N-methyl-D-aspartate receptor subunit 1; NR2A-D, N-methyl-D-aspartate receptor subunit 2A-D; NR3A-B, N-methyl-D-aspartate receptor subunit 3A-B; PV, parvalbumin.

factor 88, suggesting that a reduced NMDAR expression might be a consequence of neuroinflammation and neuronal damage.<sup>57</sup> A possible interpretation of this observation is that NMDAR hyperactivation supported by a chronic sub-phlogistic neural microenvironment associated with mood disorders, could lead to a progressive desensitization of NMDARs. This mechanism may represent a fail-safe mechanism aimed at restraining excitotoxicity and neuronal damage.<sup>57,58</sup>

All the above-mentioned studies have been carried out in post-mortem brain tissue, with all consequent limitations. The only currently available methods to explore NMDAR-mediated glutamatergic transmission in humans are mismatch negativity (MMN), which is considered an electrophysiological marker of NMDAR output, and proton magnetic resonance spectroscopy (H-MRS) which allow measurements of glutamate and glutamate-related metabolites (e.g., glutamine or glutathione) in living brain tissues.<sup>59,60</sup>

A study combining H-MRS and MMN showed a positive correlation between Glu levels and temporal-MMN amplitude, supporting the predominant neurochemical hypothesis on MMN as representative of NMDAR-mediated glutamate neurotransmission. Interestingly, this association was lost in BD subjects, suggesting a possible impairment in the regulation of NMDAR function.<sup>59</sup> Moreover, a significantly higher frontal MMN was found in BD compared with controls, but the interpretation of such finding is still

open to further research and speculations.<sup>59</sup> Another study by the same group reported a negative correlation between glutathione levels measured by H-MRS and temporal MMN in controls, suggesting that glutathione might be a negative regulator of NMDARs through a still unclear mechanism. However, such association is not observed in subjects with BD, further supporting an impaired modulation of NMDAR-mediated transmission associated with a less efficient antioxidant protection and greater oxidative stress.<sup>60</sup>

The altered NMDA-mediated transmission in BD might be caused by autoimmune mechanisms. In two studies, acute mania was associated with high titers of anti-NMDAR antibodies.<sup>61,62</sup> Accordingly, it has been suggested that lithium could exert its antimanic and mood-stabilizing/episode-preventing effect through an immunomodulatory mechanism, reducing anti-NMDAR antibodies production.<sup>61</sup> This interesting hypothesis warrants further investigation.

The study of glutamatergic transmission in BD and other mood disorders should be extended to synaptic vesicle-associated proteins, synaptotagmin-7, and non-coding RNAs (miR-223).<sup>42,63</sup>

NMDAR subunits, their related mRNA, as well as their ligands/co-agonists (such as glycine) could also represent measurable biomarkers of major psychiatric disorders, including mood disorders.<sup>64,65</sup> For example, a study reported reduced plasma concentrations of subunits in subjects with a diagnosis of psychosis (including schizophrenia, psychotic BD, and psychotic depression),

TABLE 3 Summary of the included autoradiographic studies.

Author (year)	Methods	Results	Significance
Dean et al. (2001)	Intra-channel radiolabel ([3H]MK-801 binding)	No difference in binding in the dorsolateral prefrontal cortex	No difference in the number of functional NMDARs in the dorsolateral prefrontal cortex of subjects with BD and controls.
Meador-Woodruff et al. (2001)	Intra-channel radiolabel ([3H]MK-801 binding) Glutamate site radiolabel ([3H]CGP-39653) Glycine site radiolabel ([3H]MDL105,519) Polyamine regulatory site ([3H]ifenprodil)	No difference in binding in the striatum	No difference in the number of functional NMDARs in the striatum of subjects with BD and controls.
Scarr et al. (2003)	Intra-channel radiolabel ([3H]MK-801 binding) Glutamate site radiolabel ([3H]CGP-39653)	Reduced binding in the hippocampus	Reduced density of functional NMDARs in the hippocampal region of subjects with BD.
Nudmamud-Thanoi and Reynolds (2004)	Glycine site radiolabel ([3H]L-689-560 binding)	Reduced binding in superior temporal cortex.	Reduced density of functional NMDARs in the superior temporal gyrus of subjects with BD.
Beneyto et al. (2007)	Intra-channel radiolabel ([3H]MK-801 binding) Glycine site radiolabel ([3H]MDL105,519)	Reduced [3H]MK-801 and increased [3H]MDL105,519 binding in the hippocampus, no difference in entorhinal and perirhinal cortices.	Reduced density of functional NMDARs but increased glycine sites in the hippocampal region of subjects with BD.
Beneyto and Meador-Woodruff (2008)	Intra-channel radiolabel ([3H]MK-801 binding) Glutamate site radiolabel ([3H]CGP-39653) Glycine site radiolabel ([3H]MDL105,519) Polyamine regulatory site ([3H]ifenprodil)	No difference in binding in the dorsolateral prefrontal cortex.	No difference in the number of functional NMDARs in the dorsolateral prefrontal cortex of subjects with BD and controls.
Dean et al. (2015)	Intra-channel radiolabel ([3H]MK-801 binding)	Reduced binding in the dorsolateral prefrontal and anterior cingulate cortices.	Reduced density of functional NMDARs in the dorsolateral prefrontal and anterior cingulate cortices of subjects with BD.

Abbreviations: BD, bipolar disorder; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor.

compared to controls.<sup>64</sup> Interestingly, the same study seems to point to a possible discriminatory value of NMDAR subunits, showing a reduction in both GluN1 and GluN2 in schizophrenia, and only GluN2 in BD.<sup>64</sup> Other authors measured glycine, glutamate, and tryptophan plasma levels in BD subjects with a manic relapse, comparing them to those of healthy controls and euthymic BD individuals, reporting a significant increase in the plasma concentrations of glycine during manic phases, together with a reduction in tryptophan levels.<sup>65</sup> Tryptophan is the metabolic precursor of quinolinic acid and kynurenic acid, which act as NMDAR agonist and antagonist, respectively.<sup>66</sup>

### 3.3 | Pharmacological evidence

Many psychotropic agents employed in the treatment of mood disorders, including lithium and valproic acid, have a modulatory effect on NMDAR-dependent transmission, which could be responsible for

at least some of their clinical effects (see above). It has been speculated that other drugs primarily modulating NMDAR function could exert antimanic, antidepressant, or mood-stabilizing actions. For example, memantine, a fast NMDAR channel blocker,<sup>67</sup> exhibits an antimanic and mood-stabilizing effect, reducing the total percentage of time ill, episodes duration and the number of episodes per year, especially in subjects with a complicated disease course (rapid cycling or continuous cycling).<sup>68-70</sup> Memantine can also modulate or antagonize inflammatory responses.<sup>71</sup>

Ketamine is a slow NMDAR channel blocker that displays rapid and long-lasting antidepressant action (see above).<sup>72</sup> The role of ketamine in the treatment of BD remains still controversial and currently there is no indication for the treatment of bipolar depression. Nonetheless, there is preliminary evidence that ketamine could induce rapid remission in subjects with treatment-resistant bipolar depression, especially reducing anhedonic symptoms, nighttime wakefulness, and suicidality.<sup>73-75</sup> A <sup>18</sup>F-fluorodeoxyglucose positron-emission tomography (PET-FDG) study correlated the reduction of

TABLE 4 Summary of the included immunoblot and immuno-autoradiography studies.

Author (year)	Method	Results	Significance
Thompson et al. (2003)	NMDA NR1 antibody (clone 54.1; Zymed)	No difference in NMDAR NR1 subunit levels in the hippocampus.	No difference in the number of functional NMDARs in the hippocampus of subjects with BD and controls.
Nudmamud-Thanoi and Reynolds (2004)	Polyclonal NR1 antibody (NMDA 1, Santa Cruz Biotechnology, Inc., CA)	Reduction in NR1 upper (116 KDa) immuno-reactivity band (seemingly corresponding to a specific splice-variant) in superior temporal cortex.	Reduced density of functional NMDARs in the superior temporal gyrus of subjects with BD.
Toro and Deakin (2005)	Rabbit polyclonal anti- NR1 (Chemicon AB1516)	No difference in NMDAR NR1 subunit levels in the orbitofrontal cortex and hippocampus.	No difference in the number of functional NMDARs in the orbitofrontal cortex and hippocampus of subjects with BD and controls.
Rao et al. (2010)	Primary antibodies (1:200 dilution) for the NR-1, NR-2A, NR-2B, NR-3A (Cell Signaling, Beverly, MA, USA)	Reduced NR-1 (42%, $p < 0.05$ ) and NR-3A (41%, $p < 0.01$ ) protein levels were decreased in the frontal cortex. No difference in NR-2A and NR-2B.	Reduced density of functional NMDARs in the frontal cortex of subjects with BD.

Abbreviations: BD, bipolar disorder; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; NR1, N-methyl-D-aspartate receptor subunit 1; NR2A-D, N-methyl-D-aspartate receptor subunit 2A-D; NR3A-B, N-methyl-D-aspartate receptor subunit 3A-B;

glucose metabolism in the hippocampus of BD subjects in depressive phase with the antidepressant response induced by ketamine.<sup>74</sup> As glucose metabolism is thought to be an indirect biological marker of glutamatergic transmission, this finding supports the hypothesis that BD is, at least originally, associated with NMDARs hyperstimulation and subsequent excitotoxic neuroprogression, and that ketamine could help to revert such pathogenic mechanism.

## 4 | DISCUSSION

### 4.1 | Quantitative variations of NMDAR-mediated transmission in BD

Current empirical evidence suggests that BD is associated with a hypoglutamatergic condition; whether such functional alteration is primary or secondary to other processes remains an open question.<sup>21</sup> As highlighted above, many commonly used psychotropic agents share an anti-NMDAR effect. However, with the exception of memantine and ketamine, this is not their primary mechanism of action. It should be considered that a large body of evidence derives from postmortem studies, which do not take into account how the pharmacological history of the subjects causes adaptive changes in NMDAR expression and function. Furthermore, as mood-stabilizing agents (such as lithium and valproate salts) inhibit NMDAR function, it may seem contradictory to postulate a hypoglutamatergic state in BD. It can be speculated that an increased glutamatergic transmission may cause a progressive desensitization and down-regulation of NMDARs, as already suggested for major depression and schizophrenia.<sup>45,76-78</sup> If this was the case, BD would be primarily characterized by a hyperglutamatergic rather than a hypoglutamatergic state. This is in line with previous evidence from magnetic

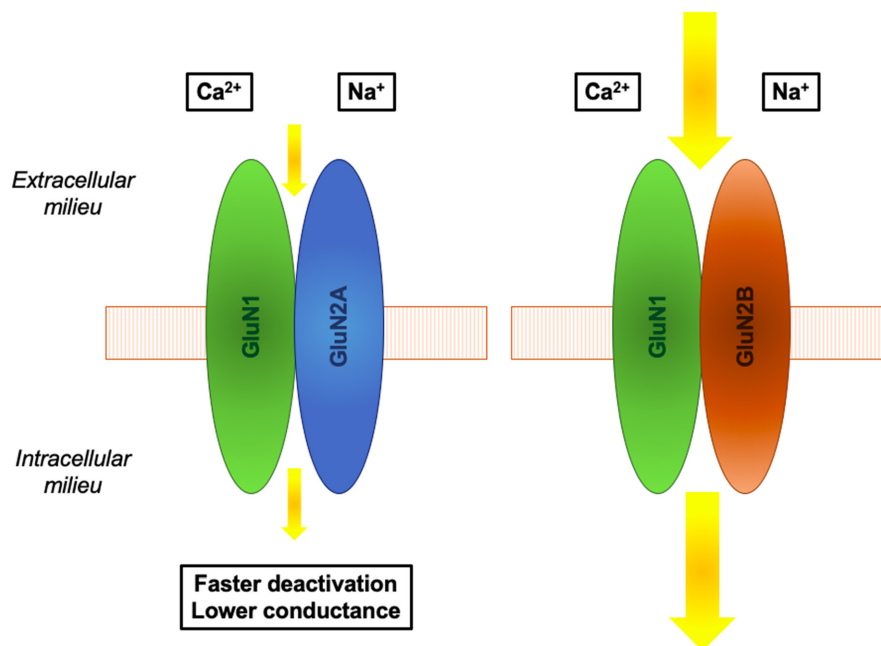
resonance spectroscopy studies, showing increased glutamate levels in the multiple cortical areas of subjects with BD.<sup>79</sup> As a further complication, alterations in glutamate homeostasis could be heterogeneously distributed in different brain areas, with diverging profiles in different mood states, illness courses and severity (e.g., higher glutamate levels in the prefrontal cortex of subjects with manic states or rapid cycling BD).<sup>79-81</sup>

Consistently, electroconvulsive therapy (ECT) was demonstrated to have a “glutamate normalizing” effect both in animals and humans, reducing the glutamate-to-GABA ratio in the hippocampus and increasing glutamatergic transmission in some cortical areas, such as the anterior cingulate cortex.<sup>82-84</sup> Such mechanism of action could explain why ECT shows clinical efficacy in the treatment of anti-NMDAR-positive autoimmune catatonia.<sup>85</sup>

Neuroinflammation could be a common pathophysiological mechanism, linking together neuroprogression and hypoplasticity with increased glutamatergic transmission and excitotoxicity, possibly involving other mechanisms such as the disruption of tryptophan metabolism and the increase in quinolinate/kynurenate ratio.<sup>86</sup>

### 4.2 | Qualitative variations of NMDAR-mediated transmission in BD

Another possibility is that NMDAR stoichiometry, more than total expression/function, is altered in BD: it appears that GluN2A-containing receptors are reduced more than NMDARs containing other subunit combinations, leading to a greater proportion of slower-kinetics, neonatal-like GluN2B-containing receptors (see Figure 3).<sup>13,21</sup> This feature could differentiate BD from the hypoglutamatergic condition thought to be involved in schizophrenia, where the GluN1 subunit (containing the binding site for the co-agonist,



**FIGURE 3** Type of GluN2 subunit present in the NMDAR complex critically influences the time constants of ion channel opening and the effect of various ligands. GluN2B and GluN2D subunits are largely expressed in the early development, whereas GluN2A and GluN2C subunits start to be expressed after birth. In the adult brain, GluN2A and GluN2B predominate, and GluN2A-containing NMDARs are found in the central region of postsynaptic densities, whereas GluN2B-containing receptors are preferentially perisynaptic/extrasynaptic. GluN2B-containing NMDARs display greater ion conductance and longer deactivation time compared to GluN2A-containing receptors (see references 13 and 16).

glycine) is found to be reduced.<sup>87</sup> Considering that GluN1 is the obligate subunit of the NMDAR heterotetramer, its reduction translates into an overall decrease in NMDAR function. On the other hand, major depression seems to be associated with increased expression of NMDARs (especially GluN2A/B/C subunits) in subcortical regions, such as the locus coeruleus and the amygdala, whereas the cortical expression of all GluN2 subunits appears to be reduced.<sup>76,77</sup> Notably, the cortical expression of the obligate GluN1 subunit seems to be unaffected in major depression, again differentiating mood disorders from schizophrenia.<sup>76,77</sup>

A recent study found increased NMDAR-genes expression in the dorsolateral prefrontal cortex of women with major depression, but not in men, and increased GRIN2B expression was associated with suicide in both sexes.<sup>88</sup> MMN studies showed comparable results in subjects with schizophrenia and BD, although MMN reduction was smaller in the latter, and some authors suggest that the hypoglutamatergic NMDAR-dependent state in the hippocampus could be a pathophysiological “trait d’union” between BD and schizophrenia.<sup>89,90</sup> However, considering that genetic studies in BD yielded mostly inconclusive and contradictory results, it is possible that alterations in NMDAR expression and function are secondary to neuroinflammation or other processes, further differentiating BD from schizophrenia, in which associations with mutations or polymorphisms of NMDAR-encoding genes seem more consistent.<sup>91</sup> Further investigations are warranted, in order to establish the relevance of these mechanistic hypotheses in the development, maintenance and progression of mood disorders and BD.

### 4.3 | NMDAR-mediated transmission in BD: a transnosographic perspective

In our view, the main drawback in the literature we have reviewed is the assumption that BD is a clinical entity clearly distinguished from schizophrenia, unipolar depression, and all other mental disorders. In contrast, BD is a heterogeneous syndrome, representing the common final pathway of a variety of etiopathogenetic processes which translate in a host of clinical forms, with different phenomenological presentations, disease courses and functional consequences. Moreover, the distinction from schizophrenia and major depression, as well as from neurodevelopmental disorders, is made difficult by the existence of a number of intermediate forms.<sup>92</sup> This problem has been raised for all genetic research on major psychosis.<sup>93</sup>

In a theoretical vein, distinguishing BD subtypes on the basis of biological or clinical features could hopefully lead to more consistent results in all biological research. Furthermore, available evidence compels us to consider a possible continuity in the diagnosis of schizophrenia, BD, and unipolar depression, implying that the application of transnosographic criteria, such illness severity and psychotic symptoms, would yield more consistent and discernible results. In this perspective, the results of the present review seem to be consistent with the hypothesis that NMDAR dysregulation should be more closely related to the severity of the clinical picture rather than to categorical diagnoses. Accordingly, NMDARs involvement would be more evident for schizophrenia and severe BD forms resistant to pharmacological treatment and responsive to ECT. Our

hypothesis about NMDARs is in agreement with other research groups also prompting a transdiagnostic continuum in white matter abnormalities and glutamatergic alterations from anxiety disorders to mood disorder and schizophrenia.<sup>94-96</sup>

#### 4.4 | Limitations

This systematic review has several limitations. First, the heterogeneity of the collected evidence, ranging from genetics, postmortem hybridization/autoradiography, and pharmacological observations, has led to results that are difficult to compare. In addition, there is considerable heterogeneity even among studies conducted with similar methodologies, with several results remaining unpublished and difficult to replicate. A further limitation is the restrictive criterion we used for article research, including only studies related to NMDARs and excluding studies examining other aspects of glutamatergic neurotransmission in BD, such as magnetic resonance spectroscopy studies and analysis of other glutamate-related genes or proteins. Future research is needed to clarify the possible involvement of NMDAR dysfunction in BD and to promote the discovery of novel tailored therapeutic agents.

#### AUTHOR CONTRIBUTIONS

Giulio Perugi and Valerio Caruso had the idea for the article. Valerio Caruso, Ugo De Rosa, and Margherita Barbuti performed the literature search and data analysis. Francesco Weiss drafted the work and finally, Margherita Barbuti, Giulio Perugi, Ferdinando Nicoletti, Valerio Caruso, Maria Francesca Beatino, and Ugo De Rosa revised the final draft. All authors have read and agreed to the published version of the manuscript.

#### CONFLICT OF INTEREST STATEMENT

GP acted as consultant to Lundbeck, Angelini, Sanofi-Aventis, Neuraxpharm. He received a scholarship/research support from Lundbeck and Angelini. He is a member of the speaker/advisory board of Sanofi-Aventis, Lundbeck, Angelini. All other authors have no conflict of interests to declare.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

#### ORCID

Francesco Weiss  <https://orcid.org/0000-0003-1935-5162>

Margherita Barbuti  <https://orcid.org/0000-0003-0077-3815>

Giulio Perugi  <https://orcid.org/0000-0001-5556-1858>

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