



Ketamine-Associated Brain Changes: A Review of the Neuroimaging Literature

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Abstract: Major depressive disorder (MDD) is one of the most prevalent conditions in psychiatry. Patients who do not respond to traditional monoaminergic antidepressant treatments have an especially difficult-to-treat type of MDD termed *treatment-resistant depression*. Subanesthetic doses of ketamine—a glutamatergic modulator—have shown great promise for rapidly treating patients with the most severe forms of depression. As such, ketamine represents a promising probe for understanding the pathophysiology of depression and treatment response. Through neuroimaging, ketamine’s mechanism may be elucidated in humans. Here, we review 47 articles of ketamine’s effects as revealed by neuroimaging studies. Some important brain areas emerge, especially the subgenual anterior cingulate cortex. Furthermore, ketamine may decrease the ability to self-monitor, may increase emotional blunting, and may increase activity in reward processing. Further studies are needed, however, to elucidate ketamine’s mechanism of antidepressant action.

Keywords: biomarkers, ketamine, neuroimaging, magnetic resonance imaging, magnetoencephalogram, positron emission tomography, treatment-resistant depression

Major depressive disorder (MDD) is devastating, serious, and prevalent. Treatment-resistant depression (TRD)—often defined as failure to respond to at least two standard antidepressant treatment trials of adequate dose and duration—encompasses up to 30% of patients with MDD.¹ Not only is TRD highly debilitating for patients and their families, the economic strain from TRD accounts for nearly \$200 billion a year from lost productivity. The more treatment failures that patients experience, the less likely they are to respond to subsequent treatment trials—perpetuating the cycle of disability. For these reasons, it is critical to find fast and effective treatments for patients with TRD.

One compound that holds promise for TRD is ketamine. While commonly considered a dissociative anesthetic, subanesthetic doses of ketamine stand out among other pharmacological interventions for MDD. While most commonly used psychiatric medications (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors) require multiple weeks to take full effect, subanesthetic doses of ketamine have rapid (within hours), robust (across a variety of symptoms), and relatively sustained (typically up to one week) antidepressant effects—even in patients with TRD.^{2–5} Clinical studies show that about 50% of patients with TRD have a significant decrease in symptoms within 24 hours of a single intravenous subanesthetic ketamine dose.⁵

Animal models show that ketamine’s antidepressant effects are likely mediated by its antagonism of N-methyl-D-aspartate (NMDA) receptors through increased α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated glutamatergic signaling. This triggers activation of intracellular synaptogenic pathways, most notably in the mechanistic target of rapamycin (mTOR)-signaling pathway, which also has implications in many other psychiatric disorders.^{1,6} In fact, ketamine was first used to probe the glutamatergic system as it relates to the pathophysiology of schizophrenia. The original neuroimaging studies on ketamine’s mechanism were thus used as working models for schizophrenia because excess glutamate has been linked to the development of schizophrenia and psychosis.⁷

With regard to MDD patients, decreased glutamate has been noted in various prefrontal regions, including the dorso-lateral prefrontal cortex (dlPFC), dorsomedial PFC (dmPFC),

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and anterior cingulate cortex (ACC), when compared to controls.^{8–10} This shortage of glutamate makes ketamine an ideal treatment for MDD; by creating a surge in glutamate levels in regions of the brain that suffer from a glutamate deficit, ketamine may provide some normalization of glutamate levels in patients with MDD. This “glutamate surge” hypothesis has dominated as the primary theory of ketamine’s antidepressant mechanism.

The glutamate surge hypothesis, however, has met with some controversy. In a review of neuroimaging studies specifically examining how ketamine modulates glutamate and gamma-aminobutyric acid (GABA), it was unclear whether glutamate levels, which surged during infusion, remained elevated postinfusion.¹¹ One study found increased glutamate levels in the ACC 35 minutes postinfusion, but another found no change.^{12,13} Multiple studies attempted to find a correlation between antidepressant response and glutamate/GABA levels before, during, and after infusion,^{14–16} but no correlations were found.

It is possible, then, that ketamine is acting indirectly to produce its antidepressant effect. Ketamine may work through additional receptors, as it is known to have effects on several opioid receptors, adrenergic receptors, and several serotonin and norepinephrine transporters.^{17–19} It is also possible that acute dissociative side effects of ketamine may be mediating antidepressant response. In turn, it is equally possible that small sample sizes among studies utilizing ketamine prevent results from converging. Methodological differences and limitations may also play a role. Due to inconsistent results and ketamine’s heterogeneity of action, it is hard to elucidate the mechanism by which ketamine produces its rapid, robust, and sustained antidepressant effects. Therefore, further research on ketamine’s antidepressant mechanism is needed, and theories on biological and clinical responses need to be explored.

One salient biological metric that may provide insight into ketamine’s mechanism of action is related to dissociation. Dissociative side effects begin from infusion, reach a peak typically within an hour of infusion, and are completely diminished 230 minutes after infusion.²⁰ The same study has shown that increased dissociation and psychotomimetic symptoms immediately following infusion may predict antidepressant response.²⁰ Further neuroimaging research has the potential not just to inform scientists of ketamine’s antidepressant mechanism but to inform clinicians as to who might best respond to ketamine as an antidepressant. Other biological metrics include baseline brain activity, psychotomimetic effects during infusion, and anxiety somatization levels.

The advent of advanced imaging techniques allows noninvasive investigations of neuronal activity in patients with TRD and in healthy controls. These imaging results can then be correlated not just with glutamate and GABA levels but with clinical and biological metrics that could provide insight into how ketamine produces its antidepressant effect.

—*Positron emission tomography (PET) and magnetic resonance spectroscopy (MRS)* provide the most direct noninvasive methods for measuring glutamatergic and GABA-ergic activity. They acquire full volumes of the brain at various time points during and after ketamine infusion.

—*Magnetoencephalogram (MEG)* recordings measure small magnetic and electric changes in the brain through sensors placed at the scalp. While MEG is a more indirect measure of GABA and glutamate, it assesses brain function of all regions on a time scale that better reflects real-time neural activity. *Functional magnetic resonance imaging (fMRI)* and resting-state fMRI provide less temporal resolution than MEG (full brain volumes are only acquired every ~3 seconds), but they provide more precise measurements of subcortical regions of the brain. This is important for studying regions such as the subgenual ACC and amygdala, which are commonly targeted in MDD.²¹ MEG and fMRI also allow investigators to study how brain function changes as subjects undergo in-scanner tasks, such as passive viewing of faces and decision making. Task-based fMRI and MEG can provide more ecologically valid information about what the brain does when faced with real-life situations. They can also tell us more about how the brain’s real-life performance is altered in patients with MDD.

—*Diffusion MRI and structural MRI* enable tracking of how ketamine may change the brain’s anatomy and how structural connections change over time. This is of interest because rapidly induced synaptogenesis has been shown in preclinical models in response to ketamine.⁶

Thus, here we review current human neuroimaging literature as it pertains to ketamine’s mechanism of action in specific brain areas, with an emphasis on key regions that are implicated in the pathophysiology of MDD. We focus this review on treatment studies of patients with MDD. However, because very little literature specifically examines ketamine’s actions in patients with MDD, we are including research with healthy volunteers. Research in healthy volunteers may enable us to understand how ketamine affects neural organization and activity without psychopathology. We end by summarizing the results as they pertain to the neurobiology of depression and ketamine’s antidepressant effects. By understanding the biological basis of disease pathology and treatment response, the field of psychiatry has the potential to practice more precise medicine—ultimately with improvements in both patient care and outcomes.

METHODS

A Medline search was conducted for articles through December 2016 using the following search terms: depression and ketamine and neuroimaging; depression and ketamine and imaging; depression and ketamine and MRI; ketamine and neuroimaging; ketamine and imaging. All articles reviewed were written and published in English, and pertained to adult

Table 1 Ketamine Neuroimaging Studies in Depression (MRI, MEG, Spectroscopy)				
Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Salvadore (2009) ²²	MEG: 1 recording 1–2 days pre-ketamine, during rapid presentation of affective stimuli (fearful face pictures) Double-blind, placebo-controlled ketamine study	n = 11 MDD (medication free) n = 11 healthy volunteers Racemic ketamine: 0.5 mg/kg over 40 minutes	Increased baseline (pre-ketamine cortical activity) to affective stimuli (fearful faces) in the ACC (especially the pregenual ACC) Decreased amygdala activation predicted antidepressant response to ketamine at 4 hours postinfusion	Small n Baseline MEG only Evidence for decreased right amygdala activity is very weak
Salvadore (2010) ²³	MEG: 2 recordings, during a working memory n-back task at 1–3 days pre-ketamine and again post-ketamine Double-blind, placebo-controlled ketamine study	n = 15 MDD (medication free) Racemic ketamine: 0.5 mg/kg over 40 minutes	Subjects with the least pre-ketamine engagement of the pregenual ACC with increasing memory load (2- vs. 1-back) showed the greatest antidepressant improvement to ketamine at 4 hours postinfusion Subjects with the lowest coherence between pregenual ACC and left amygdala were most likely to respond to ketamine High pregenual ACC activity in response to emotional activity and low pregenual ACC in response to increased cognitive demands predict an antidepressant response to ketamine; this is relatively normal, so preserving normality predicts better outcomes	Small n Not generalizable (only medication-free inpatients) Baseline MEG only
Cornwell (2012) ²⁴	MEG: 2 recordings occurred during a passive tactile stimulation to the index fingers on 3 days before and 6.5 hours after a single ketamine infusion Open-label ketamine; all patients then received a dose of riluzole or placebo at 5–6 hours post-ketamine	n = 20 MDD (medication free) Racemic ketamine: 0.5 mg/kg over 40 minutes	In ketamine responders (at 4 hours), compared to nonresponders, there was an increase in somatosensory cortical excitability responses (a measure of synaptic plasticity); there was also a positive correlation between increased cortical excitability and norketamine levels	Open-label ketamine Riluzole vs. placebo were administered just prior to MEG scanning
Carlson (2013) ²⁵	18 F-FDG PET: 2 scans, at baseline (1–3 days pre-ketamine) and 120 minutes post-ketamine Open-label ketamine	n = 20 with treatment-resistant depression (medication free) Racemic ketamine: 0.5 mg/kg over 40 minutes	Whole-brain glucose metabolism did not significantly change post-ketamine Decreased metabolism occurred in the right habenula, increased metabolism in the right amygdala, and no change in subgenual ACC metabolism; these results were not correlated with change in MADRS scores Clinical improvement correlated with increased metabolism in the STG, MTG, and cerebellum, and with decreased metabolism in the parahippocampal gyrus,	Small n Open-label No healthy volunteer comparators Post hoc clinical correlations

Table 1					
Continued					
Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations	
Lally (2014) ²⁶	18 F-FDG PET: 1 scan, 120 minutes postinfusion to measure rCMRGlu Randomized, double-blind, crossover, placebo-controlled study; 2 infusions given 2 weeks apart	n = 21 bipolar depressed patients maintained on either lithium or depakote for ≥4 weeks prior to study Racemic ketamine: 0.5 mg/kg over 40 minutes	inferior parietal cortex, and the more ventral and medial loci within the STG/MTG Decreased anhedonia was related to increased rCMRGlu in the dorsal ACC and putamen Largest improvement in depressive symptoms correlated with largest metabolic increase in right ventral striatum post-ketamine compared to placebo	Small n No baseline scans Post hoc analysis Heterogeneity of bipolar types I and II within sample	
Nugent (2014) ²⁷	18 F-FDG PET: 1 scan 120 minutes postinfusion to measure rCMRGlu Randomized, double-blind, crossover, placebo-controlled study; 2 infusions given 2 weeks apart	n = 21 bipolar depressed patients maintained on either lithium or valproic acid for ≥4 weeks prior to study Racemic ketamine: 0.5 mg/kg over 40 minutes	Bipolar patients had lower glucose metabolism in the left hippocampus post-ketamine compared to post-placebo Patients with the largest improvement in depression symptoms had the largest metabolic (rCMRGlu) increase in the right ventral striatum post-ketamine compared to placebo Metabolism of the subgenual ACC was positively correlated with improvements in depression scores post-ketamine	Small n No healthy volunteer comparator No baseline scans Heterogeneity of bipolar types I and II within sample	
Abdallah (2015) ²⁸	3 T MRI: 2 scans, at baseline and 24-hour post-ketamine vs. midazolam Randomized, double-blind, midazolam-controlled trial of ketamine	n = 24 with treatment-resistant depression (all medication free); n = 13 ketamine, n = 6 midazolam (5 were excluded because of motion artifacts) Racemic ketamine: 0.5 mg/kg over 40 minutes	Association between smaller left hippocampal volume at baseline and greater antidepressant response to ketamine at 24 hours postinfusion	No healthy volunteer comparator Small n No specific hippocampal regions targeted	
Ballard (2015) ²⁹	FDG PET: 2 scans, at baseline (1–3 days pre-ketamine) and 2 hours post-ketamine and lasting about 1.5 hours Open-label ketamine	n = 19 with treatment-resistant depression (medication free) Racemic ketamine: 0.5 mg/kg over 40 minutes	Suicidal ideation was correlated with increased metabolism in the infralimbic cortex at baseline Decreased suicidal ideation post-ketamine was correlated with decreased regional cerebral glucose metabolism in the infralimbic cortex	Post hoc Baseline PET scans occurred on a different day than baseline suicidality measures Suicidal ideation measured on a 0–4 scale on HDRS	
Lally (2015) ³⁰	18 F-FDG PET: 2 scans at baseline (1–3 days pre-ketamine) and post-ketamine (beginning 2 hours post-ketamine and	n = 20 with treatment-resistant depression (medication free)	Decreased anhedonia was associated with increased rCMRGlu in the	Post hoc Rituzole confounder	

Table 1				
Continued				
Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Murrough (2015) ³¹	lasting through 3.5 hours post-ketamine) to measure the rCMRGlU Open-label ketamine followed by 1 month of oral riluzole or placebo; anhedonia assessed with Snaith-Hamilton Pleasure Scale	Racemic ketamine: 0.5 mg/kg over 40 minutes n = 18 with treatment-resistant depression n = 20 matched healthy volunteers Racemic ketamine: 0.5 mg/kg over 40 minutes	hippocampus and dorsal ACC, and decreased rCMRGlU in the OFC Ketamine enhanced neural responses to positive emotion in the right caudate in depressed patients compared to baseline deficits Post-ketamine, greater connectivity to positive emotions was associated with improvements in depression severity	No placebo comparator No placebo comparator Only scanned at 24 hours post-ketamine (no other time points) Healthy volunteers completed only baseline
Abdallah (2016) ³²	fMRI: 2 scans, pre- (baseline) and post- (24 hours) ketamine scans with two 8-minute facial emotion-perception tasks Open-label ketamine given after baseline scan	n = 18 MDD (medication free) n = 25 healthy volunteers Racemic ketamine: 0.5 mg/kg over 40 minutes	Ketamine increased GBCr in the right lateral PFC and reduced GBCr in the left cerebellum Ketamine responders had increased GBCr in the lateral PFC, caudate, and insula MDD had decreased connectivity between PFC/subcortex and the rest of the brain, which normalized post-ketamine	High comorbidity of anxiety disorders in the sample Short medication-free period (1 week) Small n Healthy volunteers only completed baseline scan
Downey (2016) ³³	3 T pharmacological MRI: from 5 minutes pre- to 40 minutes postinfusion Randomized (ketamine vs. lanicemine vs. placebo), double-blind, parallel-group design at 2 different sites Clinical ratings completed at 24 hours and between days 8 and 11 post-ketamine	n = 60 MDD (n = 20 lanicemine, n = 21 ketamine, n = 19 placebo) Racemic ketamine: 0.5 mg/kg over 60 minutes	Both ketamine and lanicemine increased BOLD signal in the subgenual ACC; activation predicted depression improvements at 24 hours and 1 week post-ketamine No significant change in Beck Depression Inventory was observed post-ketamine vs. placebo	No comparator group of healthy volunteers Two sites (two different 3 T machines, different clinician raters) Significant place response Neither ketamine nor lanicemine group improved more than placebo
Milak (2016) ¹⁴	3 T ¹ H-MRS: six ¹ H-MRS data frames were acquired (approximately 13 minutes each): 1 pre-ketamine, 4 during ketamine infusion, and 1 post-ketamine	n = 11 MDD (medication free, 8 female); 8 subjects' data used for MRS Racemic ketamine: 0.5 mg/kg over 40 minutes n = 13 MDD	Rapid increases in the medial PFC in both Glx and GABA were observed during ketamine infusion, but dissipated by the end of the infusion	Small n
Nugent (2016) ³⁴	MEG: 2 recordings, pre- and post-ketamine		Decreased connectivity between amygdala and insulo-temporal region post-ketamine	Small n

Table 1				
Continued				
Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Vasavada (2016) ³⁵	Open-label ketamine Diffusion tensor imaging MRI: 1 scan ≤1 week pre-ketamine Clinical treatment with open-label ketamine	Racemic ketamine: 0.5 mg/kg over 40 minutes n = 10 MDD after ketamine (n = 4 nonresponders, n = 6 responders) n = 15 healthy volunteers, did not receive ketamine Racemic ketamine: 0.5 mg/kg over 40 minutes	Improvements in depressive symptoms at 24 hours post-ketamine correlated with greater fractional anisotropy in the cingulum (projecting to the PFC), decreased mean diffusivity and radial diffusivity in forceps minor, and decreased radial diffusivity in the frontostriatal track	Riluzole given before post-ketamine scan MEG used to study subcortical regions despite low spatial resolution Most patients (n = 9) were not medication free; they were maintained on stable (≥6 months) standard antidepressant treatments MRI was not done at a standardized time point Small n
ACC, anterior cingulate cortex; BOLD, blood oxygen level-dependent; GABA, gamma-aminobutyric acid; GIBCr, global brain connectivity signal regression; Glx, glutamate+glutamine; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTC, middle temporal gyrus; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; rCMRGlu, regional cerebral metabolic rate of glucose; STC, superior temporal gyrus.				

human research only. A total of 966 were initially found. After duplicate articles and nonhuman research articles were removed, 47 were found to be relevant to this review.

We segment the results into three sections: (1) Ketamine and Neuroimaging in Depression, (2) Ketamine in Nondepressed Subjects: Non-task-based Resting-State Scans, and (3) Ketamine in Nondepressed Subjects: Task-Based Scans. Though most studies examined only one modality of imaging, several^{7,9,10} employed more than one.

RESULTS

Ketamine and Neuroimaging in Depression

Thirteen studies were found to be relevant to ketamine’s effects in patients with unipolar depression, and two in patients with bipolar depression. See Table 1.

Among unipolar depression studies, several groups utilized fMRI. With regard to brain connectivity, one study found that in patients with TRD, ketamine increased neural responses to positive emotions in the right caudate; furthermore, greater connectivity in the right caudate post-ketamine was associated with improvements in depression severity.³¹ In another study, Abdallah and colleagues³² found that patients with MDD had reduced global brain connectivity (the average of the correlation between the blood oxygen level-dependent (BOLD) time series of a voxel and all other gray matter voxels in the brain) in the prefrontal cortex (PFC) compared to healthy volunteers at baseline, but increased global brain connectivity in the posterior cingulate, precuneus, lingual gyrus, and cerebellum. Ketamine significantly increased global brain connectivity in the right lateral PFC and reduced global brain connectivity in the left cerebellum. Furthermore, ketamine responders had increased connectivity in the lateral PFC, caudate, and insula compared to nonresponders. Downey and colleagues³³ recently found that ketamine increased BOLD signals in the subgenual ACC. Activation of the subgenual ACC predicted depression improvements at 24 hours and one week post-ketamine; the results are difficult to interpret, however, because in this study ketamine did not induce the pre-specified decrease in activity in the region-of-interest within the subgenual ACC and did not show any antidepressant effect superior to placebo.

With regard to structural MRI results, Abdallah and colleagues²⁸ found a significant association between smaller left hippocampal volumes at baseline and greater antidepressant responses to ketamine at 24 hours postinfusion in patients with depression. A diffusion MRI study found that at baseline, increased fractional anisotropy (a measure of connectivity strength in the principal axis of the structural connection) in the cingulum projecting the PFC, decreased mean diffusivity (a measure of membrane density) and radial diffusivity (a measure of myelination) in the forceps minor, and decreased radial diffusivity in the frontostriatal tract were associated with ketamine response, defined as 50% improvement in depression symptoms at 24 hours.³⁵

Other studies that utilized MEG provide more information about the role of the ACC. Salvatore and colleagues²² found that increased baseline cortical activity to fearful pictures in the ACC—especially the pregenual ACC—and decreased baseline amygdala activation each predicted a greater antidepressant response to ketamine at four hours postinfusion. Another study from the same group examined baseline predictors of ketamine response during a working-memory task. Patients who had the least pre-ketamine engagement of the pregenual ACC with increasing memory load showed the greatest antidepressant improvement to ketamine at four hours postinfusion.²³ In addition, those with the lowest coherence between pregenual ACC and left amygdala were most likely to respond to ketamine. Since we would expect healthy controls to have high pregenual ACC activity in response to emotional stimuli and low pregenual ACC activity in response to increased cognitive demands, these data suggest that normal baseline activity in the pregenual ACC predicts better antidepressant outcomes to ketamine.

In another MEG study, Nugent and colleagues³⁴ found decreased connectivity between the amygdala and insulo-temporal regions post-ketamine. Based on the theory by Duman and colleagues^{36,37} that ketamine's antidepressant effects result from rapid increases in synaptic plasticity, Cornwell and colleagues²⁴ designed a tactile-stimulation task as a mean of indirectly gauging synaptic plasticity in the somatosensory cortex via MEG acquisition recorded 6.5 hours post-ketamine. Compared to nonresponders, responders at four hours postinfusion had increased somatosensory cortical excitability (a measure of synaptic plasticity).

Several studies explored ketamine's effects on whole-brain metabolism using PET. Lally and colleagues³⁰ at the National Institute of Mental Health (NIMH) found that decreased anhedonia post-ketamine was associated with increased metabolism in the hippocampus and the dorsal ACC, and decreased metabolism in the orbitofrontal cortex (OFC). Another study from the same NIMH group found that decreased suicidal ideation scores post-ketamine correlated with decreased metabolism in the infralimbic cortex.²⁹ Furthermore, Carlson and colleagues²⁵ administered PET scans at 120 minutes post-ketamine and compared them to baseline scans. Decreased metabolism in the right habenula, right insula, right ventrolateral PFC, and dorsolateral PFC was found post-ketamine. Furthermore, clinical improvements significantly correlated with increased metabolism in the superior temporal gyrus, middle temporal gyrus, and cerebellum, and with decreased metabolism in the parahippocampal gyrus and inferior parietal cortex.

Two studies focused on bipolar depression using PET. Lally and Nugent³⁴ used PET scans at 120 minutes post-ketamine to measure metabolism in patients with bipolar depression; note, all patients in these studies were maintained on stable doses of either lithium or valproic acid. Specifically, Lally and colleagues²⁶ found that decreased anhedonia correlated with increased metabolism in the dorsal ACC and putamen. Nugent and colleagues³⁴ found that patients

who received ketamine had significantly lower glucose metabolism in the left hippocampus compared to those who received placebo; furthermore, patients with the largest improvement in depression symptoms had the largest metabolic increase in the right ventral striatum post-ketamine compared to placebo. In addition, metabolism of the subgenual ACC positively correlated with improvements in depression scores following ketamine.

Ketamine in Nondepressed Subjects: Non-task-based Resting-State Scans

Twenty-one resting-state scan studies were found relevant to this review—mostly using MRI and MRS (see Tables 2 and 3).

From MRI studies, some highlights emerged. Several studies examined how ketamine affected cerebral blood flow (CBF). Two studies showed that ketamine reduced CBF in the hippocampus and increased CBF in the ACC and prefrontal regions.^{38,41} Other studies found that ketamine reduced CBF in the OFC and subgenual ACC.^{40,49} In one particular study, this reduction strongly predicted dissociation ($r = 0.90$ with the Clinician Administered Dissociative States Scale scores).⁴⁰ In another study, perceptual distortions and delusion ratings following ketamine correlated with increased BOLD response in the parietal cortex.⁴⁹

With regard to resting-state fMRI, one study found that ketamine decreased connectivity in the auditory and somatosensory networks in relation to regions of physical and affective processing of pain (e.g., amygdala, insula, and ACC).⁴¹ In another study, ketamine reduced functional connectivity between the pregenual ACC and dorsal posterior cingulate cortex (dorsal PCC); this reduction in connectivity correlated significantly with increased psychotomimetic effects during the infusion.⁵⁶ Ketamine decreased functional network connectivity in healthy subjects; specifically, ketamine disrupted connectivity between the pregenual ACC, medial PFC, and the bilateral dmPFC 24 hours after infusion.⁴³ One study examined the effects of ketamine on brain connectivity with increasing levels of sedation (awake, mildly sedated, heavily sedated). Increased levels of sedation correlated significantly with decreased connectivity in the medial PFC with the default mode network and also between the left and right executive-control networks. Thalamo-cortical connectivity remained relatively preserved.⁵⁰ Ketamine also had significant effects on hippocampal connectivity. One resting-state fMRI study found that ketamine induced hyperconnectivity in hippocampal networks vulnerable to mood and cognitive disorders.⁴¹ Moreover, another study observed that hyperconnectivity between the PFC and the left hippocampus occurred after acute ketamine challenge.⁴⁷

MRS techniques have also implicated ketamine's role in brain connectivity and hippocampal function. Ketamine induced an increase in hippocampal Glx (glutamate + glutamine—an indication of enhanced excitatory neurotransmission) and a decrease in frontotemporal and temporoparietal functional connectivity in a combined MRS/fMRI study.⁵² This suggests

Table 2
Resting-State Scans and Non-task Scans (Nondepressed Populations)

Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Lahti (1995) ³⁸	PET/MRI: 2 scans, pre- and post-infusion Double-blind, placebo controlled; 4 administrations occurred over 2 weeks at the following doses: ketamine at 3 different doses vs. placebo	Patients with schizophrenia (n = 9) maintained on stable haloperidol doses Racemic ketamine: 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg	Ketamine increased regional CBF in the ACC and reduced regional CBF in the visual cortex and hippocampus	Small n Study published in 1995
Rowland (2005) ³⁹	4 T proton MRS Double-blind, placebo-controlled, crossover; 2 scanning sessions separated by 1–2 weeks	Healthy male volunteers (n = 9) analyzed Racemic ketamine: 0.27 mg/kg loading dose over 10 minutes, then 0.00225 mg/kg/min maintenance for rest of experiment (up to 2 hours)	Ketamine increased ACC glutamine (a putative marker of glutamate release) compared to placebo	Small n H-MRS does not measure glutamate release directly and instead measures glutamine, which is an index of turnover of synaptic glutamate involved in neurotransmission
Deakin (2008) ⁴⁰	Pharmacological MRI BOLD: starting 8 minutes before and for 8 minutes during the infusion Two experiments: double-blind, placebo-controlled, randomized, crossover, counterbalanced orders: first experiment, ketamine vs. placebo; second experiment, ketamine following pretreatment (2 hours before) with lamotrigine 300 mg vs. placebo	Male, right-handed, healthy volunteers in experiment 1 (n = 20) and experiment 2 (n = 19) Racemic ketamine: 0.26 mg/kg for 1-minute bolus, then 0.25 mg/kg/hr maintenance	Ketamine caused an immediate and focal reduction in subgenual ACC and OFC blood flow; this strongly predicted dissociation (r = .90 with Clinician Administered Dissociative States Scale scores) Ketamine increased activity in the mid-posterior cingulate cortex, thalamus, and temporal cortex Lamotrigine prevented many of the BOLD signal changes	
Niesters (2012) ⁴¹ Khalili-Mahani (2014) ⁴² (biomarker study)	3 T rsfMRI: 1 scan followed by pseudocontinuous ASL measurement First study: single-blind, randomized, placebo-controlled crossover study of IV S-ketamine vs. placebo during scanning; scans separated by at least 1 week; pain was also assessed with a noxious heat stimuli Second study was a biomarkers study: examined biomarkers on the extent to which ketamine infusion mimics a stress response	Healthy male volunteers (n = 12) S-ketamine: 20 mg/70 kg/hr for 1 hour, then 40 mg/70 kg/hr for 1 hour	Ketamine increased connectivity in the cerebellum and visual cortex in relation to the medial visual network Ketamine decreased connectivity in the auditory and somatosensory networks in relation to regions of pain sensing and affective processing of pain (amygdala, insula, and ACC) Ketamine caused a transient change in CBF; there was increased brain function in the prefrontal brain regions and decreased brain function in the hippocampal, visual, and parietal regions	It is unclear what (if any) scrubbing methods were used for rsfMRI ⁴¹

Table 2

Continued

Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Scheidegger (2012) ⁴³	3 T rsfMRI: 2 scans, at baseline and 24 hours postinfusion Randomized, double-blind, placebo-controlled, crossover study; ketamine and placebo infusions separated by 10 days	Healthy volunteers (n = 17) IV S-ketamine: 0.25 mg/kg over 45 minutes	Ketamine induced hyperconnectivity in hippocampal networks vulnerable to mood and cognitive disorders Biomarkers: there were increased cortisol levels with the higher dose of ketamine within 30 minutes of starting the infusion; robust cortisol response was associated with perfusion of the hippocampus and hippocampal head connectivity	Healthy controls were used to make inferences about networks commonly disrupted in MDD; as such, inferences about antidepressant effect could not be made
Taylor (2012) ¹³	3 T proton MRS Placebo-controlled, parallel-group design; IV ketamine	Healthy volunteers (n = 17); 11 male, 6 female Racemic ketamine: 0.5 mg/kg over 40 minutes	No significant difference between ketamine and placebo in Glx or glutamate concentrations in the ACC	The study tested only one voxel in the subgenual ACC; therefore changes in Glu/Glx in other parts of the brain may go undetected H-MRS does not measure glutamate release directly and instead measures glutamine, which is an index of turnover of synaptic glutamate involved in neurotransmission
Doyle (2013) ⁴⁴ Shcherbinin (2015) ⁴⁵	Resting-state pharmacological ⁴⁴ and ASL ⁴⁵ Randomized, placebo-controlled, partial crossover design; 4 scanning visits at least 2 weeks apart; sessions were as follows: PO risperidone/IV ketamine, PO lamotrigine/IV ketamine, PO placebo/ketamine, PO placebo/IV saline	Healthy male volunteers (n = 16 completers) Racemic ketamine: bolus ~0.12 mg/kg for the first minute, then 0.31 mg/kg/hr for about 20 minutes (BOLD resting state scanning for 15 minutes and ASL scanning for 5 more minutes after start of infusion)	Pharmacological MRI: pretreatment with lamotrigine and risperidone resulted in attenuation of ketamine-induced increases in BOLD signal (including medial prefrontal and cingulate regions and thalamic areas) ASL: Ketamine increased perfusions of the prefrontal and cingulate cortices; thalamus; and lateral parietal cortex; pretreatment with risperidone, but not lamotrigine,	Pharmacological dose-response curve for ketamine was based only on a few subjects

Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Joules (2015) ⁴⁶	3 T MRI: 2 scans, pre- and postinfusion Double-blind, placebo-controlled, crossover design of 4 sessions, each separated by 10 days; IV session was in the scanner; sessions were as follows: PO placebo/IV ketamine, PO placebo/IV saline, PO risperdal, IV ketamine, PO lamotrigine/IV ketamine	Healthy male volunteers (n = 16), all right-handed Racemic ketamine: IV as 0.12 mg/kg over 1 minute followed by 0.31 mg/kg/hr	increased the ketamine-induced perfusion changes Ketamine altered whole-brain connectivity compared to placebo Specifically, ketamine produced a shift from cortically centered to subcortically centered patterns of connections; this effect was modulated by pretreatment with risperidone but not lamotrigine, suggesting that the connectivity pattern shifts are due to NMDA receptor blockage (rather than downstream glutamatergic effects)	Measures of degree centrality (the metric used to determine whole-brain connectivity) cannot be used to examine region-to-region coupling; as such, some important differences in connectivity may go undetected
Grimm (2015) ⁴⁷	3 T rsfMRI: 1 scan postinfusion Double-blind, placebo-controlled, randomized; single IV infusion	Healthy volunteers (n = 24); 12 males, 12 females Racemic ketamine: 0.5 mg/kg over 40 minutes	Hyperconnectivity between the PFC and the left hippocampus occurred after acute ketamine challenge	It is unclear what (if any) scrubbing methods were used for rsfMRI
Muthukuma-raswamy (2015) ⁴⁸	MEG: Two different experiments Experiment 1: 2 MEG experiments on 2 days (ketamine vs. placebo); 5 minutes resting-state MEG, then infusion Experiment 2: 10 minutes resting-state MEG	Healthy male volunteers (n = 19 in experiment 1 and n = 6 in experiment 2) Racemic ketamine Experiment 1: 0.25 mg/kg bolus over 1 minute, then 0.375 mg/kg/hr maintenance infusion for 10 minutes Experiment 2: Same dose as experiment 1 but with maintenance infusion for 20 minutes	Ketamine decreased NMDA- and AMPA-mediated frontal-to-parietal connectivity; specifically, ketamine caused a decrease in posterior alpha band power, an increase in prefrontal theta band power, and widespread increases in gamma band power	The dynamic causal modeling approach used here found significant frontoparietal connectivity changes; however, power correlations failed to replicate this result
Stone (2015) ⁴⁹	3 T pharmacological MRI: 15-minute scan with ketamine starting at minute 5 Open-label within-subjects design	Healthy male volunteers (n = 13), aged 18–50 years Racemic ketamine: 0.26 mg/kg for 20 seconds followed by 0.42 mg/kg/hr	Ketamine led to decreases in BOLD response in subgenual ACC and widespread cortical and subcortical increases in BOLD response in the cingulate gyrus, hippocampus, insula, thalamus, and midbrain Perceptual distortions and delusion ratings correlated with increased BOLD response in the parietal cortex	Small n

Table 2
Continued

Table 2
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Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Bonhomme (2016) ⁵⁰	3 T rsfMRI: 1 scan during ketamine infusion Ketamine dose gradually increased to reach deeper levels of sedation during the scanning session	Healthy volunteers (n = 8) Racemic ketamine; dose varied based on depth of sedation	Increased depth of sedation with increased ketamine doses correlated with decreased connectivity in the medial PFC with the default mode network Thalamo-cortical connectivity remained relatively preserved, but corticocortical connections were disrupted with ketamine	Small n Heart rate and respiration not directly taken into account in analysis (though CO ₂ was) Multiple-seed region-of-interest approach may bias results Order of conditions was not randomized, due to ketamine's long recovery time
Hoflich (2016) ⁵¹	3 T rsfMRI: 1 scan during infusion Double-blind, placebo-controlled, randomized, crossover trial of IV ketamine in the scanner Infusion was administered 10 minutes after the start of the 50-minute scan; the first 5 minutes of the scan were infusion-free resting-state scans, followed by 5 minutes of saline infusion	Healthy volunteers (n = 30): 15 males, 15 females (scanner issues, full data were available for only 5 patients) S-ketamine: 0.11 mg/kg 1-minute bolus followed by 0.12 mg/kg over 19 minutes	Compared to placebo, ketamine increased neural activation in the bilateral midcingulate cortex, ACC, insula, and right thalamus	Pharmacological dose-response curve for ketamine was based only on a few subjects
Kraguljac (2016) ⁵²	3 T MRS (to measure hippocampal Glx) and rsfMRI (to measure hippocampal connectivity) Ketamine IV was given in the scanner	Healthy volunteers (n = 15) completed; 10 males, 5 females Racemic ketamine: 0.27 mg/kg bolus over 10 minutes, then 0.25 mg/kg/hr for approximately 60 minutes	Ketamine induced an increase in hippocampal Glx, a decrease in frontotemporal and temporoparietal functional connectivity, and a possible link between connectivity changes and elevated Glx	Small n; placebo control group was not included A one-sided t-test was used based on previous results from schizophrenia patients
Wong (2016) ⁵³	3 T rsfMRI: 1 scan, 15 minutes with IV ketamine started at the 5-minute point	Healthy male volunteers (n = 13) Racemic ketamine: 0.26 mg/kg rapid bolus over 20 seconds and then 0.42 mg/kg/hr infusion	Following ketamine, there was a significant reduction in subgenual ACC coupling with the hippocampus, retrosplenial cortex, and thalamus	Healthy controls were used to make inferences about brain regions implicated in MDD; as such, inferences about antidepressant effect could not be made Participants were studied 5 minutes postinfusion, and antidepressant effects were typically not seen for 1–2 hours postinfusion

ACC, anterior cingulate cortex; ASL, arterial spin labeling; BOLD, blood oxygen level dependent; CBF, cerebral blood flow; Glx, glutamate + glutamine; MDD, major depressive disorder; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMDA, N-methyl-D-aspartate; OFC, orbitofrontal cortex; PET, positron emission tomography; rsfMRI, resting-state functional magnetic resonance imaging.

a possible link between connectivity changes and elevated Glx—namely, that NMDA receptor hypofunction may lead to elevated hippocampal glutamatergic transmission and alterations in the resting-state network. This finding was supported by a study in which ketamine was found to decrease NMDA- and AMPA-mediated frontoparietal connectivity.⁴⁸

One study imaged participants using fMRI during both a ketamine infusion and placebo infusion.⁵¹ The authors found that, compared to placebo, BOLD activation increased during the ketamine condition in the bilateral middle cingulate cortex, ACC, and insula, as well as in the right thalamus.

Finally, with regard to MEG, one study found increased gamma power during the infusion, while beta band activity was decreased.⁵⁸ This effect was noted in the thalamus, hippocampus, and frontocortical regions. Connectivity, as measured by transfer entropy (how much information is transferred from a source to a target process), increased within the thalamocortical network. This study's results highlight a potential contribution of the thalamocortical pathways in ketamine's initial neuronal dysregulation.

Ketamine in Nondepressed Subjects: Task-Based Scans

Fifteen task-based scan studies were found, 14 of which used fMRI (see Tables 3 and 4).

Several studies examined ketamine's effects during and after emotion tasks. In one study, ketamine attenuated task-induced activation in the amygdalo-hippocampal complex; specifically, reductions in BOLD activation were more marked in response to negative pictures than to neutral or positive pictures.⁵⁷ Furthermore, increased intensity of the acute psychedelic side effects on consciousness during ketamine exposure predicted the reduction in neuronal responsiveness to negative (but not neutral or positive) pictures. The authors suggested that perhaps the emotional blunting (“attenuated limbic hyperactivity”) during dissociation plays a role in the alleviation of negative bias in people with depression (though no patients with depression were actually included in the study).

During a different emotion-pictures task, increased BOLD activation was observed 24 hours post-ketamine infusion in the pregenual ACC (but not the posterior control regions) during the negative picture-viewing blocks.⁵⁶ The increase in BOLD activation was more pronounced, however, in subjects with a low ability to apply distraction during the negative experiences. In another emotion task, ketamine significantly reduced BOLD activation in the right insula regardless of task's emotional valence; in the left insula and right dlPFC, BOLD activation was reduced only in response to negative stimuli.⁶⁹ Compared to placebo (in which several brain areas [amygdala, visual-processing areas, and cerebellum] significantly activated during a fearful-faces task), the ketamine group significantly activated only the left superior occipital gyrus.^{54,55} These data are somewhat related to another study in which ketamine led to impaired self-monitoring, which was related to reduced activation in the left superior temporal cortex. Together, these data

suggest that the NMDA receptor may be involved in producing the impaired self-monitoring that occurs during hallucinatory or delusional experiences.⁶⁵

Several studies examined ketamine's effects on working memory. In one study, ketamine increased activation in frontoparietal regions (dlPFC, bilateral ventrolateral areas, bilateral parietal cortices, ACC, putamen, and caudate nucleus) compared to placebo during the task phase of manipulation of verbal information (at the easiest point).⁵⁹ In another study, ketamine increased activation of the left PFC to deeply encoded items during an episodic-memory task.⁶⁰ Specifically, correctly identified items during ketamine were associated with increased activation of the right PFC during encoding compared to incorrectly identified items. Items incorrectly identified at retrieval were associated with increased activation of the right PFC and hippocampus under ketamine but not placebo. By contrast, in one study, ketamine impaired working-memory performance.⁶⁶ Ketamine reduced task-related activation in the PFC during a spatial task, especially during the encoding and early-maintenance phases. Ketamine also reduced connectivity during the task in the network brain areas involved in working memory. Reductions in activation and connectivity were related to performance.

Finally, one study found that ketamine induced a general impairment of verbal fluency.⁶⁴ During the phonic verbal-fluency task, several brain regions (left temporal gyrus, superior frontal gyrus to middle frontal gyrus, medial frontal gyrus, and left inferior parietal lobe) were more activated by ketamine than in other conditions. During the lexical verbal-fluency task, the right frontal and left supramarginal regions were activated significantly more with ketamine.

DISCUSSION

Although the neuroimaging literature on ketamine's effects is in its early stages, certain themes have emerged. First are our findings of convergent brain regions implicated in MDD and how ketamine modulates those areas. Specifically, the subgenual ACC has been a region of interest in many previous studies. In relation to emotion and cognition, ketamine appears to reduce brain activation in regions associated with self-monitoring, to increase neural regions associated with emotional blunting, and to increase neural activity in reward processing.

Overall, ketamine's effects were most notably found in the subgenual ACC, PCC, PFC, and hippocampus. Abnormalities in overlapping regions (specifically, the dorsal and subgenual ACC, amygdala, hippocampus, and ventral striatum) have been implicated, via a growing body of neuroimaging literature, in the pathophysiology of depression.^{70–74} The subgenual ACC, in particular, has been a frequently studied area of interest concerning ketamine and MDD. In healthy male volunteers, resting-state fMRI and pharmacological MRI done during ketamine infusion found significant reductions in subgenual ACC coupling with hippocampus, retrosplenial cortex, and thalamus. Immediate reductions

Table 3

Studies with Both Resting-State Scans and Task Scans (Nondepressed Populations)

Study	Scanning details and study design	Subjects and ketamine details	Significant findings
Abel (2003) ⁵⁴ and Abel (2003) ⁵⁵	1.5 T fMRI during task and rsfMRI Randomized, double-blind, placebo-controlled study; 2 scans separated by at least 1 week during resting state and cognitive/emotional facial-recognition task	Healthy male volunteers (n = 8) Racemic ketamine: 0.23 mg/kg bolus over 5 minutes, then 0.5 mg/kg for 40 more minutes	Ketamine significantly decreased activation in the middle occipital gyrus and precentral gyrus compared to placebo In the placebo group, several brain areas (amygdala, visual-processing areas, and cerebellum) were activated during fearful faces; ketamine activated only the left superior occipital gyrus during fearful faces
Lehmann (2016) ⁵⁶	3 T fMRI: 1 scan with IAPS task, and rsfMRI Double-blind, placebo-controlled, 2-arm study Arm 1: baseline scan and 24-hour follow-up scan post-placebo. Arm 2: baseline scan and 24-hour follow-up scan post-ketamine Baseline scans were at least 10 days prior to the follow-up scan	Healthy volunteers (n = 17) S-ketamine: 0.25 mg/kg	Resting state: Ketamine reduced functional connectivity between the pregenual ACC and the dorsal PCC; this reduction in connectivity correlated with increased psychotomimetic effects during the infusion IAPS task: Increased BOLD reactivity in the pregenual ACC (but not the posterior control regions) were observed during the negative pictures in the ketamine group; the increase in BOLD reactivity was more pronounced for subjects with a low ability to apply distraction during negative experiences
Scheidegger (2016) ⁵⁷	3 T fMRI during task and rsfMRI One baseline scan and one scan during an open-label ketamine infusion; ketamine was started 15 minutes before the scan start and during the 25-minute MRI scan Patients completed both resting-state and an emotional IAPS task	Healthy volunteers (n = 23) S-ketamine: 0.12 mg/kg bolus followed by continuous 0.25 mg/kg/hr infusion	Ketamine attenuated task-induced activation in the amygdalo-hippocampal complex during the emotion task; specifically, reductions in BOLD reactivity was more marked in response to negative pictures compared to neutral or positive pictures, suggesting that the processing of negative information is specifically altered in response to ketamine ⁵⁷ Also, reduced amygdala activity to negative pictures was correlated with resting-state connectivity to the pregenual ACC Increased intensity of psychedelic side effects of consciousness during ketamine predicted the reduction in neuronal responsiveness to negative (but not neutral or positive) pictures

ACC, anterior cingulate cortex; BOLD, blood oxygen level-dependent; fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; rsfMRI, resting state functional magnetic resonance imaging.

Table 4

Task-Based Scans (Nondepressed Populations)

Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Honey (2004) ⁵⁹ (working memory) Honey (2005) ⁶⁰ (episodic memory)	3 T fMRI BOLD Double-blind, placebo-controlled, randomized, within-subject comparison study; three sessions (one was placebo and two were at different doses of IV ketamine, 7 days apart); subjects completed memory tasks	Healthy volunteers (n = 12) Racemic ketamine: infusion was done to reach a ketamine level of 50 ng/ml or 100 ng/ml, depending on the day of randomization (note, both were considered subanesthetic doses)	Working-memory study: Ketamine increased activation in frontoparietal regions (dlPFC, bilateral ventrolateral areas, bilateral parietal cortices, ACC, putamen, and caudate nucleus) compared to placebo during a working-memory task in the manipulation of verbal information phase of the task at the easiest point Episodic-memory study: Ketamine increased activation of the left PFC to deeply encoded items Correctly identified items under ketamine were associated with increased activation of the right PFC during encoding compared to incorrectly identified items; items incorrectly identified at retrieval were associated with increased activation of the right PFC and hippocampus under ketamine, but not placebo	
Rogers (2004) ⁶¹	3 T fMRI BOLD Ketamine was administered at subanalgesic (50 ng/mL) and analgesic/subanesthetic (200 ng/mL) concentrations to subjects in the MRI scanner and compared to placebo; each infusion was 24 minutes and was administered as saline, ketamine, ketamine; subjects experienced noxious stimuli spread throughout the experiment	Healthy male volunteers (n = 8); average age was 28 years Racemic ketamine: ketamine was administered at increasing doses in a stepwise manner following placebo as follows: 50 ng/mL was administered at a rate of 0.18 mg/kg/hr over 24 minutes; 200 ng/mL was administered at a rate of 0.71 mg/kg/hr over 24 minutes	High doses of ketamine produced a decrease in pain scores compared to placebo; this decrease correlated with decreased activity in the insular cortex and thalamus Decreases in activity of the ACC and primary sensory cortex were also found but were statistically insignificant	Small n No female participants
Fu (2005) ⁶²	1.5 T fMRI BOLD Double-blind, placebo-controlled, crossover study; infusions and scans were separated by at least 1 day; subjects completed a verbal-fluency task with two conditions: easy and hard	Male healthy volunteers (n = 10) Racemic ketamine: bolus of 0.23 mg/kg over 30 seconds, then 0.65 mg/kg for approximately 1 hour	Ketamine did not impair task performance compared to placebo Ketamine induced greater activation in areas related to verbal fluency (ACC, prefrontal, and striatal regions) during the easy vs. hard condition	Small n No female participants

Table 4
Continued

Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations
Musso (2011) ⁶³	3 T fMRI BOLD with simultaneous EEG Randomized, double-blind, placebo-controlled, crossover trial; infusions occurred at least 1 week apart; subjects completed a visual oddball task	Male healthy volunteers (n = 24); 2 subjects were left-handed S-ketamine: 0.1 mg/kg over the first 5 minutes, then 0.015625 mg/kg/min for up to 1 hour in the scanner (with reductions in administration of 10% every 10 minutes)	There was a strong reduction in the P300 amplitude at the parietal electrode position Pz in the ketamine condition compared to placebo	No female participants
Nagels (2011) ⁶⁴	3 T fMRI BOLD Double-blind, placebo-controlled, counterbalanced study; subjects completed verbal-fluency tasks during the infusions in the scanner	Male healthy volunteers (n = 15) S-ketamine; 8 mg bolus for 5 minutes, then continuous infusion at 0.01 mg/kg/min for approximately 1 hour	Ketamine induced a general impairment of verbal fluency During the phonic verbal-fluency task, several brain regions (left temporal gyrus, superior frontal gyrus to middle frontal gyrus, medial frontal gyrus, and left inferior parietal lobe) were more activated by ketamine During the lexical verbal-fluency task, the right frontal and left supramarginal regions were activated significantly more with ketamine	No female participants
Stone (2011) ⁶⁵	1.5 T fMRI BOLD Double-blind, placebo-controlled, randomized study; two scan sessions separated by at least 1 day; subjects completed a verbal task	Male healthy volunteers (n = 8) Racemic ketamine: 0.23 mg/kg bolus, then 0.64 mg/kg/hr	Ketamine lead to impaired self-monitoring performance; this was related to reduced activation in the left superior temporal cortex during self-distorted speech (misattribution errors)	Small n H-MRS does not measure glutamate release directly; it measures glutamine, an index of turnover of synaptic glutamate involved in neurotransmission No female participants
Driesen (2013) ⁶⁶	3 T fMRI Subjects received placebo followed by ketamine while completing working-memory tasks in the scanner	Right-handed healthy volunteers (n = 22); 14 male, 8 female Racemic ketamine: 0.23 mg/kg for a 1-minute bolus, then 0.58 mg/kg/hr during the scan session	Ketamine impaired working-memory performance; ketamine reduced task related activation in the PFC during the spatial task (especially during the encoding and early maintenance phase) Ketamine also reduced connectivity during task in the network brain areas involved in working memory; reductions in activation and connectivity were related to performance	Scans were not randomized and contained long sessions; results may be due to participant fatigue

Table 4					
Continued					
Study	Scanning details and study design	Subjects and ketamine details	Significant findings	Limitations	
Shaw (2015) ⁶⁷	MEG Single blind, placebo-controlled, crossover study; infusions scheduled at least 2 weeks apart to allow for washout; 90-minute MEG scan with visuomotor task was completed pre-ketamine and during ketamine infusion in order to measure changes in oscillatory dynamics	Healthy male volunteers (n = 18 with data available); ages ranged from 18–45 years Racemic ketamine: 0.25 mg/kg bolus for the first minute, then 0.25 mg/kg over 40 minutes	Ketamine-mediated NMDA receptor antagonism reduced peak gamma frequency in the visual cortex and increased the amplitude of gamma oscillation in the motor and visual cortices Beta frequency desynchronization was reduced in both motor and visual cortices	No female participants	
Francois (2016) ⁶⁸	3 T fMRI reward task Double-blind, randomized, placebo-controlled study; a reward task occurred at 40 minutes after the start of the infusion	Healthy volunteers (n = 24) Racemic ketamine: 0.5 mg/kg over 40 minutes	Ketamine significantly attenuated the ventral striatum response to the task, particularly the nucleus accumbens, compared to placebo	BOLD data was not co-registered to each subject's individual T1-weighted scan; this could pose a problem with coregistering small regions such as the nucleus accumbens and ventral striatum	
Scheidegger (2016) ⁶⁹	3 T fMRI One baseline scan 2 days prior to the open-label ketamine session and scan; subjects completed a working memory, n-back task in the scan sessions	Healthy volunteers (n = 23); 12 male, 11 female S-ketamine: 0.12 mg/kg bolus at 25 minutes prior to task, followed by a continuous infusion of 0.25 mg/kg/hr during the entire scan and task period	Ketamine significantly reduced BOLD activation in the right insula (regardless of emotional valence of the task) There was a reduction in BOLD activity exclusively to negative stimuli in the left insula and right dlPFC	Only included up to 2 numbers back in their working-memory task; results may be limited by a ceiling effect	

ACC, anterior cingulate cortex; BOLD, blood oxygen level–dependent; dlPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex.

in subgenual ACC blood flow and focal reductions in OFC blood flow strongly predicted dissociation.^{40,53} Some other imaging studies of the subgenual ACC, however, seem to provide contradictory results. NIMH studies using PET 120 minutes postinfusion found that increased metabolism in the subgenual ACC was positively correlated with improvements in depression scores post-ketamine.²⁷ A different PET study in MDD, however, found no change in subgenual ACC metabolism post-ketamine.²⁵ In addition to indicating that larger, more controlled studies are needed, these inconsistent results suggest that the timing of the scan may matter. Changes in subgenual ACC activation may be related to ketamine's acute side effects, which begin during infusion, reach a peak typically within an hour of infusion, and are completely absent 230 minutes after infusion. Against this background, it is possible that subgenual ACC activation decreases during and immediately after ketamine infusion, but changes again a few hours later, returning to normal.

Analysis of resting-state scans in healthy volunteers further suggests that dissociation may be responsible for ketamine's antidepressant effects because it may disconnect the "excessive effects of an aversive visceromotor state on cognition and the self"—a hallmark of depression.^{40(p 163)} Related, one study found that ketamine may dampen brain regions involved in rumination (the repetitive focusing of attention on negative feelings and thoughts in response to negative mood) by reducing the functional connectivity between the pregenual ACC and the dorsal PCC, and decreasing connectivity between the left and right executive-control networks.⁵⁶ In fact, ketamine has been shown to interfere with the default mode network (a system involved in internal and external sensory processing)⁷⁵ by disrupting the "hyperconnectivity"—commonly associated with rumination—between it and the medial PFC in patients with MDD.^{50,57} One ongoing study (ClinicalTrials.gov ID: NCT02544607) aims to further investigate default mode network changes and hyperconnectivity in patients with TRD before and after a ketamine infusion. Taken together, these studies suggest that ketamine may cause a "disconnect" in several circuits related to affective processing, perhaps by shifting focus of attention away from the internal states of anxiety, depression, and somatization, and more toward the perceptual changes (e.g., hallucinations, visual distortions, derealization) induced by ketamine. Similarly, during an emotion task, ketamine attenuated responses to negative pictures, suggesting that the processing of negative information is specifically altered in response to ketamine.⁵⁷ By taking the focus off "oneself" and placing it on other stimuli, it is possible that ketamine decreases awareness of negative experiences and consequently improves mood.

Perhaps most interesting are ketamine's effects on brain connectivity as it relates to self-monitoring behaviors. Reduced connectivity between the pregenual ACC and dorsal PCC was associated with increased dissociation during infusion, and reduced activation in the left superior temporal

cortex was associated with impaired self-monitoring^{56,65}—which is disruptive to patients with psychotic illness—especially those with chronic symptoms of psychosis. By contrast, the transient dissociation experienced by depressed patients during a ketamine infusion may have the effect of dampening what the hyperactive self-monitoring associated with depressive illness.

During ketamine administration, subjects experience emotional blunting, which may be associated with reduced limbic responses to emotional stimuli.^{54,55} It is possible that by decreasing the activity of deep limbic structures (thought to be involved in the pathophysiology of depression, such as the amygdala), ketamine acutely disables the emotional resources required to perpetuate the symptoms of depression.

Ketamine may play a role in reactivating reward areas of the brain in patients with MDD. This reactivation may be especially important, as reward areas in MDD have been characterized by decreased subcortical and limbic activity and by an increased cortical response to reward paradigms.⁷⁶ In resting-state scans, BOLD activation in the cingulate gyrus, hippocampus, insula, thalamus, and midbrain increased after ketamine.⁴⁹ In addition, ketamine increases neural activation in the bilateral MCC, ACC, and insula, as well as the right thalamus.⁵¹ Activation of these areas is consistent with activation of reward-processing areas, suggesting that ketamine may play a role in activating reward neurocircuitry.⁷⁶

Though no single brain area has been singled out as the locus of depression, ketamine affects different areas of the brain in various ways, which may contribute to overall mood improvements. For example, at baseline, patients with MDD, compared to healthy volunteers, had reduced global connectivity in the PFC and increased connectivity in the posterior cingulate, precuneus, lingual gyrus, and cerebellum; post-ketamine, responders had increased connectivity in the lateral PFC, caudate, and insula.³² These findings may reflect ketamine's ability to reclaim frontal control over deeper limbic structures, thus strengthening the cognitive control of emotions and decreasing depressive symptoms. Similarly, TRD patients, compared to healthy volunteers, had reduced insula and caudate responses to positive emotions at baseline, which normalized in the caudate post-ketamine.³¹ Furthermore, while one study showed increased connectivity in the lateral PFC, caudate, and insula in ketamine responders, another found decreased connectivity between the amygdala and insulo-temporal regions.^{32,34} Improvements are correlated with increased metabolism in the hippocampus, dorsal ACC, and decreased metabolism in the OFC.³⁰ Yet another group found that improvements correlated with increased metabolism in the superior/middle temporal gyrus and cerebellum, and decreased metabolism in the parahippocampal gyrus and inferior parietal cortex.²⁵ Further investigation of these seemingly sporadic results may provide further insight into ketamine's antidepressant effects.

Several limitations in this review warrant discussion. First, it is hard to extrapolate information about ketamine's

antidepressant properties from the existent literature, because the majority of published studies are from healthy volunteers. Second, most of the task-based healthy volunteer studies used male volunteers only, which may limit generalizability. Third, most of the studies completed have very few participants; even the depression study with the most participants had only 24 subjects. Given the immense heterogeneity of depression, further studies with larger sample sizes will be necessary in order to capture the full range of patients with depression. Fourth, it is still difficult to temporally parse out which findings occur due to ketamine's antidepressant mechanism alone versus which changes are due to the appearance of psychotropic side effects immediately post-ketamine. This may be especially relevant to ketamine imaging studies because of the timing of its side effects (1–2 hours) versus antidepressant effect (hours to days) in relation to the timing of the imaging procedure. Fifth, although most studies used racemic ketamine, several others used the *S*-ketamine enantiomer. This difference may be important because *S*-ketamine may have greater affinity to the NMDA receptor than the *R*-ketamine enantiomer.⁷⁷ Finally, it is important to note that most depression studies use subanesthetic ketamine doses of 0.5 mg/kg over 40 minutes because this dose effectively treats depression. Many studies with nondepressed patients, however, used alternative doses. Though a study for ketamine's optimal antidepressant dose was recently completed (ClinicalTrials.gov ID: NCT01920555), the results are pending. Nonetheless, these reasons make it difficult to generalize the results of this review to large patient populations with depression.

Further research is necessary to uncover ketamine's antidepressant mechanism of action and address the above limitations. Such research may help to uncover new working models of the biological substrates of depression and enable new drug discovery. Specifically, based on this review, future studies should likely focus on ketamine's action in the subgenual ACC, PCC, PFC, and hippocampus. Another promising direction for research builds on the view that depression is the product of underactive prefrontal and limbic mood-regulation networks and overreactive subcortical limbic networks, which are involved in emotional and visceral responses.⁷⁸ Perhaps these network abnormalities in depression—and their improvement with treatment—can be further elucidated through the use of ketamine. Indeed, ketamine's remarkable rapid, robust, and sustained antidepressant effects are considered to be “arguably the most important discovery in half a century” for depression research.^{37(p 68)} Ketamine's potential use in both research and treatment is promising indeed.

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