Chapter 13

Glutamate-based preclinical and clinical dysfunction and treatment in bipolar disorder

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13.1 Preclinical

As described throughout this textbook, bipolar disorder (BD) is characterized by episodic mood cycling with state-specific response to mood stabilizing medications such as lithium, antiepileptics, and antipsychotics. While certain behaviors can be assayed, the thoughts and feelings contributing to behavioral states in BD are not accessible in model animals. Additionally, episodic mood cycling is very challenging to model. Therefore, instead of looking at mood cycling, many preclinical researchers have focused on hypo/manic-like behaviors. In rodents, some phenotypes resembling hypo/mania include increased locomotion/hyperactivity, increased risk-taking/impulsivity and poor decision-making, decreased anxiety and increased social affinity, and decreased depression-like behaviors. These endophenotypes can be measured in various behavioral paradigms, for example, the elevated plus maze for anxiety, or the forced swim test for despair. As with traditional antidepressants in chronic stress models, treating hyperactive animals with mood stabilizing medications such as lithium reverses these bipolar-like behaviors, for example, hyperactivity and impulsivity. In this section, we will review the glutamate-based contributors in rodent models of hypo/mania, starting with genetics.

The genetic contribution to hypo/mania has been studied in rodent models via naturally occurring mutant strains or targeted genetic manipulations. The following mouse strains have shown manic-like behaviors: Myshkin, Black Swiss, and Madison. *Clock19, Gsk-3b, Dat, Shank3, Ank3, Gclm, GluD1, Dbp*, and *Grik2* are genes that have been manipulated in mice with behavioral consequences resembling hypo/mania. These genes are also risk

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factors for BD in humans. The mouse models that have overt defects in glutamate signaling are *Clock19, Grik2, Gclm, Ank3*, *GluD1*, and *Shank3*.

The most well studied of these genes is *Clock19*. Clock19 is a transcription factor that regulates circadian rhythms, governing physiological and behavioral cycles within a 24-hour period. Mice carrying the *Clock∆19* mutation have an adenine-to-thymine transversion that results in exon skipping and a 51-amino acid deletion in the Clock19 protein. These mice display manic-like behaviors during their awake cycle, for example, hyperactivity, decreased need for sleep, decreased anxiety, decreased depression-like behaviors, and high reward-seeking/sensitivity (Kristensen, Nierenberg, & Ostergaard, 2018; Mcclung et al., 2005; Roybal et al., 2007). *Clock*Δ19 mice also display reduced synaptic glutamate uptake, presumably due to reduced expression of the astrocytic glutamate-aspartate transporter (GLAST) (Beaule, Swanstrom, Leone, & Herzog, 2009), which, as will be described later in the "Clinical" section, leads to increased synaptic glutamate levels. This bipolar-like phenotype has been recapitulated by RNA inference-mediated knockdown of Clock19 in the ventral tegmental area (VTA) (Mukherjee et al., 2010). This VTA-specific knockdown of Clock19 also increases expression of glutamate receptor subunits (Mukherjee et al., 2010). Finally, in the *Clock∆19* mouse, manic-like behaviors can be reduced by the antimanic agents lithium (Dzirasa et al., 2010) and valproate (Liu et al., 2021).

Grik2 (glutamate ionotropic receptor kainate subunit 6) is a gene that encodes a portion of the kainate glutamate receptor, which resides in a genetic linkage area for BD (6q21). GluR6 knockout mice exhibit hyperactivity, increased sensitivity to psychostimulants, and overall altered excitatory signaling, all of which are partially reversed by lithium treatment (Shaltiel et al., 2008). Glutathione is an antioxidant and its synthesis requires several components including: cysteine, glutamate, and the GCLM (glutamate-cysteine ligase modifier) enzyme. Mice with knockout of *Gclm* have manic-like behaviors that have been attributed to changed redox regulation (Kulak, Cuenod, & Do, 2012). *Ank3* is a gene that encodes one of the many ankyrin proteins responsible for bridging integral membrane proteins with the spectrin-actin cytoskeleton. The heterozygous *Ank3* mice have mislocalized glutamate receptors and ion channels due to kinesin-mediated transport dysregulation. Interestingly, this mislocalization can be alleviated by lithium (Gottschalk et al., 2017). GluD1 (glutamate receptor delta-1) is an ionotropic glutamate receptors encoded by *GRID1*. GluD1 knockout mice display both manic- and depression-like behaviors that can be partially rescued by lithium (Yadav et al., 2012). SHANK3 (SH and multiple ankyrin repeat domains 3) is a scaffolding protein found in the postsynaptic density of dendritic spines at excitatory (glutamate) synapses. Mice that overexpress SHANK3 are hyperactive, and their manic-like behaviors can be reduced with valproic acid but not lithium (Han et al., 2013). At birth, brain slices prepared from

SHANK3 knockout mice have enhanced glutamatergic currents (Chiesa et al., 2019). The mature SHANK3-overexpressing mice have altered excitatory signaling patterns, resembling the GluR6 knockout mouse described above (Logan & Mcclung, 2016).

The above-described rodent models were developed by focusing first on genetic risk loci, manipulating said gene (knockdown/out or transgenic overexpression), and then examining various neurobiological and/or behavioral measures consistent with hypo/mania and/or depression. Some mouse models, on the other hand, have been found either serendipitously in forward screens or created by selective breeding. Black Swiss mice have increased reward seeking, risk-taking, aggression, and sensitivity to amphetamines, and these behaviors can be mitigated by treatment with valproate and lithium (Flaisher-Grinberg & Einat, 2010) or by positive modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepriopionic acid (AMPA)-type glutamate receptors (Kara, Flaisher-Grinberg, & Einat, 2015). The Madison mouse strain was selectively bred for high-wheel running behavior and subsequently studied for manic-like symptoms such as increased activity, decreased need for sleep, and response to olanzapine and lithium (Scotti et al., 2011). The breeding technique used to create the Madison mouse was similarly employed with the HYPER rat, which exhibits both manic-like and depression-like behaviors when stressed (Weiss & Boss-Williams, 2017). While the HYPER rat displays greater excitation of the pituitary−adrenal axis in response to stress, the contribution of the glutamate system within remains unknown. Myshkin mice have a point mutation in the gene encoding the neuron-specific α3 sodium-potassium ATPase (Na^+,K^+ ATPase), leading to haploinsufficiency (Kirshenbaum et al., 2011). Myshkin mice exhibit sleep and circadian rhythm abnormalities, decreased anxiety, and increased reward preference, and all of these behaviors can be attenuated with either lithium or valproic acid (Kirshenbaum et al., 2011). Cortical neurons derived from Myshkin mice are more sensitive to glutamate application, and the response to glutamate in the superchiasmatic nucleus-retina is altered (Timothy et al., 2018).

Much of the information available on the aforementioned preclinical models is incomplete, and our understanding of bipolar-like behaviors in preclinical model organisms has been enhanced by pharmacological studies. To wit, several drug treatment paradigms have been developed to induce mania-like behaviors in rodents such as amphetamine (Cosgrove, Kelsoe, & Suppes, 2016), ouabain (Mack, Gao, Ratajczak, Kakar, & El-Mallakh, 2019), and ketamine (Ghedim et al., 2012), and the antimanic mood stabilizers lithium and/or valproate have been shown to attenuate these manic-like behaviors. Most of these manipulations affect dopamine and/other neurotransmitters, for example, psychostimulants; however, there is some evidence for involvement of glutamatergic neurotransmission, for example, cellular signaling pathways involving metabotropic glutamate receptors (mGluRs). Group II mGluR activity in the rat nucleus

accumbens is known to contribute to amphetamine-induced locomotion (Kim, Beeler, & Vezina, 2000). In addition, amphetamine administration leads to phosphorylation of specific sites of the glutamate N-methyl-D-aspartate (NMDA) and AMPA receptors, and lithium treatment reversed this phosphorylation (Szabo et al., 2009). In rats, NMDA receptor agonism has also been shown to activate phospholipase A2(PLA), with subsequent release of plasmalemmal arachidonic acid (AA) in multiple brain regions including the neocortex and hippocampus (Basselin, Chang, Bell, & Rapoport, 2006). Pretreatment with the NMDA receptor antagonist MK-801 and chronic (6-week) dietary administration of LiCl can block plasmalemmal AA release (Basselin et al., 2006). Next, chronic treatment of rats with lithium or valproate modulates the expression of a specific mGluR1/5-interacting/scaffolding protein, Homer1b/c isoforms (Brakeman et al., 1997), and related genes Shank and the inositol 1,4,5-trisphosphate receptor (De Bartolomeis, Tomasetti, Cicale, Yuan, & Manji, 2012).

Glutamatergic dysfunction has also been linked to environmental manipulations resembling or contributing to manic-like symptoms/behaviors. Altered sleep and chronic stress have been shown to elicit manic-like and/or depression-like behaviors in preclinical models. Sleep deprivation has been shown to affect the trafficking of AMPA receptors in mice, which altered neuronal activity (Del Cid-Pellitero, Plavski, Mainville, & Jones, 2017). Sleep deprivation also modulates phosphorylation of NMDA and AMPA receptors (Szabo et al., 2009). In mice, lithium treatment can reverse some of the consequences of sleep deprivation in the brain, and, in addition to effects on the hypothalamic−pituitary−adrenal (HPA) axis, oxidative stress and inflammation, some of the sleep normalizing effects of lithium may be mediated through the reversal of glutamatergic abnormalities (Valvassori et al., 2017).

While the rodent models have contributed significantly to our understanding of the processes that give rise to mania-like behaviors, human cell culture models have also played a significant role. To date, two main approaches have been taken to modeling aspects of BD in vitro. First, human genes/mutations associated with BD may be manipulated in rodent cell lines or primary cultures. For example, ANK3 knockdown in mouse primary cortical neurons leads to qualitative changes in glutamatergic synaptic markers (Smith et al., 2014). Similarly, knockdown of Shank3 leads to reduced expression of the metabotropic glutamate receptor type 5 (mGluR5) in rat cortical neurons (Verpelli et al., 2011). Second, induced pluripotent stem cells (iPSCs) may be created from patients and controls and then differentiated into central nervous system-like tissue, for example, glutamatergic neurons and astrocytes (Haggarty, Silva, Cross, Brandon, & Perlis, 2016). This stem cell-based approach may provide insights into cell-specific mechanisms inherent to the individual from whom the cells were derived. Using this approach, iPSC-derived glutamatergic neurons from BD patients with a PCDH15 (protocadherin related 15) deletion had decreased dendrite length

and synapse number when compared to iPSC-derived glutamatergic neurons from controls (Ishii et al., 2019). In another iPSC-based study, the glutamate decarboxylase gene was among the differently expressed genes in neurons generated from bipolar versus unaffected siblings in an Old Order Amish Pedigree (Kim et al., 2015). Next, electrophysiological differences have been investigated in both fibroblast- (Mertens et al., 2015) and B lymphocyte (Stern et al., 2018)-derived iPSCs that have been differentiated into hippocampal dentate gyrus (DG) granule-like cells (who use glutamate as their primary neurotransmitter in "mossy fiber" DG-to-CA3 synapses) from BD patients compared to controls. In the fibroblast-based study, iPSC-derived vGLUT1-positive cells resembling DG granule neurons from BD patients displayed hyperexcitability and mitochondrial abnormalities, which, in lithium responders only, could be reversed by lithium application in vitro (Mertens et al., 2015). In the lymphocyte study, BD subjects were again a priori stratified on the basis of their clinical response to lithium, and iPSC-derived DG granule cells from lithium responders and lithium non-responders displayed intrinsic differences, for example, a 45% decrease in baseline sodium currents in lithium non-responders compared to both control and lithium responders (Stern et al., 2018).

13.2 Clinical

The relationship between BD and glutamate has been extensively investigated in clinical studies, which has been primarily studied by three noninvasive modalities in awake, alert subjects: magnetic resonance spectroscopy (MRS), electroencephalography (EEG), and, to a lesser extent, positron emission tomography (PET). There are also postmortem studies reporting increased glutamate and differential expression of glutamate receptors in the brain.

13.2.1 Magnetic resonance spectroscopy

MRS is a noninvasive, ionizing radiation-free imaging modality, applying a magnetic field to a sample of tissue—in the case of most studies reviewed here, a voxel localized in a specific brain region—to generate a chemical trace based on the selected endogenous nuclei (Maddock & Buonocore, 2012). There are many different elements that can be used for MRS, but the most commonly used is the hydrogen proton, that is [^{1}H]-MRS. [^{1}H]-MRS allows for visualization of glutamate both globally across the brain as well as regionally as defined by the voxel parameters used (Maddock & Buonocore, 2012; Yuksel & Ongur, 2010). This approach, depending on the strength of the magnetic field used, allows measurement of either glutamate (Glu) and glutamine (Gln) separately or as a joined signal termed Glx (Govindaraju, Young, & Maudsley, 2000; Yuksel & Ongur, 2010). Thus, in

BD, [^{1}H]-MRS is particularly valuable for the purposes of measuring baseline levels in comparison to healthy controls and within-subjects in response to therapeutic interventions. [^{13}C]-MRS has also proven useful in studying glutamate cycling in healthy controls and MDD patients (Abdallah et al., 2014), including in response to ketamine (Abdallah et al., 2018), but, based on our search, there are currently no published [^{13}C]-MRS studies in BD.

In confirmation of the initial postmortem observations (Hashimoto, Sawa, & Iyo, 2007), three separate metaanalyses found broadly increased Glx in the brains of individuals with BD (Gigante et al., 2012; Maddock & Buonocore, 2012; Yuksel & Ongur, 2010) (Table 13.1). Interestingly, increased Glx is state-independent and does not correlate with symptom intensity (Yuksel & Ongur, 2010). When adjusting for medication status (a key confounder across many studies), this finding persisted in adult bipolar subjects (Gigante et al., 2012). Currently available studies regarding Glx in bipolar adolescents and children do not show elevated Glx but may be confounded by diagnostic considerations and medication status (Gigante et al., 2012).

In terms of specific brain regions, increased Glx has been observed in the cingulate, prefrontal, insular, parieto-occipital, and occipital cortices and the hippocampal gray matter (Bhagwagar et al., 2007; Colla et al., 2009; Dager et al., 2004; Frye et al., 2007; Lan et al., 2009; Michael et al., 2003; Ongur et al., 2008; Senaratne, Milne, Macqueen, & Hall, 2009). One study showed increased Glx signal in the left frontal white matter of subjects in younger as compared to older BD subjects (Bustillo et al., 2019). A study that separated Glx signal into Glu and Gln showed increased Glu signaling in the medial prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (Frye et al., 2007). Of note, an inverse relationship between ACC Glu level and number of lifetime mood episodes in bipolar subjects, that is decreasing ACC Glu with greater number of episodes, has been reported (Ehrlich, Schubert, Pehrs, & Gallinat, 2015).

In addition, there have been many studies to examine Glx changes in brain areas depending on bipolar type, that is bipolar I and II, or episodicity, that is hypo/manic, depressed and euthymic. For example, increased glutamine in the ACC and parieto-occipital cortex has been found during mania (Ongur et al., 2008). In addition, there is increased hippocampal Glu, but not Glx, in euthymic individuals (Colla et al., 2009; Senaratne et al., 2009). Increased Glx has been reported in the left dorsolateral prefrontal cortex (dlPFC) of hospitalized manic patients but, in mostly depressed medication-free BD outpatients, increased Glu levels were not observed in the dlPFC (Frey et al., 2007; Michael et al., 2003).

In addition to tissue concentrations, various ratios of glutamine-to-glutamate provide parameter estimates of tripartite glutamatergic neurotransmission (Patel et al., 2004) describing, for example, the efficiency of synaptic Glu reuptake and enzymatic conversion to Gln by astrocytes (Kubo et al., 2017; Ongur et al., 2008). Thus, the baseline Gln/Glu ratio is reflective of

TABLE 13.1 Select brain magnetic resonance spectroscopy findings in bipolar disorder (in order of presentation from cortical-to-subcortical-to-other and therein alphabetically).

Region	Study	Subjects	Medication status	Field strength	Main findings
Cingulate cortex	Dager et al. (2004)	28 BD (11 BD-I, 17 BD-II), 26 HC	Mf (8 wk)	1.5 T	Nonsignificant ↑ in Glx in left cingulate cortex
	Ehrlich et al. (2015)	21 BD-I (euthymic), 42 HC	M	3 T	↑ Glu in ACC, with inverse correlation of ACC Glu and # of depressive/manic episodes
	Frye et al. (2007)	23 BD (depressed), 12 HC	M	1.5 T	↑ Glx and Glu in ACC
	Kubo et al. (2017)	31 BD, 31 HC	M	3 T	↑ Gln/Glu ratio in ACC, after adjusting for medication effects
	Ongur et al. (2008)	15 BD-I (manic), 21 HC	M	4 T	↑ Gln and Gln/Glu ratio in ACC
Insular cortex	Dager et al. (2004)	28 BD (11 BD-I, 17 BD-II), 26 HC	Mf (8 wk)	1.5 T	↑ Glx in left insular cortex
OCC	Bhagwagar et al. (2007)	16 BD-I (euthymic), 15 MDD (remitted), 18 HC	Mf (3 mo)	3 T	↑ Glx relative to HC
	Senaratne et al. (2009)	12 BD (euthymic), 12 HC	M	3 T	↑ Glx
POC	Ongur et al. (2008)	15 BD-I (manic), 21 HC	M	4 T	↑ Gln and Gln/Glu ratio

(*Continued*)

TABLE 13.1 (Continued)

Region	Study	Subjects	Medication status	Field strength	Main findings
dlPFC	Frey et al. (2007)	32 BD (20 BD-I, 12 BD-II with 17 depressed, 7 hypomanic, 1 mixed and 7 euthymic), 32 HC	Mf (2 wk)	1.5 T	No significant Δ
	Lan et al. (2009)	10 BD postmortem (8 BD-I, 1 BD-II, 1 BD NOS), 10 HC	5 M, 5 Mf (at time of death)	N/A (NMR)	↑ Glu
	Michael et al. (2003)	8 BD (manic), 8 HC	6 Mf, 2 M	1.5 T	↑ Glu
mPFC	Frye et al. (2007)	23 BD (depressed), 12 HC	M	1.5 T	↑ Glx and Glu
Hippocampus	Colla et al. (2009)	21 BD-I (euthymic), 19 HC	M	3 T	↑ Glu in L hippocampus
	Senaratne et al. (2009)	12 BD (euthymic), 12 HC	M	3 T	No significant Δ in L hippocampus
White matter	Bustillo et al. (2019)	43 BD-I (psychotic features), 41 schizophrenia, 45 HC	M	3 T	↑ Glu in L frontal white matter of young vs older BD subjects

Abbreviations: *ACC,* anterior cingulate cortex; *BD,* bipolar disorder; *BD-I,* bipolar I disorder; *BD-II,* bipolar II disorder; *BD-NOS,* bipolar disorder not otherwise specified; *dlPFC,* dorsolateral prefrontal cortex; *Gln,* glutamine; *Glu,* glutamate; *Glx,* MRS-detectable glutamine, glutamate, etc. signal; *M,* medicated; *Mf,* medication-free; *MDD,* major depressive disorder; *mPFC,* medial prefrontal cortex; *MRS,* magnetic resonance spectroscopy; *OCC,* occipital cortex; *POC,* parieto-occipital cortex.

efficient reuptake of synaptic glutamate and glutamine synthetase activity, and disturbances in this ratio may reflect abnormalities in glutamate−glutamine cycling (Kubo et al., 2017; Ongur et al., 2008). Increased ACC and parieto-occipital Gln/Glu ratio have been reported during acute mania (Ongur et al., 2008), and this increased ratio in the ACC has been replicated in a mostly euthymic sample (Kubo et al., 2017). Taken together, this is consistent with state-independent glutamate hyperactivity and/or abnormal neuronal−glial coupling.

Increased Glx and Gln/Glu ratios across the bipolar brain are distinctions in relation to other mood disorders including major depressive disorder (MDD). In fact, subjects with unipolar depression commonly exhibit both decreased Glx and Gln/Glu ratios relative to healthy controls (Ongur et al., 2008). The sensitivity and specificity of diagnosing bipolar depression based on ACC Glx signal (Taylor, 2014) have been studied, which yielded a sensitivity and specificity of 0.85 and 0.66, respectively. Therefore, when clinical examination, longitudinal course and/or treatment efficacy do not offer the usual diagnostic clarity, increased Glx and/or Gln/Glu ratios may be adjunctive biomarkers to aid in distinguishing unipolar depression from BD.

The MRS approach is not without caveats. First, in many older studies using weaker magnetic strength scanners, for example, 1.5 or 3 T, individual component signals cannot be ascertained (Govindaraju et al., 2000). Such studies combine the glutamate and glutamine pool as "Glx" signal, which also includes weak contributions from gamma-aminobutyric acid (GABA) and glutathione. Second, MRS is unable to resolve certain pools of glutamate, such as glutamate bound to macromolecules and packaged into vesicles. As such, it is estimated that as much as 20% of glutamate in the brain may be undetectable by MRS (Kauppinen & Williams, 1991; Waagepetersen, Sonnewald, & Schousboe, 2007). Finally, it should be noted that increased Glx does not necessarily correlate with increased neurotransmission throughout the lifespan, as increased synaptic glutamate may reflect increased neurotoxicity, especially in the context of late-life neurological disorders often comorbid with BD (Ongur, Drevets, & Price, 1998; Theberge et al., 2002).

In summary, the most consistent MRS BD finding is increased Glx and Gln/Glu ratio with the most consistently implicated brain area for signal perturbation being the ACC. As the ACC functions in decision-making and impulse regulation, both impaired in BD, it is logical that this area appears neurochemically overactive.

13.2.2 Electroencephalography

EEG is another noninvasive methodology that is used to capture changes in electrical signaling across the brain via scalp electrodes placed at fixed locations. While this approach may have poorer spatial resolution compared to

other functional imaging approaches, such as functional magnetic resonance imaging (fMRI), EEG poses a distinct temporal advantage by directly measuring changes in electrical activity as opposed to differential blood flow and other metabolic measurements (Maggioni, Bianchi, Altamura, Soares, & Brambilla, 2017). In addition, EEG does not require exorbitantly priced scanning devices in fixed locations, making it more applicable as a community- and/or office-based procedure if simplified to only a few leads/cap.

Neural firing patterns/oscillations are present throughout the brain at rest, and these oscillations display characteristic, well-described frequencies. Neuronal firing patterns have been broadly categorized based upon their frequencies as follows: delta—0.5−3.5 Hz; theta—3.5−7 Hz; alpha—8−13 Hz; beta—18−25 Hz; gamma—30−70 Hz (Buzsaki & Wang, 2012; Gurtubay, Alegre, Labarga, Malanda, & Artieda, 2004; Klimesch, Doppelmayr, Pachinger, & Ripper, 1997; Yordanova & Kolev, 1998). Each of these so-called "bands" arises from myriad neurochemical and circuit-level synergy, contributing to their formation and dependent upon the location where the band is measured. Of particular interest in this section is the gamma band, which has been shown to strongly reflect excitatory/inhibitory balance as, simplistically speaking, reflected by the balance of glutamatergic/GABAergic neurotransmission (Lally et al., 2014).

There are many disturbances in gamma band oscillations that have been correlated with specific or broad symptom patterns in BD (Table 13.2). Firstly, as described throughout this textbook, BD patients very commonly report state-specific impairments in sleep (Harvey, Talbot, & Gershon, 2009). This is backed up by a potential EEG biomarker present in the pedunculopontine nucleus (PPN) (Garcia-Rill, D'onofrio, Mahaffey, Bisagno, & Urbano, 2019). As the PPN is part of the reticular activating system (RAS), it is postulated to have an important role in arousal and consciousness (Moruzzi & Magoun, 1949; Wijdicks, 2019). Indeed, neurons in the PPN exhibit differential gamma and beta band activity during wakefulness and rapid eye movement (REM) sleep (Datta & Siwek, 2002; Kayama, Ohta, & Jodo, 1992; Steriade, Pare, Datta, Oakson, & Curro Dossi, 1990). It is theorized that increased neuronal calcium sensor-1 (NCS-1) in the PPN may decrease the drive toward wakefulness and promote REM sleep (Garcia-Rill et al., 2019). Another phenomenon of gamma band activity is so-called mismatch negativity (MMN). MMN is a negative spike in EEG recordings that may be elicited when a series of similar stimuli is interrupted by a deviant, often disruptive, stimulus, for example, a train of low-pitched tones interrupted by a high-pitched tone (Onitsuka, Oribe, & Kanba, 2013). MMN is thought to be illustrative of the brain's capacity to match an incoming sensory stimulus with sensory memory traces of similar stimuli (Hermens, Chitty, & Kaur, 2018). Frontocentral MMN amplitude and hippocampal Glu concentrations have been positively correlated in healthy controls but were not associated in bipolar patients (Chitty, Lagopoulos, Hickie, & Hermens,

TABLE 13.2 Select EEG findings in bipolar disorder (in order of presentation from cortical-to-subcortical-to-global and therein alphabetically).

Region	Study	Subjects	Medication status	Main findings
Fronto-temporal cortex	Ozerdem et al. (2010)	10 BD (7 BD-I, 3 BD-II, 6 manic, 5 hypomanic), 10 HC	Mf (2 wk, 24 h for benzodiazepines)	↓ Long distance gamma band coherence of right fronto-temporal region
	Ozerdem et al. (2011)	20 BD (18 BD-1, 2 BD-II), 20 HC	Mf	↓ Long distance gamma band coherence
	Velasques et al. (2013)	20 BD (10 manic, 10 depressed), 12 HC	M	↓ Long distance gamma band coherence
Temporal cortex	Chitty et al. (2015)	35 BD (14 BD-I, 15 BD-II, 4 BD-NOS, 2 BSwFHx), 23 HC	M (adjusted analysis)	Positive correlation b/w MMN amplitude and [Gln] in HC but not BD
PPN/RAS	Garcia-Rill et al. (2019)	N/A ("limited review")	N/A	↑ [NCS-1] associated with ↓ gamma amplitude oscillations
N/A (Global)	Kaur et al. (2019)	47 BD, 13 schizophrenia	M	MMN amplitude in frontal and temporal regions are positively correlated with [glutamate] in ACC in schizophrenia but not BD
	Onitsuka et al. (2013)	19 BD, 14 MDD, 29 HC	M	↓ ASSR power relative to MDD and HC

Abbreviations: *ACC*, anterior cingulate cortex; *ASSR*, auditory steady state response; *BD*, bipolar disorder; *BD-I*, bipolar I disorder; *BD-II*, bipolar II disorder; *BD-NOS*, bipolar disorder not otherwise specified; *BSwFHx*, bipolar spectrum with a family history of bipolar disorder; *M*, medication: *Mf*, medication-free; *MDD*, major depressive disorder; *MMN*, mismatch negativity; *N/A*, not applicable; *PPN*, pedunculopontine nucleus; *RAS*, reticular activating system.

2015), suggesting uncoupling of hippocampal NMDA receptor functioning. Similarly, in bipolar patients, MMN amplitudes in the frontal and temporal regions were not associated with ACC Glu changes, but, in schizophrenia subjects, a trend-level association was observed (Kaur et al., 2019). As MMN-related ACC glutamate associations are seen in schizophrenic patients, which can be difficult to discern between bipolar mania with psychotic features, this potential nosological biomarker may be especially useful in distinguishing the two disorders (Catts et al., 1995; Hermens et al., 2018; Umbricht et al., 2003).

Next, the auditory steady state response (ASSR) is a gamma band pattern elicited most prominently by administering an auditory click stimulus at 40 Hz(Onitsuka et al., 2013). ASSR differences between bipolar and unipolar depressed patients have also been investigated as a potential glutamate-based diagnostic tool. In a study comparing ASSR in BD and MDD subjects, the MDD group exhibited similar findings to the healthy control group, whereas the bipolar group exhibited decreased ASSR power and phase-locking factors relative to the MDD and healthy control groups (Isomura et al., 2016). This distinction may be another means to neurobiologically differentiate these two disorders.

Next, there is an ample body of research on brain network synchronization as a possible biomarker in BD. While some findings are contested, one *meta*analysis describes a role for frontocortical changes in synchronization across many EEG bands (Maggioni et al., 2017). Studies have shown decreased gamma band coherence in the right hemispheric frontotemporal region in bipolar patients during euthymia and mania (Ozerdem, Guntekin, Atagun, Turp, & Basar, 2011; Ozerdem, Guntekin, Saatci, Tunca, & Basar, 2010; Velasques et al., 2013). Compared to healthy controls, depressed and manic bipolar patients exhibited decreased coherence in right hemispheric frontal, motor, and occipital cortices but increased coherence in the left hemisphere in those same areas.

Taking the results of this EEG section together, there are multiple putative glutamate-based diagnostic biomarkers in BD with some evidence of replicability, e.g. decreased gamma band coherence.

13.2.3 Positron emission tomography

As most metabolic PET studies in BD have used [^{18}F]-deoxyglucose (Baxter et al., 1985; Baxter et al., 1989; Buchsbaum et al., 1986) instead of [^{11}C]-glucose, measuring glucose metabolism/utilization and amino acid pools, respectively, there is a dearth of information on glutamate dysfunction in BD using PET. To date, there has been a single study that shows, in contrast to active unipolar depression, increased [^{11}C] counts, reflective of increased amino acid pools, in the brains of subjects with active bipolar mania (Kishimoto et al., 1987). While a large amount is glutamate, the brain amino acid pool also includes other amino acid-based neurometabolites, for

example, alanine, aspartate, and GABA, so this global increase is unlikely specific to glutamate.

Although PET ligands exist for mGluR5 and the synaptic vesicle glycoprotein 2 A (SV2A) [a proxy of synaptic, including excitatory/glutamatergic, density (Mendoza-Torreblanca, Vanoye-Carlo, Phillips-Farfan, Carmona-Aparicio, & Gomez-Lira, 2013)], which have been successfully used in MDD studies (Abdallah et al., 2017; Deschwanden et al., 2011; Holmes et al., 2019), including in response to ketamine (Delorenzo et al., 2015; Esterlis et al., 2018), there have been no published reports with these PET ligands in BD. Such studies may confirm or extend the literature of enhanced excitatory synaptic neurotransmission and neuroplasticity in the bipolar brain, for example increased levels of vesicular glutamate transporter (vGluT1) and netrin family members, respectively, in the ACC (Eastwood & Harrison, 2010).

13.2.4 Glutamate receptor-based biomarkers

13.2.4.1 Ionotropic

There are two types of excitatory glutamate receptors, ionotropic and metabotropic. In brief, ionotropic glutamate receptor opening fluxes cations, that is Na^+ and Ca^{2+}, down their concentration gradient, that is from the extracellular space to the cysotol, leading to neuronal depolarization (Niciu, Kelmendi, & Sanacora, 2012). There are three classes of ionotropic glutamate receptors: N-methyl-D-aspartate receptors (NMDARs), a heterotetramer consisting of subunits NR1, NR2A, NR2B, NR2C, NR2D, NR3A, and NR3B (Kew & Kemp, 2005; Niciu et al., 2012); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), another heterotetramer formed by subunits GluR1, GluR2, GluR3, and GluR4; and kainate receptors, homo- and heterotetramers formed by subunits GluR5, GluR6, GluR7, KA1, and KA2.

Several postmortem studies have investigated NMDAR subunit expression in BD across various brain regions (Table 13.3). Unfortunately, these postmortem expression profiles are not specific to BD, often being seen in other mood and psychotic disorders. In particular, NR1 subunit expression was decreased in the dlPFC of BD, MDD, and schizophrenia (Beneyto & Meador-Woodruff, 2008). Decreased NR2A subunit concentration in layer 2 of the ACC has also been observed in BD and schizophrenia, with BD NR2A exhibiting a 60% decrease (Woo, Walsh, & Benes, 2004). However, in Brodmann's area 9 of the PFC, the density of NMDARs containing the NR2A subunit was decreased in schizophrenia but not in BD (Fountoulakis, 2012). In the perirhinal cortex of the medial temporal lobe, decreased NR2B was observed in MDD, BD, and schizophrenia as well as decreased NR1 in BD and decreased NR2A in MDD (Beneyto, Kristiansen, Oni-Orisan, Mccullumsmith, & Meador-Woodruff, 2007).

There have been several inconsistent NMDAR findings in the BD hippocampus. Decreased binding of radiolabeled MK-801, a noncompetitive

TABLE 13.3 Select glutamate receptor-based biomarker findings (mostly postmortem and genetics) in bipolar disorder (in order of ionotropic-to-metabotropic and alphabetical therein).

Receptor	Study	Subjects	Main findings
Ionotropic			
AMPA	Beneyto et al. (2007)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↓ GluR2 and GluR3 mRNA expression in BD entorhinal cortex; ↓ GluR1 and GluR3 in BD and MDD perirhinal cortex
	Meador-Woodruff et al. (2001)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↓ GluR1 mRNA expression in the caudate, putamen, and NAcc in BD but not MDD and schizophrenia; ↑ radiolabeled AMPA binding in the same brain regions
KA	Beneyto et al. (2007)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↓ GluR6 mRNA expression in the entorhinal cortex of BD; ↓ GluR5 in all disorders
	Pickard et al. (2006)	368 BD, 386 schiziophrenia, 458 HC	A two-SNP haplotype in *GRIK4* (KA1) protective against BD
	Woo et al. (2007)	20 BD, 20 schizophrenia, 20 HC	↓ GluR5 in ACC layer 2 in BD and schizophrenia
NMDA	Amoah et al. (2020)	26 BD, 29 schizophrenia, 25 HC	[miR223] negatively correlated with orbitofrontal NR2B in BD with psychotic features and schizophrenia
	Beneyto et al. (2007)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↓ NR1 in BD, ↓ NR2B in BD and MDD perirhinal cortex; ↓ radiolabeled MK-801 (binds to intrachannel, i.e., open channel, site) in hippocampus of BD and schizophrenia; ↑ MDL105,519 (binds to glycine/D-serine coagonist site) in BD hippocampus
	Beneyto and Meador-Woodruff (2008)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↓ NR1 in dlPFC in all disorders

(*Continued*)

TABLE 13.3 (Continued)

Receptor	Study	Subjects	Main findings
	Fabbri and Serretti (2016)	723 BD (broad spectrum in STEP-BD)	*GRIN2A* (NR2A) and *GRIN2B* (NR2B) SNPs associated with long-term treatment outcome in BD, cyclothymic disorder, and schizoaffective disorder bipolar type
	Mccullumsmith et al. (2007)	8 BD, 8 schizophrenia, 8 HC	↓ NR1 and NR2A in the hippocampus of BD but not schizophrenia
	Meador-Woodruff et al. (2001)	15 BD, 15 MDD, 15 schizophrenia, 15 HC	↑ NR2D expression in caudate, putamen and NAcc in BD relative to MDD (but not HC)
	Mullins et al. (2021)	41,917 BD, 371,549 HC (metaanalysis)	↑ *GRIN2A* (NR2A) SNP rs7199910
	Scarr et al. (2003)	8 BD, 8 HC	↓ radiolabeled MK-801 in the subiculum and CA3 hippocampus; ↓ radiolabeled CGP39653 across hippocampus (no subregion specificity)
	Stahl et al. (2019)	20,352 BD, 31,358 HC → follow-up of 822 variants in 9,412 BD, 137,760 HC	↑ *GRIN2A* (NR2A) SNP rs11647445
	Woo et al. (2004)	17 BD, 17 schizophrenia, 18 HC	↓ NR2A in ACC layer 2 in BD and schizophrenia
Metabotropic			
mGluR3	Dalvie et al. (2010)	191 BD-I, 188 HC	*GRM3* SNP rs6465084 heterozygosity associated with fourfold ↑ risk of BD with psychotic features

(*Continued*)

TABLE 13.3 (Continued)

Receptor	Study	Subjects	Main findings
	Kandaswamy et al. (2013)	1,099 BD (915 BD-I, 184 BD-II), 1,152 HC	*GRM3* SNPs rs2237563 and rs2158786 associated with BD
mGluR4	Fabbri and Serretti (2016)	723 BD (broad spectrum in STEP-BD)	*GRM4* SNPs associated with long-term treatment outcome in BD, cyclothymic disorder, and schizoaffective disorder bipolar type
mGluR7	Kandaswamy et al. (2014)	32 BD, 32 HC	Multiple *GRM7* SNPs and point mutations associated with BD

Abbreviations: *ACC*, anterior cingulate cortex; *AMPA*, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *BD*, bipolar disorder; *BD-I*, bipolar I disorder; *BD-II*, bipolar II disorder; *dlPFC*, dorsolateral prefrontal cortex; *HC*, healthy control; *KA*, kainate; *mGluR*, metabotropic glutamate receptor; *miR*, microRNA; *MDD*, major depressive disorder; *N/A*, not applicable; *NAcc*, nucleus accumbens; *NMDA*, *N*-methyl-D-aspartate; *SNP*, single nucleotide polymorphism; *STEP-BD*, Systematic Treatment Enhancement Program for Bipolar Disorder.

NMDAR antagonist, was observed in the subiculum and CA3, suggestive of decreased open channel availability in BD (Scarr, Pavey, Sundram, Mackinnon, & Dean, 2003). Another radiolabeled NMDAR ligand used in the same study, D,L-(E)-2-amino-4-propyl-5-phosphono-3-pentenoic acid (CGP39653), which competes with the glutamate-binding site, displayed decreased binding density across the hippocampus, but no specific subregions reached statistical significance (Scarr et al., 2003). Taken together, these results indicate decreased open channel availability without an overall decrease in NMDAR density. Yet, another study reported decreased RNA expression of transcripts encoding NR1, NR2A, and NMDAR-associated postsynaptic density proteins in the hippocampus of BD but not in schizophrenia patients (McCullumsmith et al., 2007). Interestingly, an age-associated NMDAR decrease has been observed in the PFC of healthy controls, but no age-dependent effects were observed in BD and schizophrenia (Fountoulakis, 2012).

There are also numerous reports of AMPAR alterations in BD (Table 13.3). A study described earlier examining the medial temporal lobe of schizophrenia, BD, and MDD patients found altered AMPAR subunit expression in the entorhinal and perirhinal cortices (Beneyto et al., 2007). In particular, decreased GluR2 and GluR3 (as well as kainate receptor subunit GluR6) mRNA expression in BD patients and decreased expression of GluR5 in BD, MDD, and schizophrenia patients in the entorhinal cortex were observed. Yet, in Scarr et al. (2003) referenced above, using [^{3}H]-

AMPAR as a radioligand, there was no change in AMPAR density in postmortem BD hippocampus (Scarr et al., 2003). Next, the expression of an astrocytic exosome-secreted microRNA (miRNA) that targets glutamate receptors, miR223, was increased in postmortem orbitofrontal cortex in schizophrenia and BD with psychosis subjects at the time of death (Amoah et al., 2020). Exosome-derived miR223 levels were also negatively correlated with GluR2 (and NMDAR subunit NR2B) expression (Amoah et al., 2020). Finally, BD patients were shown to have decreased GluR1 mRNA expression in the nucleus accumbens and striatum (caudate and putamen) (Meador-Woodruff, Hogg, & Smith, 2001). This same study showed increased radiolabeled AMPA binding in the nucleus accumbens, caudate and putamen in BD patients but not MDD or schizophrenia patients, relative to healthy controls.

Kainate receptors also show subunit expression changes in BD (Table 13.3). In layer 2 of the ACC, there was a 40% reduction in GluR5 (Woo et al., 2007). In the same study above using radiolabeled AMPA, there was decreased radiolabeled kainate binding in the nucleus accumbens, caudate and putamen in MDD, but no evidence of altered expression in BD or schizophrenia, subjects relative to healthy controls (Meador-Woodruff et al., 2001). As such, alterations in kainate receptor expression may be valuable in differentiating MDD from BD and schizophrenia.

In genome-wide association studies (GWAS), some of which will be discussed in greater detail in the context of mGluR genetics that follows, including a 2021 metaanalysis of 41,917 BD patients relative to 371,549 controls, 2 *GRIN2A* (NR2A) single nucleotide polymorphisms (SNPs)—rs11647445 (Stahl et al., 2019) and rs7199910 (Mullins et al., 2021) —were overrepresented in cases relative to controls. In an Ashkenazi Jewish case-parent trio study of BD1 ($n = 323$) and schizophrenia ($n = 274$), a *GRIN2B* (NR2B) SNP was associated with BD (Fallin et al., 2005), but this failed to replicate in either of the above two GWAS. Furthermore, no AMPAR or kainate receptor subunit genesconferred risk for BD in the aforementioned GWAS. Yet, a two-SNP haplotype, rs602104 and rs22822586, in the kainate receptor gene *GRIK4* (KA1) has been reported as *protective* against BD (Pickard et al., 2006).

13.2.4.2 Metabotropic

mGluRs are slower-acting relative to their ionotropic counterparts, as is typical of seven-transmembrane G-protein-coupled receptors, which act through second messenger/signal transduction cascades to modulate protein activity, gene expression, and other effects (Niciu, Ionescu, Mathews, Richards, & Zarate, 2013). It has been shown that mGluRs play pivotal roles in neuronal plasticity and learning (Niciu et al., 2012; Niswender & Conn, 2010). There are eight receptors in this family, mGluR1−mGluR8, encoded by

GRM1−*GRM8* (with the given gene number corresponding to the receptor protein, i.e., *GRM1* encoding mGluR1). mGluRs are subdivided into three groups on the basis of amino acid homology, agonist binding, and signal transduction pathway activation (Kim, Lee, Lee, & Roche, 2008). Group 1 includes mGluR1 and mGluR5, group 2 contains mGluR2 and mGluR3, and group 3 consists of mGluR4, mGluR6, mGluR7, and mGluR8.

GRMs have been extensively studied in BD (Table 13.3) (Blacker, Lewis, Frye, & Veldic, 2017). The most studied/identified gene has been *GRM3*. Human *GRM3* consists of six exons with four variants detected in human brain (Sartorius et al., 2006). In a German BD sample ($n = 46$), three sequences variants were present, but, in an attempted expansion ($n = 283$), there was no overrepresentation of the T-allele in the rs2228595 SNP [1131 C/T (A291A)] in BD patients versus ethnically matched controls ($n = 227$), albeit an overrepresentation was observed in schizophrenia ($n = 265$) when compared to controls (Marti, Cichon, Propping, & Nothen, 2002). Next, in the Ashkenazi Jewish case-parent trio study discussed above, *GRM3* (and *GRM4*) SNP(s) displayed an association with BD (Fallin et al., 2005). 2 *GRM3* SNPs, rs2237563 and rs2158786, have also been associated with BD in a combined University College London (UCL) dataset of BD ($n = 1099$) and healthy volunteers ($n = 1152$) (Kandaswamy et al., 2013). This study also identified a rare SNP in the *GRM3* Kozak sequence, rs148754219, as overrepresented in BD relative to controls, that is BD 19/1099 (1.9%) versus healthy comparators 4/1152 (0.3%) [$P = .005$; odds ratio (OR) 4.20; 95% CI 1.43−12.37] (Kandaswamy et al., 2013). Another *GRM3* SNP that may have diagnostic value in discerning MDD and BD is rs6465084, which was shown to associate with unipolar depression but not BD (Tsunoka et al., 2009). Yet, the rs6465084 SNP has also been shown to confer risk for BD psychosis (Dalvie et al., 2010). Finally, although there was suggestive evidence in the GWAS replication cohort ($n = 365$ BD, $n = 351$ controls) of (Sklar et al., 2008), in the two subsequent GWAS reports described above (Mullins et al., 2021; Stahl et al., 2019), no BD risk *GRM3* SNPs were identified.

In terms of other mGluR gene association studies, intronic SNPs rs1109654, rs2499724, rs2499726, and rs9380406 in *GRM4* have been associated with mood episode frequency in the broad-spectrum BD phenotype ($n = 723$) of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) "real-world" effectiveness trial (Fabbri & Serretti, 2016). SNPs rs2402007 and rs2499724 were also associated with the frequency of depressive episodes in STEP-BD. Next, several *GRM7* haplotypes have been associated with BD. Specifically, rs6769814 has been reported to be overrepresented in BD, with rs138571076 underepresented, that is being only present in three BD subjects (Kandaswamy, Mcquillin, Curtis, & Gurling, 2014). In this study, point mutations in *GRM7*, specifically GRM7_3f_7313045 and GRM7_nPb_7467774, were observed in two and one BD patients, respectively (Kandaswamy et al., 2014).

13.3 Treatment

Several glutamatergic modulators have been studied for the treatment of BD, particularly major depressive episodes (MDEs). In this section, we will focus primarily on subanesthetic dose ketamine for bipolar depression but will also first briefly discuss other agents, for example, lamotrigine and riluzole (Table 13.4).

13.3.1 Lamotrigine

Lamotrigine is a triazine derivative that inhibits synaptic glutamate release, which is believed to arise downstream of its inhibition of voltage-gated sodium channels and/or weak antagonism at the 5HT3 (serotonin) receptor. Like several other voltage-gated sodium channel inhibitors, it is a United States Food and Drug Administration (FDA)-approved antiepileptic medication, and it has been approved as a maintenance treatment in bipolar I and II disorders. In a metaanalysis of three maintenance trials ($n = 588$), lamotrigine reduced the risk of relapse to any mood episode relative to placebo [risk ratio (RR) 0.84; 95% confidence interval (CI) 0.71−0.99], an ∼16% reduction in relapse risk (Smith et al., 2007). However, lamotrigine did not separate from placebo in specifically reducing the risk of relapse to mania ($n = 411$; RR 0.91; 95% CI 0.64−1.30) or an MDE (RR 0.77; 95% CI 0.58−1.02). In the same metaanalysis, the efficacy of lamotrigine was compared with lithium in relapse prevention. Lamotrigine and lithium were comparable in preventing relapse to any mood episode ($n = 387$; RR 0.99; 95% CI 0.59−1.67) or MDE (RR 1.18; 95% CI 0.88−1.57); however, lithium reduced the risk of relapse to mania relative to lamotrigine (RR 0.53; 95% CI 0.32−0.87). Yet, discontinuation of therapy due to an adverse event was greater with lithium than with lamotrigine ($n = 447$; RR 2.20; 95% CI 1.31−3.70). It should be noted that the studies included in the aforementioned metaanalysis were short-term and industry-sponsored. An open-label, randomized Danish trial of lithium [$n = 78$ at therapeutic serum levels (0.5−1.0 mmol/L)] and lamotrigine ($n = 77$, uptitrated to 400 mg/day) revealed similar efficacy out to 5 years (albeit very few patients were successfully maintained on monotherapy); lamotrigine was also better tolerated than lithium in this study (Licht, Nielsen, Gram, Vestergaard, & Bendz, 2010).

There is insufficient literature support for lamotrigine in the treatment of acute mania or mixed episodes. Although it is frequently prescribed off-label for this indication, the evidence in support of lamotrigine as mono- or adjunctive therapy for an acute MDE in BD is, at best, modest. An initial metaanalysis of five randomized, placebo-controlled trials ($n = 1072$) of lamotrigine 100−400 mg/day for 7−10 weeks indicated improvement in both the Hamilton Depression Rating Scale (RR 1.27; 95% CI 1.09−1.47)

TABLE 13.4 Ketamine bipolar depression study findings (in order of presentation in text).

Study	Number of bipolar patients (% female)	Design	Intervention	Control	Adjunctive medications	Efficacy/Response/ Remission
Diazgranados et al. (2010)	18 (66.7%)	Randomized, double-blind, placebo-controlled, crossover (2 wk apart)	Racemic ketamine 0.5 mg/kg IV over 40 min	0.9% (normal) saline IV over 40 min	Therapeutic dose lithium or valproate acid; otherwise medication-free for at least 2 wk before first infusion	Antidepressant efficacy at end of infusion ($d = 0.52$) to 3 d postinfusion; 71% ketamine response, 6% placebo response
Zarate et al. (2012)	15 (53.3%)	Randomized, double-blind, placebo-controlled crossover (2 wk apart)	Racemic ketamine 0.5 mg/kg IV over 40 min	0.9% (normal) saline IV over 40 min	Therapeutic dose lithium or valproate acid; otherwise medication-free for at least 2 wk before first infusion	Antidepressant efficacy ($d = 0.89$) at end of infusion to 3 d postinfusion; 79% ketamine response, no placebo response
Rybakowski et al. (2013)	25 (84%)	Open-label, single-arm	Racemic ketamine 0.5 mg/kg IV over 40 min	N/A	≥ 1 mood stabilizer, antidepressant-free ≥ 7 d	13 responders, 12 nonresponders; remission achieved in 8 and 12 at 1 and 2 wk, respectively, postinfusion
Permoda-Osip et al. (2014)	42 (76.2%)	Open-label, single-arm	Racemic ketamine 0.5 mg/kg IV over 40 min	N/A	≥ 1 mood stabilizer, antidepressant-free ≥ 7 d	Antidepressant efficacy at 24 h, 1 wk and 2 wk, with continued numerical improvement

Rybakowski et al. (2017)	53 (75.5%)	Open-label, single-arm	Racemic ketamine 0.5 mg/kg IV over 40 min	N/A	≥1 mood stabilizer, antidepressant-free ≥7 d	Antidepressant efficacy at 24 h, 3 d, 1 wk and 2 wk, with continued numerical improvement
Grunebaum et al. (2017)	16 (62.5%)	Randomized, double-blind, psychoactive placebo-controlled, parallel	Racemic ketamine 0.5 mg/kg IV over 40 min	Midazolam 0.02 mg/kg IV over 40 min	No benzodiazepines within 24 h of infusion	Depression and suicidality reduction with ketamine> midazolam but not statistically significant
Zheng et al. (2020)	19 (31.6%)	Open-label, single-arm	Racemic ketamine 0.5 mg/kg IV over 40 min × 6 infusions (3 ×/wk)	N/A	Stable psychotropic medication regimen ≥4 wk and during study	first infusion: 21.1% response, 15.8% remission sixth infusion: 73.7% response, 63.2% remission
Mcintyre, Lipsitz, et al. (2020), Mcintyre, Rodrigues, et al. (2020)[a]	30 (unknown)	Open-label, single-arm	Racemic ketamine 0.5−0.75 mg/kg IV over 40−45 min × 4 infusions	N/A	No monoamine oxidase inhibitors for ≥2 wk, no naltrexone, no benzodiazepines 12 h preinfusion	Antidepressant efficacy, 27% response, 13% remission, after fourth infusion
Correia-Melo et al. (2017)[a]	4 (unknown)	Open-label, single-arm	Esketamine 0.25 mg/kg IV over 10 min	N/A	No restrictions reported	48.1% response, 37.0% remission at 1 wk postinfusion

Abbreviations: *IV*, intravenous; *kg*, kilogram; *mg*, milligram.
[a]*Mixed diagnostic study of unipolar and bipolar depression in current major depressive episode; antidepressant measures reported for the entire population as no group (diagnostic) analyses were reported.*

and Montgomery Åsberg Depression Rating Scale (RR 1.22; 95% CI 1.06−1.41) (Geddes, Calabrese, & Goodwin, 2009). Interestingly, there was an interaction with severity, as bipolar I/II patients with severe depression (HDRS > 24) demonstrated improvement with lamotrigine (RR 1.47; 95% CI 1.16−1.87) but, in those with mild-to-moderate depression severity (HDRS ≤ 24), lamotrigine did not separate from placebo (RR 1.07; 95% CI 0.90−1.27). In addition, there was no difference in efficacy based on primary diagnosis, that is bipolar I versus II depression. A subsequent metaanalysis again reported modest efficacy of lamotrigine relative to placebo but greater risk of affective switch, which led the authors to deter its use in bipolar I/II depression (Taylor, Cornelius, Smith, & Young, 2014). Yet, the lack of robust efficacy may be due to the long-dose titration (necessary to mitigate the risk of potentially lethal rash, i.e., Stevens−Johnson syndrome/toxic epidermal necrolysis) to reach therapeutic doses in these short clinical trials. Lamotrigine is otherwise well tolerated in bipolar I//II patients, with comparable discontinuation rates as placebo in both acute and maintenance trials (Bowden et al., 2004). As a result, many experts would consider lamotrigine as a second- or third-line medication, that is after quetiapine, lurasidone, olanzapine/fluoxetine, and valproate alone or in combination, in the treatment of bipolar I/II depression.

13.3.2 Riluzole

Riluzole is a United States FDA-approved therapy for amyotrophic lateral sclerosis (Bensimon, Lacomblez, & Meininger, 1994). Similar to lamotrigine, it reduces synaptic glutamate levels, and, as a result, is hypothesized to reduce excitotoxicity in neurodegeneration. In addition to decreasing release through inhibition of presynaptic voltage-dependent sodium channels, riluzole also stimulates the expression of an astrocytic glutamate transporter, GLT-1, that promotes synaptic reuptake and recycling. An open-label 6-week trial of riluzole monotherapy (100−200 mg/day) in medication-free, treatment-resistant MDD ($n = 19$) revealed preliminary antidepressant response (Zarate et al., 2004) as well as a case report of riluzole augmentation having antidepressant efficacy in a treatment-resistant depressed bipolar patient who developed a rash with lamotrigine (Singh, Zarate, & Krystal, 2004). These studies set the stage for subsequent investigative use in bipolar I/II depression. Riluzole was added onto therapeutic dose lithium in treatment-resistant bipolar I/II depression ($n = 14$), and, in this 8-week dose escalation study (maximum dose 200 mg/day), had antidepressant efficacy without evidence of affective switching or intolerable side effects (Zarate et al., 2005). Next, in MRS study with 14 bipolar I/II depressed subjects who received open-label riluzole (100−200 mg/day over 6 weeks), antidepressant efficacy was observed, which correlated with *N*-acetylaspartate (NAA) increase and decrease in the ACC and parietal-occipital cortex, respectively,

from baseline to the end of the study (Brennan et al., 2010). Of note, increased Gln/Glu ratio was observed after only 2 days of treatment, suggestive, as discussed earlier, of increased cycling/synaptic plasticity and a putative early treatment response biomarker.

The discussed studies have all been open label, and, to date, there has only been one double-blind placebo-controlled trial of riluzole in bipolar I/II depression. In this study, 19 bipolar I/II depressed, psychotropic medication-free patients were randomized to placebo ($n = 11$) or riluzole ($n = 8$) 50−200 mg/day for 8 weeks (Park et al., 2017). There was not a statistically significant drug ($F1,16 = 3.36$, $P = .09$) or drug-by-time interaction ($F7,7 = 0.99$, $P = .45$) on the primary outcome measure (MADRS); for the main anxiety measure used in the study, the Hamilton Rating Scale for Anxiety (HAM-A), there was a significant anxiolytic effect of *placebo* over riluzole ($F1,15 = 4.74$, $P = .046$). Eight subjects required as-needed benzodiazepines in this study ($n = 4$ placebo, $n = 4$ riluzole). As no subjects achieved antidepressant response at the interim analysis, the trial was stopped for futility. The authors also noted that the study was limited by a high attrition rate, that is 10 subjects with 5 randomized to each arm, and speculated that, although ineffective as monotherapy, riluzole may still have an adjunctive role in acute bipolar depression.

13.3.3 Ketamine

Ketamine is a United States FDA-approved anesthetic with, at subanesthetic doses, off-label efficacy in multiple neuropsychiatric disorders, particularly treatment-resistant MDD, with the next-best studied psychiatric disorder being bipolar depression. Ketamine is a noncompetitive NMDAR antagonist and enhancer of glutamatergic neurotransmission (Lener et al., 2017). More specifically, subanesthetic dose ketamine increases synaptic glutamate release through NMDAR-dependent disinhibition of inhibitory interneurons and increased postsynaptic AMPAR throughput (Henter, Park, & Zarate, 2021).

Unlike the initial MDD trials where subjects were unmedicated, the treatment-resistant bipolar I/II depressed subjects enrolled in the initial ketamine trials were maintained on therapeutic dose lithium and valproate to mitigate the risk of affective switching. In the initial randomized, double-blind, placebo-controlled, crossover trial at the National Institute of Mental Health (NIMH)'s Experimental Therapeutics and Pathophysiology Branch, 18 subjects with bipolar I/II depression were randomized to a single subanesthetic dose ketamine (0.5 mg/kg over 40 minutes) or normal saline infusion. Ketamine separated from placebo as early as infusion termination (Cohen's $d = 0.52$; 95% CI 0.28−0.76), maximal antidepressant efficacy was observed at day 2 ($d = 0.80$; 95% CI 0.55−1.04), and sustained for 3 days post-infusion (Diazgranados et al., 2010). At some point during the study, 71% and 6% responded to ketamine or placebo, respectively. The same NIMH

group replicated this protocol with 15 treatment-resistant bipolar I/II depressed subjects (Zarate et al., 2012). In this second study, within 40 minutes, subjects randomized to a single subanesthetic dose ketamine infusion demonstrated a large-to-very large antidepressant ($d = 0.89$; 95% CI 0.61−1.16) and antisuicidal ($d = 0.98$; 95% CI 0.64−1.33) response immediately at the end of infusion, which again sustained for 3 days post-infusion (Zarate et al., 2012). In the ketamine group, there was a 79% response rate within the 2 weeks following ketamine infusion while there were no responders to placebo. In this NIMH sample, bipolar I/II subjects with active anxious depression (as defined as a current MDE with HDRS Anxiety/Somatization Factor score of ≥ 7) displayed similar antidepressant efficacy to the non-anxious group (Ionescu, Luckenbaugh, Niciu, Richards, & Zarate, 2015). Finally, in a combined MDD and bipolar depressed cohort ($n = 133$), a single subanesthetic ketamine infusion had a significant antisuicidal effect, which persisted when controlling for the antidepressant ($F1,587 = 10.31$; $P = .001$) and anxiolytic ($F1,567 = 8.54$; $P = .004$) effects (Ballard et al., 2014).

A Polish group has similarly studied the antidepressant response to subanesthetic dose ketamine. Twenty-five (21 female, 4 male) active bipolar depressed patients on ≥ 1 mood stabilizer(s) (but tapered off antidepressants for >7 days post-infusion) received an single, subanesthetic dose ketamine infusion and were followed for up to 2 weeks (Rybakowski, Permoda-Osip, Skibinska, Adamski, & Bartkowska-Sniatkowska, 2013). At 1-week post-infusion, they observed 13 responders and 12 nonresponders. There were 8 and 12 participants who achieved remission at 1 and 2 weeks, respectively. In a similarly designed follow-up with 42 (32 women, 10 men) active bipolar depressed patients, depression severity was decreased at 24 hours, 1 week and 2 weeks post-infusion (Permoda-Osip et al., 2014). In a third study by the same group, 53 inpatients (13 male, 40 female) on ≥ 1 mood stabilizing medication(s) and non-responsive to traditional antidepressants received open-label ketamine as before (Rybakowski, Permoda-Osip, & Bartkowska-Sniatkowska, 2017). In this sample, there were 27 responders (10/13 male, 17/40 female). These studies also successfully identified and/or replicated several biomarkers of antidepressant response, for example, serum brain-derived neurotrophic factor (BDNF) (Rybakowski et al., 2013), vascular endothelial growth factor receptor-1 (VEGFR-1/Flt-1) (Permoda-Osip et al., 2014), and vitamin B12 (Permoda-Osip, Dorszewska, Bartkowska-Sniatkowska, Chlopocka-Wozniak, & Rybakowski, 2013) levels; baseline neurocognitive performance (Permoda-Osip, Kisielewski, Bartkowska-Sniatkowska, & Rybakowski, 2015); a personal and family history of an alcohol use disorder (Permoda-Osip et al., 2014); and male gender (Rybakowski et al., 2017).

One of the major concerns with placebo-controlled subanesthetic dose ketamine infusion studies has been functional unblinding and, concomitantly,

patient expectancies. Therefore, as occurred in treatment-refractory MDD (Grunebaum et al., 2018; Murrough et al., 2013), a psychoactive (midazolam 0.02 mg/kg IV × 40 minutes)-controlled, parallel trial in BD was conducted by investigators at Columbia University (Grunebaum et al., 2017). In this adjunctive bipolar trial, 16 subjects with active bipolar depression and Scale for Suicidal Ideation (SSI) score ≥4 were randomized to either ketamine or midazolam with the primary outcome measure SSI improvement at 24 hours post-infusion. Although it did not reach statistical significance over midazolam, there was a ∼6-point decrease in SSI in the ketamine group at 24 hours post-infusion; the number needed to treat for ketamine:midazolam was 2.2 and 3.2 for SSI response (SSI < 4 and 50% improvement from baseline) and remission (SSI = 0), respectively. This study also demonstrated a correlation between the antisuicidal effect of ketamine with memory improvement and increased peripheral BDNF levels.

All of the aforementioned studies were single infusion, and, to date, there have been no placebo-controlled multiple infusion trials in bipolar depression; yet, there have been open-label studies with combined diagnostic groups that may shed light on the efficacy of repeated infusions. 97 patients with MDD ($n = 77$) and BD ($n = 20$) in an active MDE received six subanesthetic (0.5 mg/kg) ketamine infusions over two weeks and were followed with depression, anxiety and suicidal ideation measures for 26 days post-initial infusion. There were significant decreases in all measures within 4 hours of the initial infusion that were sustained for the trial duration, for example 68% depression response and 50% depression remission. Interestingly, an antisuicidal effect was also observed in ketamine non-responders. In a secondary analysis of this cohort restricted to those with baseline suicidal thinking, 57% and 65.1% displayed an antisuicidal effect after the first and sixth infusions, respectively; suicidal ideation was more likely to improve in those with low (SSI < 4) versus high (SSI ≥ 5) scores (Zhan et al., 2019). This antisuicidal response further supports the prevailing hypothesis that the antidepressant and antisuicidal effects of ketamine are dissociable (Ballard et al., 2014). Neurocognitive improvement was also reported, that is increased verbal learning and processing speed, in this combined unipolar and bipolar dataset ($n = 84$) (Zhou et al., 2018). Unfortunately, the authors did not offer any statistical group (diagnosis) analyses in the aforementioned reports, but most recently published a secondary analysis of treatment efficacy in the bipolar subjects (Zheng et al., 2020). In 19 treatment-resistant bipolar depressed subjects, the response and remission rates were modest - 21.1% (CI 0.9−21.2%) and 15.8% (CI 0−33.9%), respectively - after the first infusion. However, after infusion six, they were increased to 73.7% (CI 51.9−95.5%) and 63.2% (CI 39.3−87.0%) with an average time to response and remission of 9.1 and 12.5 days, respectively.

A community-based but academically affiliated multidisciplinary clinic, the Canadian Rapid Treatment Center of Excellence, has also published

several reports of open-label repeated dose ketamine in a combined treatment-resistant unipolar ($n = 183$) and bipolar depression ($n = 30$) dataset. In the primary efficacy report, subjects received four open-label 0.5 mg/kg ketamine infusions with potential dose escalation after infusion two (0.75 mg/kg) if they displayed suboptimal response [as defined by <20% improvement on the Quick Inventory of Depressive Symptomatology (QIDS-SR_{16})] (Mcintyre, Rodrigues, et al., 2020). After infusion four, there was a large antidepressant effect [(F4,465) = 53, $P < .0001$, Cohen's $f = 0.67$]. Yet, the response and remission rates were more modest compared to other multiple infusion studies. At ~1 week after the fourth infusion, 26% and 13% met response and remission criteria, respectively, on this self-reported primary outcome. On the secondary outcomes measures, including in follow-up studies, improvement were observed in suicidality (Mcintyre, Rodrigues, et al., 2020); psychosocial functioning (Mcintyre, Rodrigues, et al., 2020); anhendonia (Rodrigues et al., 2020); anxiety, irritability and agitation (AIA), or mixed features (Mcintyre, Lipsitz, et al., 2020); and cognition (Mcintyre et al., 2021). No group (diagnostic) analyses were reported, likely due to the small number of bipolar subjects.

The S-enantiomer of ketamine, esketamine, has been approved in the United States as an adjunctive agent for treatment-resistant depression and, more recently, suicidal thinking and behavior. To date, there have been no reports of intranasal esketamine for active bipolar depression. However, esketamine has been approved for anesthesia in other parts of the world and, such as racemic ketamine, has been leveraged for neuropsychiatric disorders. A Brazilian group performed brief (10 minutes) 0.25 mg/kg esketamine infusions in 27 subjects with unipolar ($n = 23$) and bipolar ($n = 4$) depression (Correia-Melo et al., 2017). Based on MADRS change from baseline, 13 subjects responded and 10 patients remitted within 1 week. However, 11.1% reported severe dissociation during esketamine administration, which, the authors proposed, may limit its tolerability in repeated-dose paradigms.

In continuation of ketamine's safety and tolerability in bipolar depression, one of the major theoretical concerns has been the risk of rapid affective switching. As alluded to in the "Preclinical" section of this chaper, intraperitoneal injection of moderate dose ketamine, for example, 25 mg/kg, to adult mice induces hyperactivity resembling hypo/mania in humans. In addition, there have been several case reports of ketamine-induced manic-like symptoms/behavior (Allen, Rodysill, & Bostwick, 2019; Banwari, Desai, & Patidar, 2015; Lu, Lin, & Lane, 2016; Mandyam & Ahuja, 2017; Ricke, Snook, & Anand, 2011; Valdez & Makhinson, 2019). However, in a secondary analysis including data from the initial two NIMH ketamine bipolar depression studies, there was no increase in affective switching over placebo using the more inclusive International Society for Bipolar Disorders Task Force criteria for a "likely" "treatment-emergent affective switch" (Tohen et al., 2009) and consistent with a mild (type I) threshold on the Young

Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). In two recent metaanalyses, ketamine did not increase the risk of hypo/mania symptoms (Bahji, Zarate, & Vazquez, 2021; Joseph, Parsaik, Ahmed, Erwin, & Singh, 2021). Interestingly, YMRS scores *decreased* at 1- and 2 days post-infusion (Bahji et al., 2021).

13.4 Conclusion

In this chapter, we have reviewed biomarkers of glutamate-based dysfunction and treatment response in BD. Yet, glutamatergic excitatory neurons have been shown to co-secrete and/or interact with other neurotransmitter-secreting neurons, for example, dopaminergic neurons at postsynaptic densities (De Bartolomeis, Buonaguro, Iasevoli, & Tomasetti, 2014), with evidence for potential combinatorial effects in the etiopathogenesis, pathophysiology and treatment of a complex neuropsychiatric disorder like BD. These other neurotransmitter systems and their potential cross-talk with glutamate will be discussed in other chapters.

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