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Glutamate and GABA Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine

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Abstract

In patients with major depressive disorder (MDD) or bipolar disorder (BD), abnormalities in excitatory and/or inhibitory neurotransmission and neuronal plasticity may lead to aberrant functional connectivity patterns within large brain networks. Network dysfunction in association with altered brain levels of glutamate (Glu) and gamma-aminobutyric acid (GABA) have been identified in both animal and human studies of depression. In addition, evidence of an antidepressant response to subanesthetic dose ketamine has led to a collection of studies that have examined neurochemical (e.g. glutamatergic and GABA-ergic) and functional imaging correlates associated with such an effect. Results from these studies suggest that an antidepressant response in association with ketamine occurs, in part, by reversing these neurochemical/physiological disturbances. Future studies in depression will require a combination of neuroimaging approaches from which more biologically homogeneous subgroups can be identified, particularly with respect to treatment response biomarkers of glutamatergic modulation.

Keywords

major depressive disorder; bipolar disorder; mood disorder; glutamate; NMDA receptor antagonist; ketamine

Introduction

In rodent studies, pharmacological- and stress-induction paradigms that lead to depressive-like behaviors have been associated with alterations in cortical glutamate (Glu) (1–3); findings that have been reversed by monoaminergic antidepressants and electroconvulsive

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therapy (4, 5). As a result, a glutamatergic hypothesis of depression was posited that extends beyond monoaminergic dysfunction in patients with major depressive disorder (MDD) or bipolar disorder (BD) (6). Interestingly, clinical studies of depression using magnetic resonance spectroscopy (MRS) as well as positron emission tomography (PET) have identified alterations in Glu and gamma-aminobutyric acid (GABA) concentrations and activity, suggesting that dysfunction in excitatory and/or inhibitory neurotransmitter signaling mechanisms may play a critical role in depression. In this review, we examine studies that use electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) techniques to identify aberrant functional neural circuitry patterns in patients with MDD and BD. We then hypothesize links between neurotransmitter abnormalities and functional neurocircuitry deficits in depression, from which we encourage future work using MRS or PET techniques in conjunction with functional imaging techniques to elucidate and characterize these relationships.

Furthermore, a pivotal role of glutamatergic neurotransmission in the pathophysiology of and treatment response in MDD and BD has been supported by studies that demonstrate antidepressant efficacy of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (7) in preclinical and clinical studies (8, 9). Here we highlight ketamine as the best available molecular tool with which to probe the impact of glutamatergic modulation on excitatory/inhibitory neural circuitry dynamics in healthy and depressed subjects with MDD or BD due to evidence supporting ketamine's efficacy and its lower burden of side effects compared to other glutamatergic modulating agents (9–14). Within this framework, we review clinical studies using MRS, PET, fMRI, and MEG to explore how glutamatergic modulation may alleviate aberrant functional neurocircuitry in depression and mediate antidepressant response to ketamine. Lastly, we emphasize the importance of utilizing a combinatorial approach to better identify and predict treatment responders to ketamine.

Dysregulation of Glutamatergic and GABAergic Neurotransmission in Depression

Proton MRS (^1H -MRS) is an *in vivo* imaging technique for total tissue detection of neurochemicals, including N-acetylaspartate (NAA), GABA, Glu, glutamine (Gln), and a combination of Glu-Gln with a minor contribution from GABA (known as Glx) that is often reported due to poor signal resolution between these metabolites in weaker magnetic fields. ^1H -MRS studies examining levels of GABA, Glu, Gln, and Glx in the brain require an appreciation of Glu metabolism, particularly the Glu/Gln cycle (15, 16) (see Figure 1). Briefly, Glu is produced in neurons from glucose-derived tricarboxylic acid cycle intermediates and branched-chain amino acids. Cytosolic Glu is packaged into vesicles via vesicular glutamate transporters (vGluTs) for exocytotic release. After neuronal depolarization and release into the synaptic cleft, Glu binds to one of three types of ionotropic Glu receptors: NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainate, all of which are embedded in the postsynaptic membrane and clustered within postsynaptic densities. Glu also binds to metabotropic receptors (mGluRs), typically found extrasynaptically and presynaptically. To prevent synaptic spillover and excitotoxicity, Glu is removed from the synapse by Glu transporters in astrocytes and metabolically

converted into Gln via glutamine synthetase. Gln is released by astrocytes into presynaptic neurons where it is converted back to Glu via cytosolic glutaminase (15, 16). Inhibitory GABAergic neurons also contain the enzyme glutamic acid decarboxylase (GAD), which converts Glu to GABA.

In comparison to healthy subjects, aberrant amino acid neurotransmitter levels measured by ^1H -MRS have been found in individuals with MDD (6, 17–19) and BD (20, 21). Specifically, in MDD patients, Glu and Glx reductions were found in the dorsolateral prefrontal cortex (dlPFC) (22) and other prefrontal cortical (PFC) areas such as the dorso-medial and dorso-anterolateral PFC (23) and anterior cingulate cortex (ACC) (24), with increased levels in the occipital cortex (OCC) (25) to a degree that may be related to duration of illness (26). In a meta-analysis of 17 ^1H MRS studies of MDD patients, reductions of Glx in the PFC were associated with number of failed antidepressant treatments, a measure of chronicity and proxy for severity of depressive illness course (19). Surprisingly, this study found no isolated reductions in Glu, implicating astrocyte-mediated metabolic alterations in Glu metabolism underlying the pathophysiology of MDD (19). A possible explanation may be related to abnormal mitochondrial energy production in glutamatergic neurons. In an *in-vivo* ^{13}C MRS and ^1H -MRS study that examined the potential relationship between the Glu/Gln cycle and mitochondrial energy production (27), patients with MDD showed a 26% reduction in mitochondrial energy production compared to healthy subjects, though no differences were found in Glu/Gln cycle rate. The authors suggested that reductions in energy production within glutamatergic neurons resulted from reduced synaptic strength via reductions in AMPA or NMDA receptors in the postsynaptic neuron. Additionally, although performed post-hoc without correction for multiple comparisons, the authors found a negative association between Glu concentrations and the number of depressive episodes (27), suggesting that reductions in synaptic strength may reduce Glu neurotransmission over successive episodes of depression.

Neurochemical studies in BD patients have shown mixed results. Although some studies found no differences in Glu between BD patients and healthy subjects (28–31), two meta-analyses of ^1H MRS studies in BD noted increased Glx in the PFC regardless of mood state, as well as in the ACC in depressed states (20, 32). A recent study showed that elevated Glu in the ACC associated with BD patients in euthymic states was related to number of depressive/manic episodes (21); notably, this finding may allow for differentiation of depression between BD and MDD. Impaired oxidative metabolism in glutamatergic neurons has been hypothesized to explain elevated Glx and lactate levels associated with mixed or depressed states in BD (33), and further supports a contributory role of inflammation in the pathophysiology of depression (34). Wide and overlapping ranges of mood and neurocognitive states in BD (35) increase variation within and between study samples, contributing to challenges in interpreting neurochemical and functional imaging studies of BD. Therefore, further studies of BD may require a larger number of patients to better examine state- vs. trait-related brain correlates in addition to the development of novel and sophisticated models of BD subphenotypes (36). Lastly, in addition to known sources of heterogeneity between ^1H -MRS studies of depression (37), such as subject selection, field strength, MRS sequences, and anatomical placement of the voxel of interest (18), studies of BD patients are further confounded by concurrent use of medications (e.g. valproate and

lithium), which has been shown to alter Glu and GABA levels in the brain (20, 38). Unsurprisingly, ¹H-MRS studies in MDD have consistently shown reduced levels of Glu, Gln, Glx, and GABA (39), whereas in BD studies, elevated levels of Glu have been observed inconsistently without differences in Gln, Glx, or GABA (20).

Detection and quantification of neurotransmitter receptors using PET imaging, in conjunction with administration of a radioactive ligand that is displaced by the endogenous neurotransmitter of interest at its receptor, provides complementary information to MRS studies regarding neurotransmitter signaling mechanisms. For example, reduced mGluR5 (see Figure 1) density in MDD patients was observed in two clinical PET studies that used an mGluR5-specific radioligand (40, 41). Taken together with animal studies showing antidepressant-like effects associated with the mGluR5-specific antagonists MPEP and MTEP (42–44), these findings suggest that abnormal mGluR5 signaling may be involved in the pathophysiology of depression. One of the studies was of patients aged 55 to 80 (40) and may be confounded by comorbid medical conditions, their treatment, and age-related brain changes. Nevertheless, a clear need exists to develop specific Glu receptor ligands for mGluRs and ionotropic Glu receptor subunits (45) to better understand abnormal glutamatergic neurotransmission and plasticity in depression.

Studies of inhibitory neurotransmitter systems in depression have also obtained mixed results. In ¹H-MRS studies of MDD patients, lower GABA levels were reported in the PFC (23), ACC (37), and OCC (46) compared to healthy subjects, and these changes may be more pronounced in association with melancholia (25). One negative study found no group differences in GABA concentrations in remitted MDD patients (47), but the authors suggested that GABA concentrations (and activity) may be sensitive to the presence of a depressive episode. Moreover, a ¹H-MRS study of MDD patients found no group differences in Glx concentrations within the ventromedial PFC (vmPFC) compared to healthy subjects, but observed an increased ratio of Glx to GABA associated with lower age of depression onset, suggesting that an increased excitatory/inhibitory neurotransmitter ratio may be associated with depression vulnerability (47). In studies of euthymic BD patients, decreased (48) and increased (49) GABA levels have been observed compared to healthy subjects, as have no differences in GABA levels (50).

Based on the hypothesized excitatory/inhibitory imbalance in depression (51), ¹H-MRS studies of Glu and Glu/GABA ratios suggest that a deficiency of excitatory neurotransmission or an imbalance of excitatory/inhibitory neurotransmission characterizes a subset of depressed patients. Despite the clinical efficacy of GABAergic medications (e.g. valproic acid, lamotrigine, and carbamazepine) in BD (52, 53), inconsistent reports of GABA levels associated with BD does not support an isolated deficiency in GABA in depression. Abnormalities in glutamatergic neuronal metabolism may be experienced in a proximal stage of the underlying pathophysiology of MDD and BD. For example, in a study of schizophrenia patients randomized to receive pomaglumetad (a metabotropic glutamate 2/3 receptor agonist) versus placebo for 6 weeks, greater improvement in symptoms were experienced earlier in the course of illness or with history of a medication targeted at the D2 receptor (54). Future prospective investigations in larger clinical samples may allow identification of subgroups of depressed patients who better respond to GABA- or Glu-

modulating therapies along the illness course. Moreover, innovations to current MRS techniques (27), such as application of novel pulse sequences at higher magnetic field strengths (e.g., 7 Tesla (T)) that can better resolve cerebral Glu, Gln, and GABA concentrations (55) could facilitate identification of biologically homogeneous and enriched subgroups (39) to which directed clinical interventions can be addressed (56).

Functional Circuitry Abnormalities in Depression

Neural circuitry describes the complex array of interconnected neurons in the brain from which simultaneous and coordinated information processing is refined and reorganized via experience-related synaptic changes (57). Neuroimaging methods that indirectly (e.g., fMRI blood-oxygen level dependent (BOLD) signal) or directly (e.g., EEG and MEG) examine neural activity aim to identify circuitry-level abnormalities and/or response to behavioral or neurochemical interventions (17). Considerations are necessary to address before links can be drawn between amino acid neurochemistry and functional imaging. First, MEG possesses greater spatial resolution than EEG (58, 59); thus, we focus primarily on MEG studies. Second, although functional neuroimaging can be used in conjunction with cognitive and/or emotionally-salient tasks, we focus on studies performed at resting-state (task-free) from which functional connectivity patterns are derived as EEG and MEG frequency findings will be reviewed in further detail. Third, functional connectivity patterns within larger interconnected neural circuits have emerged from novel statistical techniques (60, 61). Lastly, we examine studies of abnormal functional connectivity networks as they may relate to neurochemical studies of Glu and GABA in depression.

Abnormalities in resting state functional connectivity patterns in patients with MDD have been found within and between large brain networks. The default mode network (DMN), which includes the medial prefrontal cortex (mPFC) and posterior cingulate cortex, has been shown to deactivate during cognitive tasks, and is associated with introspection or self-referential thought when not actively recruited in task performance (62). The DMN and other networks involved in cognitive control of attention and emotion have been shown differ in MDD patients compared to healthy controls (63). In MDD, reduced connectivity has been shown in fronto-parietal brain networks and hyperconnectivity (increased positive or reduced negative connectivity) within the DMN and between the subgenual ACC (sgACC) and mPFC (63); regions that have been linked to abnormalities in GABA in animal models (64, 65), as well as GABA reductions (66) and Glx/GABA imbalances (47) in MDD patients.

In a systematic review of eight resting-state fMRI studies of BD patients in all mood states, abnormalities in functional connectivity were found in the mPFC and ACC with limbic-striatal regions (67). Compared to MDD patients, BD patients show significantly stronger functional connectivity within the dorsolateral PFC and ventrolateral PFC, as well as inferior frontal/dorsolateral PFC to ACC (68), suggesting that changes in functional connectivity between the ACC and PFC, as well as differences in Glu neurotransmission within the ACC, may differentiate the two disorders. This is supported by studies that compared BD and MDD patients and found differences in PFC activation during emotionally-laden tasks (69).

Similarities between functional connectivity patterns derived from resting state fMRI studies and MEG studies across multiple frequency bands were demonstrated in healthy subjects using a model-free independent component analysis (ICA) (70–72). Using a similar model on beta band filtered MEG data (73), our group identified decreased connectivity between the sgACC and a network within the precentral motor cortex and precuneus, and increased connectivity in limbic areas (i.e. amygdala and temporal cortex) in MDD patients compared to healthy subjects. These results support the role of the sgACC and other cortical and subcortical regions (17, 63, 74) in impaired cognitive control, psychomotor retardation, and other symptom clusters in depression (75). In a study using both ¹H-MRS and fMRI in MDD patients, Glu levels in the mPFC associated with connectivity to subcortical regions (76), and Glx reductions in the sgACC predicted decreased functional connectivity between the sgACC and the anterior insula (77). Decreased Glu levels corresponded with decreased BOLD response to an emotional stimulus in MDD patients with prominent anhedonia (78), suggesting that reduced glutamatergic neurotransmission and/or signaling may contribute to alterations in functional connectivity (79) at specific electrophysiological oscillation frequencies relating to cognitive and limbic-related symptomatology in depression.

Ketamine in Depression

Ketamine's antidepressant effects were demonstrated over a decade ago in a double-blind, placebo-controlled clinical study of eight depressed patients randomized to receive either a subanesthetic dose (0.5 mg/kg IV over 40 minutes) of ketamine or saline. Four of the eight patients (n=7 completers) had an antidepressant response to ketamine (defined as a reduction of 50% or greater on the Hamilton Depression Rating Scale (HAM-D)) (10). Subsequently, our group and others replicated IV ketamine's antidepressant effects in both MDD and BD patients across single and repeated administrations under various study designs (8, 9). The time course of the antidepressant response is characterized by an initial reduction in depressive symptoms within 2 hours, a maximal reduction in depressive symptoms within 24 hours, and a sustained response for up to 1 week after administration (9, 11).

Ketamine's effect on glutamatergic and GABAergic neurons has emerged from pre-clinical studies (80–83) (see Figure 1). Ketamine antagonizes NMDA receptors on GABAergic interneurons and on post-synaptic neurons; the former disinhibits cortical glutamatergic neurons (83) and the latter increases synthesis of intracellular growth factors, such as brain-derived neurotrophic factor (BDNF) (81, 82). Additionally, via the kainate receptor, ketamine increases activity of mammalian target of rapamycin (mTOR) and other molecules responsible for neuroplasticity and synaptogenesis (81, 82). A recent study examining both signaling pathways found that ketamine increased BDNF by generating nitric oxide, leading to the stabilization of Nitric Rheb, a small G-protein that enhances mTOR signaling (80). These findings have shifted our conceptualization of the pathophysiology and treatment of depression (17, 84), and encouraging the development of Glu-based treatments for depressive disorders (12, 56, 85, 86).

Antidepressant Response to Ketamine and Glutamate/GABA Neurotransmission

To date, five ¹H-MRS studies have examined Glu, Gln, Glx, and/or GABA levels, and one PET study used an mGluR5 ligand before and after IV ketamine infusion; all were conducted in healthy subjects (87–90) (see Table 1). In a double-blind, placebo-controlled, crossover study of 10 males (n=8 completers), elevated Gln levels were observed in the ACC two hours post-infusion, correlating with psychotomimetic symptoms (87). In an open-label study of 13 males, significantly elevated Glu levels were observed in the ACC 35 minutes post-infusion that did not correlate with psychotomimetic symptoms (89). A third double-blind, placebo-controlled, parallel group design study of 17 males (ketamine: n=8; placebo: n=9) found that ketamine administration was not associated with changes in Glx, Glu, or GABA levels in the mPFC/ACC 40 minutes post-infusion (88). Inconsistent results in small samples make it challenging to draw definitive conclusions about ketamine-induced amino acid neurotransmitter changes in healthy volunteers. In addition, one study (87) did not measure Glu directly, and scan quality was too poor in another study (89) to measure Gln levels. Nevertheless, consistent with the “glutamate surge” hypothesis, Glu levels increased during ketamine infusion, leading to psychotomimetic effects, with a subsequent decrease of Glu to baseline levels after infusion ceased. In support of this hypothesis, Delorenzo and colleagues (40) examined pre- and post-infusion PET scans with an mGluR5 ligand to measure the degree of ketamine binding to the mGluR5 receptor in 10 healthy control subjects who received IV ketamine. Reduced mGluR5 ligand (or increased ketamine) binding was found in the ACC, mPFC, orbital PFC, ventral striatum, parietal lobe, dorsal putamen, dorsal caudate, amygdala, and hippocampus (90). The ligand used in this study (ABP-688) is an allosteric modulator, and therefore may not be a valid method of measuring Glu release. Although basimglurant (RO4917523, RG7090), a negative allosteric modulator at the mGlu5R, has shown promise as an adjuvant medication to traditional antidepressant medications (91) in one study, a significant reduction in MADRS was found in the self-reported rather than clinician-administered MADRS and therefore, replication is necessary to support its antidepressant efficacy.

Three ¹H-MRS studies examined ketamine-related changes in Glu, Glx, and/or GABA in MDD patients (92–94) (see Table 1); two uncovered no neurochemical signature associated with antidepressant response to ketamine (93, 94). The third study observed improved depressive symptoms in 14 unmedicated, treatment-resistant MDD patients in association with increased pretreatment Glx/Glu ratio in the dorsomedial PFC/dorsal anterolateral PFC. Pretreatment measures of GABA or Glu did not correlate with reduction in depressive symptoms in either of these two regions of interest ($p>0.1$) (92). In another study of 11 unmedicated MDD patients, no association was observed between antidepressant response to ketamine and Glx or GABA levels in the mPFC before, during, or after ketamine infusion (93). Interestingly, in this study, ketamine was associated with increased Glx/water and GABA/water ratios, indicating target engagement and suggesting that ketamine transiently increases excitatory and inhibitory neurotransmission. Finally, in a single-blind study of 10 patients with MDD, ketamine was associated with reduced depressive symptoms at one hour to seven days post-infusion; however, antidepressant efficacy was not associated with

baseline levels or change in any amino acid neurotransmitter within the OCC (94). Therefore, it is unclear whether amino acid neurometabolite levels or their ratios can help predict antidepressant response to ketamine due to inconsistent results in small samples across different imaging platforms.

Ketamine and Functional Neural Circuitry in Depression

Increased pre-treatment neural activity in the rostral ACC (rACC) associates with antidepressant response across different pharmacologic, electrophysiological, and behavioral interventions (74), suggesting a common neurobiological signature may be associated with antidepressant response to treatment. In healthy subjects, functional connectivity between the rACC and mPFC increased acutely (95) and decreased 24 hours after ketamine infusion (96). Furthermore, using PET imaging methods, ketamine associated with increased glucose metabolism in the dorsal ACC (dACC) (97), altered glucose metabolism in PFC regions (97–99) in MDD, and increased glucose metabolism in the dACC and putamen in BD patients (100). Our group has shown that sgACC hypermetabolism predicted response to ketamine in BD patients (101). Taken together, the evidence suggests that specific activation patterns in the sgACC and dACC lead to disrupted functional engagement of PFC regions that is partly modifiable in patients with depression through glutamatergic interventions. This adds to the substantial and mounting evidence that the ACC is not only a key hub connecting limbic dysfunction with clinical symptomatology in MDD, but also that its functional response may correlate with ketamine's antidepressant efficacy.

Excitatory/inhibitory neurotransmitter imbalances may be inferred through specific electrophysiological measures. For example, interactions between superficial excitatory pyramidal cells and inhibitory GABAergic interneurons are attributed to oscillations in the gamma-frequency band as measured by MEG (83, 102, 103). Increases in gamma-band power (104, 105), reduced coupling of spike-rate and local field potential power within the gamma band (105), and disruptions in neuronal plasticity within prefrontal-hippocampal circuits (106) have been associated with NMDA receptor blockade with ketamine in the rodent neocortex. Similarly, in humans, subanesthetic dose ketamine infusion associates with increased gamma-band amplitudes in motor and visual cortices (102), and decreased peak gamma frequency in the visual cortex (107). Given the correlation between gamma band oscillations and BOLD connectivity in both rodents (108) and humans (109), ketamine may be associated with abnormalities in functional connectivity and disruptions in neuronal plasticity, particularly in circuits interconnecting the hippocampus and PFC (108, 110). Glu levels in the posterior cingulate cortex strongly correlate with connectivity in the DMN (111), suggesting that Glu alterations via ketamine administration may give rise to alterations in brain function at rest (ie. non-task) as well as during a task. Finally, a MEG study in healthy volunteers (n=25 males) found that subanesthetic dose ketamine increased anterior theta and gamma power but decreased posterior theta, delta, and alpha power; these changes were sustained for up to 50 minutes post-ketamine infusion (that is, after the resolution of perceptual distortions) (112). The authors reported frontoparietal connectivity changes, with ketamine reducing NMDA- and AMPA-mediated frontoparietal connectivity. If replicated, the antidepressant effects of ketamine may depend upon acute and prolonged changes in MEG spectral power as well as in electrophysiological synchrony in

frontoparietal circuitry. The extent to which gamma-band changes measured by MEG reflect altered glutamatergic neurotransmission and/or signaling in association with ketamine administration is unclear. Furthermore, given that current studies are limited to healthy subjects (see Table 1), it is not known whether ketamine-related electrophysiological changes are similar in depressed patients.

Ketamine as a Functional Neurocircuitry Modulator: Future Directions

In depressed patients, evidence from neurochemical studies of MDD and BD suggests that alterations in Glu-related excitatory neurotransmission exist in a subset of patients. Although evidence of isolated abnormalities in GABA-related inhibitory neurotransmission in depression has been less clear, a reduction in efficient energy metabolism in glutamatergic neurons may lead to an imbalance of Glu over GABA neurotransmission that manifests as network connectivity perturbations in BD and MDD. Moreover, given the small number of existing clinical studies with low-powered samples of MDD patients, it is unclear how ketamine's antidepressant efficacy is associated with specific Glu and/or GABA levels. Further studies are needed at higher magnetic field strength with attention to specific regions of interest such as the sgACC, dACC, fronto-parietal cortices, mPFC, and limbic areas (see Figure 2). In addition, resting-state MEG studies—particularly those focused on beta and gamma band activity—may reveal connectivity changes that correlate with and/or predict ketamine's antidepressant response.

Evidence of large variations in Glu levels during and after ketamine infusion in healthy and depressed subjects warrants examination of changes in Glu/GABA neurochemistry in conjunction with functional neuroimaging before, during, and after ketamine infusion (87–89, 92–94). Pharmacodynamic fMRI (phfMRI) is a functional imaging technique that measures brain response during infusion of pharmacologic agents, thus providing early and longitudinal measures of drug action in the brain (113). phfMRI studies conducted in healthy volunteers have established test-retest reliability (114) and specificity (115) in association with ketamine infusions (see Table 1), further supporting that such an approach in future ketamine studies may help predict those who may experience an antidepressant response.

Lastly, identifying reliable diagnostic and treatment response biomarkers in MDD has been a challenge given the clinical heterogeneity of this disorder and the wide variability of treatment response (17, 84, 116). Neuroendocrine, neurochemical, and neurophysiological assays in the search for MDD biomarkers have been replicated in some, but not all, translational studies (117–120). Moreover, the general consensus within the field has been that neuroimaging techniques, in conjunction with other illness biomarkers, may be required to diagnose and treat psychiatric disorders (119–121). A combinatorial approach of diverse techniques and modalities (122), will be required to identify underlying neural system abnormalities that are unique to subgroups of MDD patients and/or correlate with antidepressant response.

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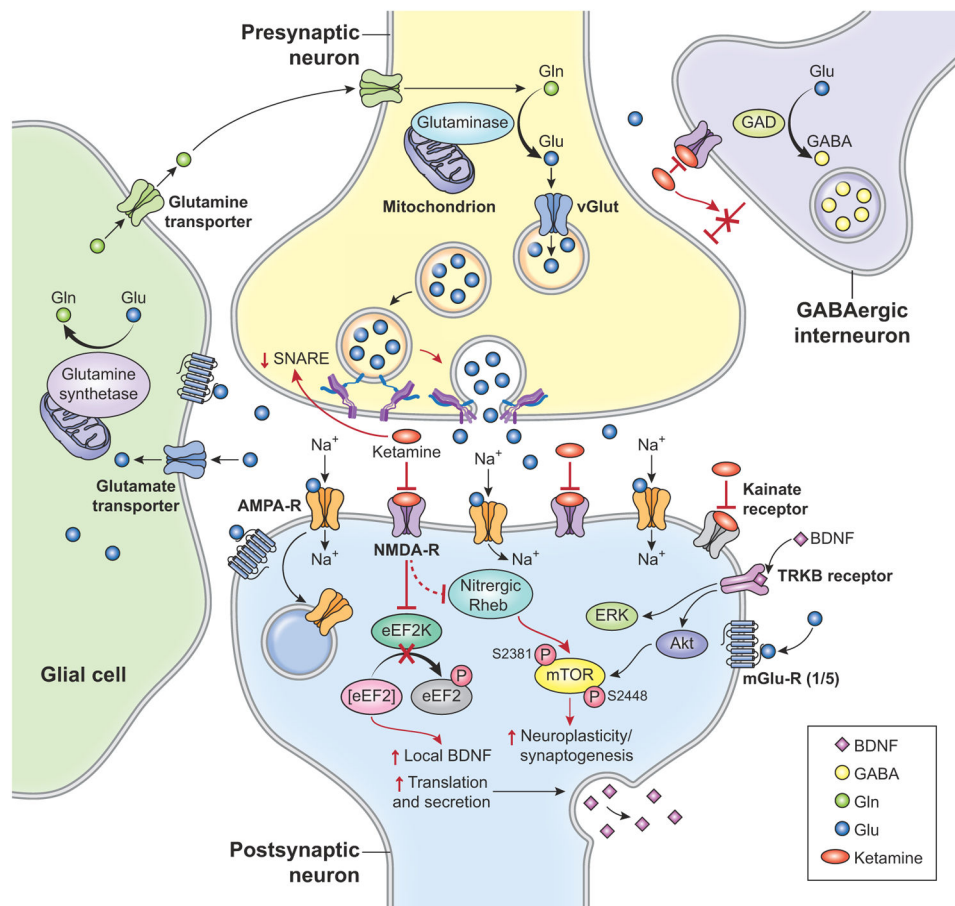


Figure 1. The Cellular and Molecular Effects of Ketamine on Glutamatergic and GABAergic Metabolism and Neurotransmission

(A) Normal glutamatergic and GABAergic metabolism and neurotransmission: Glutamate (Glu) is packaged into vesicles via vesicular glutamate transporters (vGluTs) for exocytotic release. After neuronal depolarization and release into the synaptic cleft, Glu binds to NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, or metabotropic receptors (mGluRs). Glu is removed from the synapse by Glu transporters in astrocytes and metabolically converted into glutamine (Gln) via glutamine synthetase. Gln is released by astrocytes into presynaptic neurons where it is converted back to Glu via cytosolic glutaminase. Inhibitory GABAergic neurons contain the enzyme glutamic acid decarboxylase (GAD), which converts Glu to GABA.

(B) Ketamine-induced changes, depicted in red: Ketamine antagonizes N-methyl-D-aspartate (NMDA) receptors on GABAergic interneurons and on post-synaptic neurons; the former disinhibits cortical glutamatergic neurons and the latter increases synthesis of brain-derived neurotrophic factor (BDNF). Via the kainate receptor, ketamine increases activity of mammalian target of rapamycin (mTOR) leading to neuroplasticity and synaptogenesis. Ketamine also increases BDNF via nitric oxide production, leading to stabilization of Nitric Rheb and enhancement of mTOR signaling.

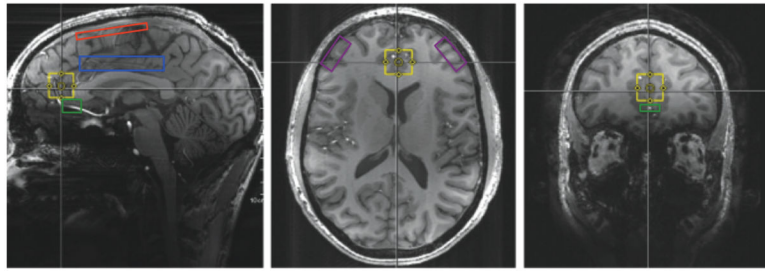


Figure 2. Proposed Regions of Interest to Identify Alterations in Glu/GABA and Abnormalities in Functional Connectivity

Sagittal, axial, and coronal viewpoints showing the medial prefrontal cortex (mPFC) in yellow. Sagittal viewpoint showing the fronto-parietal cortical region in red and the dorsal anterior cingulate cortex (dACC) in blue. Sagittal and coronal viewpoints showing the subgenual anterior cingulate cortex (sgACC) in green. Axial viewpoint showing the dorsolateral prefrontal cortex (DLPFC) in purple. Hippocampus and amygdala not shown in figure.

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Table 1

Neural Correlates of Antidepressant Response to Ketamine

Citation	Sample Size and Diagnostic Groups	Neuroimaging Method	Trial Design and Ketamine Dose	Significance and Findings
Rowland et al., 2005 (87)	Healthy subjects N = 10 (10M)	¹ H-MRS, 4T MRI, 8cc voxel placed in the ACC bilaterally; quantification of Gln, NAA, choline, creatine, Glu; images acquired before, during, and at end of loading dose prior to maintenance dose	Double-blind, placebo-controlled, single infusion; IV ketamine 0.27 mg/kg loading dose over 10 min, 0.00225 mg/kg per min thereafter for up to 2 hrs until end	Increased Glu in the ACC associated with ketamine infusion
Taylor et al., 2012 (88)	Healthy subjects N = 17 (11M, 6F)	¹ H-MRS, 3T MRI, 30×20×20mm voxel placed in the ACC and mPFC; quantification of Glx, Glu, Gln; images acquired before, during, and after infusion	Double-blind, placebo-controlled, single infusion; IV ketamine 0.5 mg/kg over 40 min	No increase in Glu or Gln in the ACC or mPFC associated with ketamine infusion
Stone et al., 2012 (89)	Healthy subjects N = 13 (13M)	¹ H-MRS, 3T MRI, 30×30×30 mm voxel placed over the thalami bilaterally and surrounding subcortical structures, 20×20×20 mm voxel placed over the ACC; quantification of Glu, Gln, GABA; images acquired before and after infusion at 25 min and 35 min	Open-label, single infusion; IV ketamine 0.5 mg/kg over 40 min	Increased Glu in the ACC but no effect on ACC Glu + Gln, or subcortical GABA levels associated with ketamine infusion
Valentine et al., 2011 (94)	MDD subjects N = 10 (4M, 6F)	¹ H-MRS, 3T MRI, 3.0×1.5×3.0 cm voxel placed in the OCC; quantification of Glu, Gln, GABA; images acquired before, 3 hrs after, and 48 hrs after infusion	Single-blind, placebo-controlled, two infusions 1 week apart; IV ketamine 0.5 mg/kg over 40 min	Improvement in depressive symptoms at 1 hr and for at least 7 days after ketamine infusion was not associated with baseline measures of, or changes in, occipital Glu, Gln, or GABA
Salvadore et al., 2012 (92)	MDD subjects N = 14 (9M, 5F)	¹ H-MRS, 3T MRI, 5×3×2 cm voxel placed in the DM/DA-PFC, 3×3×2 cm voxel placed in the vmPFC; quantification of Glu, Gln, Glx, GABA; images acquired 1–3 days before infusion	Open-label, single infusion; IV ketamine 0.5 mg/kg over 40 min	Pretreatment GABA or Glu was not associated with a decrease in depressive symptoms in either of the two ROIs; pretreatment Glx/glutamate ratio in the DM/DA-PFC was negatively correlated with improvement in depressive symptoms
Milak et al., 2015 (93)	MDD subjects N = 11 (3M, 8F)	¹ H-MRS, 3T MRI, 3.0×2.5×2.5 cm voxel placed in the mPFC and pgACC; quantification of Glu, Gln, Glx, GABA; images acquired before, during, and after infusion	Double-blind, placebo-controlled, two infusions 1 week apart; IV ketamine 0.5 mg/kg over 40 min	Increased Glx and GABA in the mPFC associated with ketamine infusion
Scheidegger et al., 2012 (96)	Healthy subjects N = 19 (9M, 10F)	fMRI, 3T MRI, SPM8, seed ROIs in the CCN, the DMN, and affective networks, bilateral DLPFC, dACC, sgACC, and amygdala; images acquired before and 24 hr after infusion	Double-blind, placebo-controlled, crossover of two infusions 2 weeks apart; IV ketamine 0.5 mg/kg over 40 min	Decreased functional connectivity of the DMN to a network of dorsal brain regions and to the sgACC and mPFC via the dACC associated with ketamine infusion
Grimm et al., 2015 (95)	Healthy subjects N = 24 (12M, 12F)	fMRI, 3T MRI, SPM8, seed ROIs in the DLPFC and hippocampus bilaterally; images acquired before and 20 min after infusion	Single-blind, placebo-controlled, crossover of 3 single infusions; IV ketamine 0.5 mg/kg over 40 min	Increased functional connectivity between the DLPFC bilaterally and the left hippocampus associated with ketamine infusion

Citation	Sample Size and Diagnostic Groups	Neuroimaging Method	Trial Design and Ketamine Dose	Significance and Findings
Carlson et al., 2013 (98)	MDD (TRD) subjects N = 26 (20M, 6F)	PET, ¹⁸ F]-FDG, 3T MRI, SPM5, whole-brain and ROI analyses at amygdala, anterior hippocampus, medial thalamus, habenula, and sgACC; images acquired before and after	Open-label, single infusion; IV ketamine 0.5 mg/kg over 40 min	Reduction in depressive symptoms associated with increased metabolism in STG/MTG, and cerebellum as well as decreased metabolism in ventral and medial loci within the STG/MTG, parahippocampal gyrus, inferior parietal cortex, and temporo-occipital cortex
Lally et al., 2015 (97)	MDD (TRD) subjects N = 20 (14M, 6F)	PET, ¹⁸ F]-FDG, 3T MRI, SPM5, whole-brain and ROI analyses at ventral striatum and OFC; images acquired before and at 240 min after infusion	Open-label, single infusion; IV ketamine 0.5 mg/kg over 40 min	Reduction in anhedonia was associated with increased metabolism in the hippocampus and dACC as well as decreased metabolism in the inferior frontal gyrus and OFC
Li et al., 2016 (99)	MDD (TRD) subjects N = 48 (no gender breakdown given)	PET, ¹⁸ F]-FDG, 3T MRI, SPM5, whole-brain and ROI analyses at PFC and amygdala; images acquired before and at 40 min after infusion	Double-blind, placebo-controlled, single infusion; Group A: IV ketamine 0.5 mg/kg over 40 min, Group B: IV ketamine 0.2 mg/kg over 40 min, Group C: IV normal saline	Reduction of depressive symptoms was associated with increased metabolism in the PFC in Groups A and B, but not C; whole-brain analysis confirmed a group effect on the PFC (Group A<C, Group B<C); metabolic differences in the PFC predicted response at 40 and 240 min
Lally et al., 2014 (100)	BD-I and BD-II subjects N = 21 (6M, 15F) (all on lithium or valproic acid)	PET, ¹⁸ F]-FDG, 3T MRI, SPM5, whole-brain and ROI analyses at ventral striatum and OFC; images acquired before and at 120 min after infusion	Double-blind, placebo-controlled, crossover of two infusions 2 weeks apart; IV ketamine 0.5 mg/kg over 40 min	Reduction of depressive symptoms but not anhedonic symptoms was associated with increased metabolism in the ventral striatum; reduction in anhedonia was associated with increased metabolism in the dACC
Nugent et al., 2014 (101)	BD-I and BD-II subjects N = 21 (6M, 15F) (all on lithium or valproic acid)	PET, ¹⁸ F]-FDG, 3T MRI, SPM5, whole-brain and ROI analyses at left and right amygdala, hippocampus, vIPFC, anteromedial PFC, DLPFC, ventral striatum, pgACC, sgACC, medial thalamus, dACC, lateral orbital cortex, superior temporal gyrus, frontal polar cortex, habenula, and anterior insula; images acquired before and at 120 min after infusion	Double-blind, placebo-controlled, crossover of two infusions 2 weeks apart; IV ketamine 0.5 mg/kg over 40 min	Reduction in depressive symptoms was associated with increased metabolism in the right ventral striatum as well as reduced metabolism in left hippocampus in whole brain analysis
Shaw et al., 2015 (107)	Healthy subjects N = 18 (18M)	MEG acquired during visuomotor task before and after infusion, 3T MRI	Single-blind, placebo-controlled, crossover of two infusions; initial IV ketamine bolus of 0.25 mg/kg delivered over 1 min, followed by maintenance infusion at a rate of 0.25 mg/kg	Increased beta amplitudes and decreased peak gamma frequency in the visual cortex as well as amplified gamma-band amplitudes in motor and visual cortices were associated with ketamine infusion
Muthukumaraswamy et al., 2015 (112)	Healthy subjects N = 25 (25M)	MEG acquired at rest and during visuomotor task before and during infusion, 3T MRI	Single-blind, placebo-controlled, crossover of two infusions; initial IV ketamine bolus of 0.25 mg/kg delivered over ~1 min, followed by maintenance infusion at a rate of 0.375 mg/kg/h	Decreases in OCC, parietal, and ACC alpha power, increases in medial frontal theta power, and increases in parietal and cingulate cortex high gamma power in association with ketamine infusion; dynamic causal modeling showed that oscillatory changes were accompanied by temporally sustained reductions in frontoparietal effective connectivity

Citation	Sample Size and Diagnostic Groups	Neuroimaging Method	Trial Design and Ketamine Dose	Significance and Findings
De Simoni et al., 2013 (114)	Healthy subjects N = 10 (10M)	phfMRI, 3T MRI, BOLD signal, initiated 5 min prior to infusion, SPM5	Open-label, two infusions, IV ketamine (target plasma levels 50 ng/mL and 75 ng/mL)	Widespread changes present in ACC, mid-posterior cingulate and paracingulate cortices, hippocampal and parahippocampal regions, bilateral insula, DLPFC, vlPFC, thalamus, supplementary motor area, bilateral operculum, precuneus and medial occipital lobes in association with ketamine infusion.
Doyle et al., 2013 (115)	Healthy subjects N = 16 (16M)	phfMRI, 3T MRI, BOLD signal, initiated at 15 min prior to infusion, SPM5	Double-blind, placebo-controlled, partial crossover design of four infusions, two with pre-treatment risperidone or lamotrigine or placebo; IV ketamine (target plasma levels of 75 ng/mL) initially at 0.003 mg/kg for 1 min, then at ~0.31 mg/kg/h	Lamotrigine and risperidone resulted in widespread attenuation of the ketamine-induced increases in signal, including the frontal and thalamic regions; a contrasting effect across both pretreatments was observed only in the sgPFC, in which ketamine reduced the signal

ACC = anterior cingulate cortex; BD = bipolar disorder; BOLD = blood oxygen level dependent; CCN = cognitive control network; dACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral PFC; DM/DA-PFC = dorsomedial/dorsal anterolateral prefrontal cortex; DMN = default mode network; ^{18}F -FDG = ^{18}F fluoro-deoxyglucose; fMRI = functional magnetic resonance; GABA = gamma-aminobutyric acid; Gln = glutamine; Glu = glutamate; Glx = combination of Glu and Gln; ^1H -MRS = proton magnetic resonance; IV = intravenous; MDD = major depressive disorder; MEG = magnetoencephalography; mPFC = medial prefrontal cortex; MRI = magnetic resonance imaging; NAA = N-acetylaspartate; OCC = occipital cortex; OFC = orbitofrontal cortex; PET = positron emission tomography; PFC = prefrontal cortex; pgACC = perigenual ACC; phfMRI = pharmacologic fMRI; ROI = region of interest; sgACC = subgenual anterior cingulate cortex; sgPFC = subgenual PFC; SPM = statistical parametric mapping; STG/MTG = superior and middle temporal gyri; T = tesla; TRD = treatment resistant depression; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex.