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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. Interestingly, 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 outlined by neuroimaging studies. Taken together, some important brain areas emerge, especially the subgenual anterior cingulate cortex. Furthermore, ketamine may decrease the ability to self-monitor, increase emotional blunting, and increase activity in reward processing. However, further studies are necessary to elucidate ketamine's mechanism of antidepressant action.

Keywords

Ketamine; Neuroimaging; Biomarkers; MRI; PET; MEG; Treatment-Resistant Depression

Introduction

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, economic strain from TRD accounts for nearly $200 billion dollars a year from lost productivity. The more treatment failures a patient experiences, the less likely they are to

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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 such compound that holds promise for TRD is ketamine. While commonly thought of as a dissociative anesthetic, subanesthetic doses of ketamine stand out among other pharmacological interventions for MDD. While most commonly used psychiatric medications (e.g. SSRIs, SNRIs, TCAs, MAO 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.[3]

Animal models show that ketamine's antidepressant effects are likely mediated by its antagonism of NMDA receptors through increased AMPA-mediated glutamatergic signaling. This triggers activation of intracellular synaptogenic pathways, most notably in the mTOR signaling pathway, which also has implications in many other psychiatric disorders.[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]

In terms of MDD, decreased glutamate has been noted in various prefrontal regions, including the dorsolateral prefrontal cortex (dlPFC), dorsomedial PFC (dmPFC), and the anterior cingulate cortex (ACC) when compared to controls.[8–10] This 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.

However, the glutamate surge hypothesis is met with some controversy. Neuroimaging studies specifically examining how ketamine modulates glutamate and gamma-aminobutryic acid (GABA) have been reviewed.[11] Despite the immediate glutamate surge during infusions, it is unclear if glutamate levels remain elevated post-infusion. One study finds increased glutamate levels in the ACC 35 minutes post infusion, and 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] However, no such 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 the biological and clinical level need to be explored.

One salient biological metric that may provide insight into ketamine's mechanism of action is 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] One study has shown increased dissociation and psychotomimetic symptoms immediately following infusion may predict antidepressant response.[20] Further neuroimaging research has the potential to not just inform scientists of ketamine's antidepressant mechanism, but may 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 non-invasive investigations of neuronal activity in patients with TRD and healthy controls. These imaging results can then be correlated with not just glutamate and GABA levels, but 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 to measure glutamatergic and GABA-ergic activity. They acquire full volumes of the brain at various time points during and after ketamine infusion. In turn, 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 (rsfMRI) provide less temporal resolution than MEG (full brain volumes are only acquired every ~3 seconds), however provide more precise measurements of subcortical regions of the brain. This is important for studying regions such as the subgenual ACC (sgACC) and amygdala, as they 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, decision making, etc. Task-based fMRI and MEG can provide more ecologically valid information about what the brain does when faced with real-life situations. It can also tell us more about how the brain's real-life performance is altered in patients with MDD. Finally, 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 there is very little literature that 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 impacts 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 patient care and outcomes as a result.

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

In this review, we segment the results into three sections: Ketamine and Neuroimaging in Depression, Ketamine in Non-Depressed Subjects: Non-Task Based Resting State Scans, and Ketamine in Non-Depressed: Task-Based Scans. Though most papers only examined one modality of imaging, several papers[6–9] tackled more than one imaging technique.

Results

Ketamine and Neuroimaging in Depression

Thirteen papers were found to be relevant to ketamine's effects in patients with unipolar depression, and two papers in patients with bipolar depression. (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.[22] Another study by Abdallah and colleagues found that patients with MDD had reduced global brain connectivity (the average of the correlation between the BOLD time series of a voxel and all other gray matter voxels in the brain) in the prefrontal cortex 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 non-responders.[23] Downey and colleagues recently found that ketamine increased blood oxygen level dependent (BOLD) signals in the sgACC. Activation of the sgACC predicted depression improvements at 24 hours and 1 week post-ketamine.[24] However, this group had no significant antidepressant response to ketamine, as well as strong placebo response and significant baseline differences in depression severity between the ketamine and placebo groups.

With regard to structural MR results, Abdallah and colleagues found a significant association between smaller left hippocampal volumes at baseline and greater antidepressant

responses to ketamine at 24 hours post-infusion in patients with depression.[25] A diffusion MRI study found that at baseline, greater fractional anisotropy (a measure of connectivity strength in the principal axis of the structural connection) in the cingulum projecting the PFC, decreased mean diffusivity (MD, a measure of membrane density) and radial diffusivity (RD, a measure of myelination) in forceps minor, and decreased RD in the frontostriatal tract predicted improvements in depression symptoms 24 hours post ketamine.[26]

Other studies that utilized MEG provide more information about the role of the ACC. Salvadore and colleagues found that increased baseline cortical activity to fearful pictures in the ACC—especially the pregenual ACC (pgACC)—and decreased baseline amygdala activation predicted a greater antidepressant response to ketamine at 4 hours post-infusion.[27] 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 pgACC with increasing memory load showed the greatest antidepressant improvement to ketamine at 4 hours post-infusion. In addition, those with the lowest coherence between pgACC and left amygdala were most likely to respond to ketamine.[28] Since we would expect healthy controls to have high pgACC activity in response to emotional stimuli and low pgACC activity in response to increased cognitive demands, these data suggest that normal baseline activity in the pgACC predicts better antidepressant outcomes to ketamine.

In another MEG study, Nugent and colleagues found decreased connectivity between the amygdala and insulo-temporal regions post-ketamine.[29] Cornwell and colleagues used a tactile stimulation task to indirectly gauge synaptic plasticity in the somatosensory cortex during MEG acquisition at 6.5 hours post-ketamine, since ketamine's antidepressant effects may be the result of rapid increases in synaptic plasticity.[30, 31] Indeed, responders at 4-hours post-infusion had an increase in somatosensory cortical excitability (a measure of synaptic plasticity) compared to non-responders.[32]

Several studies explored ketamine's effects on whole brain metabolism using positron emission tomography (PET). Lally and colleagues at the NIMH found that decreased anhedonia post-ketamine was associated with increased metabolism in the hippocampus and the dorsal anterior cingulate cortex (dACC), and decreased metabolism in the orbitofrontal cortex (OFC).[33] Another study from the same NIMH group found that decreased suicidal ideation scores post-ketamine correlated with decreased metabolism in the infralimbic cortex.[34] Furthermore, Carlson and colleagues 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 (STG), middle temporal gyrus (MTG), and cerebellum, and with decreased metabolism in the parahippocampal gyrus and inferior parietal cortex.[35]

Two studies focused on bipolar depression using PET imaging. Lally and Nugent 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 colleagues found that decreased anhedonia

correlated with increased metabolism in the dACC and putamen.[36] Nugent and colleagues 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 sgACC positively correlated with improvements in depression scores following ketamine.[37]

Ketamine in Non-Depressed Subjects: Non-Task Based Resting State Scans

Twenty-one resting state scan papers were found relevant to this review, mostly using MRI and MRS (see Table 2 and Table 4). 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, 39] Other studies found that ketamine reduced CBF in the OFC and sgACC.[40,41] In one particular study, this reduction strongly predicted dissociation (r=0.90 with the Clinician Administered Dissociative States Scale (CADSS) scores).[40] In another study, perceptual distortions and delusion ratings following ketamine correlated with increased BOLD response in the parietal cortex.[41]

With regard to rsfMRI, 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).[38] During another study, ketamine reduced functional connectivity between the pACC and the dPCC; this reduction in connectivity correlated significantly with increased psychotomimetic effects during the infusion.[42] Ketamine decreased functional network connectivity in healthy subjects; specifically, ketamine disrupted connectivity between the pgACC, mPFC, 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 mPFC with the Default Mode Network (DMN) and also between the left executive control network and the right executive control network. Thalamo-cortical connectivity remained relatively preserved.[44] Ketamine also had significant effects on hippocampal connectivity. One rsfMRI study found that ketamine induced hyperconnectivity in hippocampal networks vulnerable to mood and cognitive disorders.[38] Moreover, another study observed that hyperconnectivity between the PFC and the left hippocampus occurred after acute ketamine challenge.[45]

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), a decrease in fronto-temporal and temporo-parietal functional connectivity. This suggests a possible link between connectivity changes and elevated Glx. These data suggest that NMDA receptor hypofunction may lead to elevated hippocampal glutamatergic transmission and alterations in resting-state network.[46] Ketamine was found to decrease NMDA- and AMPA-mediated frontal-to-parietal connectivity.[47]

One study imaged participants using fMRI during both a ketamine infusion and placebo infusion. They analyzed a ketamine – placebo contrast and found that, compared to placebo,

BOLD activation increased during the ketamine condition in the bilateral middle cingulate cortex, ACC, and insula, as well as the right thalamus.[48]

Finally, with regard to MEG, one study found increased gamma-power during the infusion while beta band activity was decreased. This effect was noted in the thalamus, hippocampus, and fronto-cortical regions. Connectivity, as measured by transfer entropy (how much information is transferred from a source to a target process), increased within the thalamo-cortical network. This study's results highlight a potential contribution of the thalamo-cortical pathways in ketamine's initial neuronal dysregulation.[49]

Ketamine in Non-Depressed: Task-Based Scans

Fifteen task-based scan papers were found, fourteen of which used fMRI (see Table 3 and Table 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 compared to neutral or positive pictures. Furthermore, increased intensity of the acute psychedelic side effects on consciousness during ketamine 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).[50]

During a different emotional pictures task, increased BOLD activation was observed 24-hours post-ketamine infusion in the pgACC (but not the posterior control regions) during the negative picture viewing blocks. However, the increase in BOLD activation was more pronounced in subjects with a low ability to apply distraction during the negative experiences.[42] In another emotion task, ketamine significantly reduced BOLD activation in the right insula regardless of emotional valence of the task; there was a reduction in BOLD activation exclusively to negative stimuli in the left insula and right DLPFC.[51] Compared to placebo (in which several brain areas—amygdala, visual processing areas, and cerebellum—significantly activated during a fearful faces task), the ketamine group only significantly activated the left superior occipital gyrus.[52, 53] 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 the production of the impaired self-monitoring that occurs during hallucinatory or delusional experiences.[54]

Several studies examined ketamine's effects on working memory. In one study, ketamine increased activation in fronto-parietal 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).[55] In another study, ketamine increased activation of the left PFC to deeply encoded items during an episodic memory task. 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.[56] In contrast, in one study,

ketamine impaired working memory performance. Ketamine reduced task-related activation in the PFC during a spatial task, especially during the encoding and early maintenance phase. 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.[57]

Finally, one study found that 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 compared to other conditions. During the lexical verbal fluency task, the right frontal and left supramarginal regions were activated significantly more with ketamine.[58]

Discussion

Although the extant neuroimaging literature on ketamine's effects is in its early stages, certain themes have emerged. First, we review our findings of convergent brain regions implicated in MDD and how ketamine modulates those areas. Specifically, the sgACC 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, increase neural regions associated with emotional blunting, and increase neural activity in reward processing.

Overall, ketamine's effects were most notably found in the sgACC, PCC, PFC, and hippocampus. These areas overlap with the growing body of neuroimaging literature that implicates abnormalities of certain brain networks in the pathophysiology of depression (specifically, the dorsal and subgenual ACC, amygdala, hippocampus, and ventral striatum).[59–63] The sgACC in particular has been a frequently studied area of interest in MDD and ketamine. In healthy male volunteers, rsfMRI and phMRI done during ketamine infusion found significant reduction in sgACC coupling with hippocampus, RSC, and thalamus. Immediate reductions in sgACC blood flow and focal reductions in OFC blood flow strongly predicted dissociation.[40,64] However, some other imaging studies of the sgACC seem to provide contradictory results. NIMH studies using PET 120 min post infusion have found that increased metabolism in the sgACC was positively correlated with improvements in depression scores post ketamine.[37] However, a different PET study in MDD found no change in sgACC metabolism post ketamine.[35] These inconsistent results not just indicate the need for larger, more controlled studies, but also may suggest that the timing of the scan matters. Changes in sgACC 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 diminished 230 minutes after infusion. Following this, perhaps sgACC activation decreases during and immediately after ketamine, but changes a few hours post infusion.

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 aversive visceromotor state on cognition and self—a hallmark of depression.[40] Related, one study found that ketamine may dampen brain regions involved in rumination via reduction

of the functional connectivity between the pACC and the dPCC.[42] Ketamine also disrupts the "hyperconnectivity" of the DMN (e.g., by decreasing connectivity between the mPFC and DMN) found in patients with MDD. DMN hyperconnectivity is commonly associated with increased rumination.[31,44] This study also found decreased connectivity between the left and right executive control networks, which are involved in internal and external sensory processing.[65] One ongoing study (ClinicalTrials.gov ID: NCT02544607) aims to investigate this further in patients with TRD before and after a ketamine infusion. In other words, these studies suggest that ketamine causes a "disconnect" in several circuits related to affective processing, perhaps by shifting focus away from the internal states of anxiety, depression, and somatization and more towards the perceptual changes induced by ketamine. Similarly, during an emotional task, ketamine attenuated responses to negative pictures, suggesting that the processing of negative information is specifically altered in response to ketamine.[50] By taking the focus off of "oneself" and placing the focus on other stimuli, perhaps ketamine decreases awareness during negative experiences.

Perhaps most interesting is ketamine's effects on brain connectivity as it relates to self-monitoring behaviors. Reduced connectivity between the pACC and dPCC was associated with increased dissociation during infusion, and reduced activation in the left superior temporal cortex was associated with impaired self-monitoring.[42, 54] Such self-monitoring is disruptive to patients with psychotic illness—especially those with chronic symptoms of psychosis. However, perhaps the transient dissociation experienced by depressed patients during a ketamine infusion is essential for dampening what could be considered as hyperactive self-monitoring that results from depressive illness.

During ketamine administrations, subjects experience emotional blunting, which may be associated with reduced limbic responses to emotional stimuli.[52, 53] Perhaps by decreasing the activity of deep limbic structures (thought to be involved in the pathophysiology of depression, such as the amygdala), ketamine acutely alleviates 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 may be especially important, as reward areas in MDD have been characterized by decreased subcortical and limbic activity and an increased cortical response to reward paradigms.[66] In resting-state scans, BOLD activation in the cingulate gyrus, hippocampus, insula, thalamus, and midbrain increased after ketamine.[41] In addition, ketamine increases neural activation in the bilateral MCC, ACC, and insula, as well as the right thalamus.[48] Activation of these areas is consistent with activation of reward processing areas, suggesting that ketamine may play a role in activation of reward neurocircuitry.[66]

Though convergence onto a specific brain area is elusive in 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 had reduced global connectivity in the PFC and increased connectivity in the posterior cingulate, precuneus, lingual gyrus, and cerebellum compared to healthy volunteers; responders had increased connectivity in the lateral PFC, caudate, and insula post ketamine.[23] Perhaps this represents ketamine's ability to reclaim frontal control over deeper limbic structures, thus resulting in the ability to have

more cognitive control of emotions that enables a decrease in depression symptoms. Similarly, TRD patients had reduced insula and caudate responses to positive emotions at baseline compared to healthy volunteers, which normalized in the caudate post-ketamine.[22] 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.[23,29] Improvements are correlated with increased metabolism in the hippocampus, dACC, and decreased metabolism in the OFC.[33] Yet another group found that improvements correlated with increased metabolism in the STG/MTG and cerebellum, and decreased metabolism in the parahippocampal gyrus and inferior parietal cortex.[35] 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 extant literature, because the majority of published studies are from healthy volunteers. Second, most of the task-based healthy volunteer studies used male volunteers only. Third, most of the studies completed have very low numbers of participants; the depression study with the most number of participants was still 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 chronologically parse out which findings occur due to ketamine's mechanism alone versus which changes are due to alterations in mood post ketamine. This may be especially relevant to ketamine imaging due to its rapid antidepressant effect (within hours). Fifth, although most studies used racemic ketamine, several others used the S-ketamine enantiomer. This may be an important difference because S-ketamine may have greater affinity to the NMDA receptor than its enantiomer, R-ketamine.[67] Finally, it is important to note that most depression studies use subanesthetic ketamine doses of 0.5mg/kg over 40 minutes because this dose effectively treats depression. However, many studies with non-depressed patients 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 aforementioned limitations. This may be particularly helpful as it may uncover new working models of the biological substrates of depression and enable new drug discovery. Specifically, based on this review, future studies may focus on ketamine's action in the sgACC, PCC, PFC, and hippocampus as regions of interest. Furthermore, it has been suggested that depression is the result of underactive prefrontal and limbic mood regulation networks and over-reactive subcortical limbic networks involved in emotional and visceral responses.[68] Perhaps these network abnormalities in depression—and their resulting improvements with treatment—can be further elucidated with 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.[31] Given this, ketamine's potential use for uncovering important advances in depression research are very promising.

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Abbreviations

ACC	anterior cingulate cortex
AD	axial diffusivity
ASL	arterial spin labeling
BOLD	blood oxygen level dependent
CADSS	Clinician Administered Dissociative States Scale
dACC	dorsal anterior cingulate cortex
DB	double-blind
dlPFC	dorsolateral prefrontal cortex
DMN	default mode network
DTI	diffusion tensor imaging
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
GABA	gamma-Aminobutyric acid
GBCr	global brain connectivity signal regression
Glx	glutamate+glutamine

HV	healthy volunteer
MCC	midcingulate cortex
MD	mean diffusivity
MDD	major depressive disorder
MEG	magnetoencephalography
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MTG	middle temporal gyrus
NMDA	N-methyl-D-aspartate
RD	radial diffusivity
OFC	orbitofrontal cortex
OL	open label
PBO	placebo
PCASL	pseudocontinuous arterial spin labeling
phMRI	pharmaco magnetic resonance imaging
PFC	prefontal cortex
rCBF	regional cerebral blood flow
rCMRGlu	regional cerebral metabolic rate of glucose
RSC	retrosplenial cortex
rsfMRI	resting state functional magnetic resonance imaging
rsfcMRI	resting state functional connectivity magnetic resonance imaging
sgACC	subgenual anterior cingulate cortex
SHAPS	Snaith–Hamilton Pleasure Scale
STG	superior temporal gyrus
TRD	treatment resistant depression
vlPFC	ventrolateral prefrontal cortex
WM	white matter

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Table 1

Ketamine Neuroimaging Studies in Depression (MRI, MEG, Spectroscopy)

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
Murrough 2015[22]	fMRI – 2 scans, pre-(baseline) and post-(24 hours) ketamine scans with two 8-min facial emotional perception tasks OL ketamine given after baseline scan	*n*=18 with TRD and *n*=20 matched HVs Racemic ketamine; 0.5mg/kg over 40 min	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 PBO comparator; only scanned at 24 hours post ketamine (no other time points); HVs only completed baseline
Abdallah 2016[23]	rsfMRI — 2 scans pre and post ketamine, using GBCr to quantify functional connectivity measured by resting-state BOLD Pre-(within 1 week of ketamine) and post-(24 hours) OL ketamine rsfMRI scans	*n*=18 MDD (medication-free); *n*=25 HV Racemic ketamine; 0.5mg/kg over 40 min	Ketamine significantly 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 med free period (1 week); Small *n*; HVs only completed baseline scan
Downey 2016[24]	3T phMRI – from 5 min before to 40 min during infusion Randomized (ketamine vs. lanicemine vs. PBO), DB, parallel group design at 2 different sites. Clinical ratings completed at 24 hour and between day 8–11 post-ketamine	*n*=60 MDD (*n*=20 lanicemine, *n*=21 ketamine, *n*=19 PBO) Racemic ketamine; 0.5mg/kg over 60 min	Both ketamine and lanicemine increased BOLD signal in the sgACC; activation predicted depression improvements at 24 hours and 1 week post-ketamine. No significant change in BDI was observed post ketamine.	No comparator HV group; Two sites (two different 3T machines, different clinician raters); Significant place response; Neither ketamine nor lanicemine groups significantly improved
Abdallah 2015[25]	3T MRI – 2 scans, at baseline and 24-hour post-ketamine vs. midazolam Randomized, DB, midazolam-controlled trial of ketamine	*n*=24 with TRD; all medication-free; (*n*=13 ketamine; *n*=6 midazolam) Racemic ketamine; 0.5mg/kg over 40 min	Significant association between smaller left hippocampal volume at baseline had a greater antidepressant response to ketamine at 24 hours post-infusion	No HV comparator; small *n*; no specific hippocampal regions targeted.
Vasavada 2016[26]	DTI MRI – 1 scan ≤1-week pre-ketamine; measured the following as predictors of response: FA, RD, AD, and MD Clinical treatment with OL ketamine	MDD patients (*n*=10) after ketamine (*n*=4 nonresponders, *n*=6 responders); HVs (*n*=15) did not receive ketamine Racemic ketamine; 0.5mg/kg over 40 min	Improvements in depressive symptoms at 24 hours post-ketamine correlated with greater FA in the cingulum (projecting to the PFC), decreased MD and RD in forceps minor, and decreased RD in the frontostriatal track.	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*
Salvadore 2009[27]	MEG – 1 recording 1–2 days pre-ketamine, during rapid presentation of affective stimuli (fearful face pictures) DB, PBO controlled ketamine study	*n*=11 with MDD; all medication free; and *n*=11 HV Racemic ketamine; 0.5mg/kg over 40 min	Increased baseline (pre-ketamine cortical activity) to affective stimuli (fearful faces) in the ACC (especially the pgACC) and decreased amygdala activation predicted antidepressant response to ketamine at 4 hours post-infusion.	Small *n*; Baseline MEG only; Evidence for decreased right amygdala activity is very weak.
Salvadore 2010[28]	MEG – 2 recordings, during a working memory N-back task at 1–3 days prior to ketamine infusion and again post-ketamine DB, PBO controlled ketamine study	*n*=15 with MDD; all were medication free Racemic ketamine; 0.5mg/kg over 40 min	1. Subjects with the least pre-ketamine engagement of the pgACC with increasing memory load (2 vs 1 back) showed the greatest antidepressant improvement to ketamine at 4 hours post infusion 2. Those with the lowest coherence between pgACC and left amygdala	Small *n*; Not generalizable (only medication-free inpatients); Baseline MEG only

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
			were most likely to respond to ketamine High pgACC activity in response to emotional activity and low pgACC in response to increased cognitive demands predicts an antidepressant response to ketamine. This is relatively normal, so preserving normality predicts better outcomes	
Nugent 2016[29]	MEG – 2 recordings, pre- and post-ketamine OL ketamine	*n*=13 MDD Racemic ketamine; 0.5mg/kg over 40 min	Decreased connectivity between amygdala and insulo-temporal region post-ketamine	Small *n*; Riluzole given before post-ketamine scan; MEG used to study subcortical regions despite low spatial resolution
Cornwell 2012[32]	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 OL ketamine; all patients then received a dose of riluzole or placebo at 5–6 hours post ketamine	*n*=20 with MDD; all were medication free Racemic ketamine; 0.5mg/kg over 40 min	In ketamine responders (at 4 hours), there was an increase in somatosensory cortical excitability responses (a measure of synaptic plasticity) compared to nonresponders. There was also a positive correlation between increased cortical excitability and norketamine levels.	OL ketamine; Riluzole vs. PBO were administered just prior to MEG scanning
Lally 2015[33]	18F-FDG PET – 2 scans at baseline (1–3 days prior to ketamine) and post-ketamine (beginning 2 hours post-ketamine and lasting through 3.5 hours post ketamine) to measure the rCMRGlu OL ketamine followed by 1 month of oral riluzole or PBO; anhedonia assessed with SHAPS	*n*=20 with TRD; all medication free Racemic ketamine; 0.5mg/kg over 40 min	Decreased anhedonia was associated with increased rCMRGlu in the hippocampus and dACC, and decreased rCMRGlu in the OFC	Post-hoc; riluzole confounder; no PBO comparator
Ballard 2015[34]	FDG PET -2 scans, at baseline (1–3 days prior to ketamine) and 2 hours post-ketamine and lasting about 1.5 hours. OL ketamine	*n*=19 with TRD; all medication free Racemic ketamine; 0.5mg/kg over 40 min	Suicidal ideation was correlated with increased metabolism in the infralimbic cortex at baseline, and decreased suicidal ideation post-ketamine were correlated with decreased regional cerebral glucose metabolism in the infralimbic cortex	Post-hoc; baseline PET scans occurred on a different day than baseline suicide measures; SI measured on a 0–4 scale in HDRS.
Carlson 2013[35]	18F-FDG PET – 2 scans, at baseline (1–3 days before ketamine) and 120-minutes post-ketamine OL ketamine	*n*=20 with TRD; all were medication free Racemic ketamine; 0.5mg/kg over 40 min	Whole brain glucose metabolism didn't significant change post-ketamine. Decreased metabolism occurred in the right habenula, increased metabolism in the right amygdala, and no change in sgACC metabolism were found. These results were not correlatated with change in MADRS scores. Clinical improvement significantly correlated with increased metabolism in the STG, MTG, and cerebellum, and with decreased metabolism in the parahippocampal gyrus, inferior parietal cortex, and the more ventral and medial loci within the STG/MTG.	Small *n*; OL; no HV comparators; post-hoc clinical correlations.
Lally 2014[36]	18F-FDG PET – 1 scan, 120 min post-infusion to measure rCMRGlu; metabolism Randomized, DB, crossover, PBO controlled study; two	*n*=21 bipolar depressed patients maintained on either lithium or depakote for ≥4 weeks prior to study	Decreased anhedonia was related to increased rCMRGlu in the dACC and putamen. Largest improvement in depressive symptoms correlate with largest metabolic increase in	Small *n*; No baseline scans; Post-hoc analysis; Heterogeneity of bipolar types I and II within sample

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
	infusions given two weeks apart	Racemic ketamine; 0.5mg/kg over 40 min	right ventral striatum post-ketamine compared to placebo.	
Nugent 2014[37]	18F-FDG PET – 1 scan 120 min post-infusion to measure rCMRGlu; metabolism Randomized, DB, crossover, PBO controlled study; two infusions given two weeks apart	*n*=21 bipolar depressed patients maintained on either lithium or depakote for ≥4 weeks prior to study Racemic ketamine; 0.5mg/kg over 40 min	Bipolar patients had significantly lower glucose metabolism in the left hippocampus following the ketamine infusion compared to after PBO. Patients with the largest improvement in depression symptoms had the largest metabolic increase (rCMRGlu increase) in the right ventral striatum post-ketamine compared to PBO. Metabolism of the sgACC was positively correlated with improvements in depression scores following ketamine.	Small *n*; No HV comparator; No baseline scans; Heterogeneity of bipolar types I and II within sample
Milak 2016[15]	3T ^{1}H MRS. Six 1H MRS data frames were acquired (approximately 13 min each); one pre-ketamine, four during ketamine, and one post-ketamine	*n*=11 med free MDD patients (8 female); 8 subjects' data used for MRS Racemic ketamine; 0.5mg/kg over 40 min	Rapid increases in the mPFC in both Glx (glutamate+glutamine) and GABA were observed during ketamine infusion, but dissipated by the end of the infusion.	Small *n*

Table 2

Resting State Scans and Non-Task Scans (Non-Depressed Populations)

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
Deakin 2008[40]	phMRI BOLD – starting 8 minutes and 8 minutes during the infusion Two experiments: DB, PBO controlled, randomized, crossover, counterbalanced orders. First experiment was ketamine vs. PBO; second experiment was ketamine following pre-treatment (2 hours before) with lamotrigine 300mg vs. PBO	Male right handed healthy volunteers in experiment 1 (n=20) and experiment 2 (n=19) Racemic ketamine; 0.26mg/kg for 1 minute bolus, then 0.25mg/kg/hr maintenance	Ketamine caused an immediate and focal reduction in sgACC and OFC blood flow; this strongly predicted dissociation (r=0.90 with CADSS scores). Furthermore, ketamine increased activity in the mid-posterior cingulate cortex, thalamus, and temporal cortical regions. Lamotrigine prevented many of the BOLD signal changes.	
Stone 2015[41]	3T phMRI—15-minute scan with ketamine starting at minute 5 OL within-subjects design	Male healthy volunteers (n=13), ages 18–50 years old Racemic ketamine; 0.26mg/kg for 20 seconds followed by 0.42mg/kg/hr	Ketamine led to decreases in BOLD response in sgACC 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
Doyle 2013[71] Shcherbinin 2015[72]	rs-phMRI[71] and ASL[72] Randomized, PBO controlled, partial crossover design. Four scanning visits separated by at least 2 weeks apart. Sessions were as follows: PO risperidone/IV ketamine; PO lamotrigine/IV ketamine; PO PBO/ ketamine; PO PBO/IV saline	Male healthy volunteers (n=16 completers) Racemic ketamine; Bolus ~0.12mg/kg for the first minute, then 0.31mg/kg/hr for about 20 min (BOLD resting state occurred for 15 min and ASL scanning occurred for 5 more min after start of infusion)	phMRI: Pre-treatment 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, significantly increased the ketamine induced perfusion changes.	Pharmacological dose – response curve for ketamine is only based on a few subjects.
Scheidegger 2012[43]	3T rsfMRI—2 scans, at baseline and 24 hours post infusion. Randomized, DB, PBO controlled, crossover study. Ketamine and PBO infusions separated by 10 days.	Healthy volunteers (n=17) IV S-ketamine; 0.25mg/kg over 45	Ketamine decreases resting state functional network connectivity in healthy subjects; specifically, ketamine disrupted connectivity between the pgACC and the mPFC and the bilateral dmPFC) 24 hours after ketamine.	Healthy controls were used to make inferences about networks commonly disrupted in MDD. As such, inferences about antidepressant effect could not be made.
Bonhomme 2016[44]	3T rsfMRI – 1 scan during ketamine infusion Ketamine dose gradually increased to reach deeper levels of sedation during the scanning session.	Healthy volunteers (n=8) analyzed Racemic ketamine; dose varied based on depth of sedation	Increased depth of sedation with increased ketamine doses correlated significantly with decreased connectivity in the mPFC with the DMN. Thalamo-cortical connectivity remains relatively preserved, but	Small n; heart rate and respiration not directly taken into account in analysis (though CO2 was). Multiple-seed ROI approach may bias results. Order of conditions was not randomized due to

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
			corticocortical connections were disrupted with ketamine.	ketamine's long recovery time.
Grimm 2015[45]	3T rsfMRI – 1 scan post infusion DB, PBO-controlled, randomized; single IV infusion	Healthy volunteers (n=24); 12 males and 12 females Racemic ketamine; 0.5mg/kg over 40 min	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.
Hoflich 2016[48]	3T rsfMRI – 1 scan during infusion DB, PBO-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 and 15 females (Because of scanner trouble, full data was available for only 5 patients) S-ketamine; 0.11mg/kg 1 min bolus followed by 0.12mg/kg over 19 minutes	Compared to PBO, ketamine increases neural activation in the bilateral MCC, ACC, and insula, as well as the right thalamus.	Pharmacological dose – response curve for ketamine is only based on a few subjects.
Wong 2016[64]	3T rsfMRI—1 scan, 15 minute scan with IV ketamine started at the 5 minute point	Male healthy volunteers (n=13) Racemic ketamine; 0.26mg/kg rapid bolus over 20 seconds and then 0.42mg/kg/hr infusion	Following ketamine, there was a significant reduction in sgACC coupling with the hippocampus, RSC, 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 5min after infusion, and antidepressant effects are typically not seen for 1–2hrs post infusion.
Joules 2014[70]	3T MRI – 2 scans, pre and post infusion DB, PBO controlled, crossover design of four sessions, each separated by 10 days. IV session was in the scanner. Sessions were as follows: PO PBO/IV ketamine, PO PBO/IV saline, PO Risperdal, IV ketamine, and PO lamotrigine/IV ketamine	Male healthy volunteers (n=16), all right handed Racemic ketamine; IV form given as 0.12mg/kg over 1 minute followed by 0.31mg/kg/hr	Ketamine significantly altered whole brain connectivity compared to PBO. Specifically, ketamine produced a shift from cortically-centered to subcortically-centered patterns of connections. This effect was modulated by pre-treatment with risperidone, but not lamotrigine, suggesting that the connectivity pattern shifts are due to NMDAR 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.
Niesters 2012[38] Khalili-Mahani 2014[73] (Biomarker study)	3T rsfMRI – 1 scan followed by PCASL measurement First study: Single blind, randomized, PBO 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	Male healthy volunteers (n=12) S-ketamine; 20mg/70kg/hr for 1 hour, then 40mg/70kg/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).	It is unclear what (if any) scrubbing methods were used for rsfMRI (Niesters 2012).

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
	Second study was a biomarkers study: examine biomarkers on the extent to which ketamine infusion mimics a stress response		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 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	
Lahti 1995[39]	PET/MR – 2 scans, pre- and post-infusion DB, PBO controlled; Four administrations occurred over 2 weeks at the following doses: ketamine at three different doses vs. placebo	Patients with schizophrenia (n=9) maintained on stable haloperidol doses Racemic ketamine; 0.1 mg/kg, 0.3mg/kg, and 0.5mg/kg	Ketamine significantly increased rCBF in the ACC and reduced rCBF in the visual cortex and hippocampus.	Small n; Study was published in 1995.
Taylor 2012[13]	3T proton MRS PBO-controlled, parallel group design; IV ketamine	Healthy volunteers (n=17); 11 male and 6 female Racemic ketamine; 0.5mg/kg over 40 minutes	No significant difference between ketamine and PBO in Glx or Glutamate concentrations in the ACC.	The study only tested one voxel in the sgACC, therefore changes in Glu/Glx in other parts of the brain may go undetected. n=11. H-MRS does not measure glutamate release directly and instead measures glutamine, which is an index of turnover of synaptic glutamate involved in neurotransmission.
Rowland 2005[74]	4T proton MRS DB, PBO-controlled, crossover; 2 scanning sessions separated by 1–2 weeks	Male healthy volunteers (n=9 analyzed) Racemic ketamine; 0.27mg/kg loading dose over 10 minutes, then 0.00225mg/kg/min maintenance for the rest of the experiment (up to 2 hours)	Ketamine significantly increased ACC glutamine (a putative marker of glutamate release) compared to PBO.	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.
Kraguljac 2016[46]	3T 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 and 5 females Racemic ketamine; 0.27mg/kg bolus over 10 min then 0.25mg/kg/hr for approximately 60 minutes	Ketamine induced an increase in hippocampal Glx, a decrease in frontotemporal and temporo-parietal 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.

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)	Limitations
Muthukumaraswamy 2015[47]	MEG – Two different experiments Exp. 1: Two MEG experiments on 2 days (ketamine vs. placebo); 5 min resting state MEG, then infusion Exp. 2: 10 minute resting state MEG	Male healthy volunteers (n=19 in Exp. 1 and n=6 in Exp. 2) Racemic ketamine Exp 1: 0.25mg/kg bolus over 1 min, then 0.375mg/kg/hr maintenance infusion for 10 minutes Exp 2: Same dose as Exp. 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 (DCM) approach used here found significant frontoparietal connectivity changes. However, power correlations fail to replicate this result.

Table 3

Task-Based Scans (Non-Depressed Populations)

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all p<0.05 unless otherwise noted)	Significant Limitations
Francois 2016[75]	3T fMRI reward task DB, randomized, PBO-controlled study; a reward task occurred at 40 minutes after the start of the infusion.	Healthy volunteers (n=24) Racemic ketamine; 0.5mg/kg over 40 min	Ketamine significant attenuated the ventral striatum response to the task, particularly the nucleus accumbens, compared to PBO.	BOLD data was not coregistered to each subject's individual T1 weighted scan; this could pose a problem with coregistering small regions such as the NAc and ventral striatum.
Scheidegger 2016[51]	3T fMRI One baseline scan 2 days prior to the OL 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; 0.12mg/kg bolus at 25 minutes prior to task, followed by a continuous infusion of 0.25mg/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-back in their working memory task, and results may be a result of a ceiling effect.
Driesen 2013[57]	3T fMRI Subjects received PBO followed by ketamine while completing working memory tasks in the scanner.	Right-handed healthy volunteers (n=22); 14 were male and 8 were female Racemic ketamine; 0.23mg/kg for a 1 minute bolus, then 0.58mg/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.
Nagels 2011[58]	3T fMRI BOLD DB, PBO-controlled, counterbalanced study. Subjects completed verbal fluency tasks during the infusions in the scanner.	Male healthy volunteers (n=15) S-ketamine; 8mg bolus for 5 minutes, then continuous infusion at 0.01mg/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[54]	1.5T fMRI BOLD DB, PBO controlled, randomized study. Two scan sessions separated by at least 1 day. Subjects completed a verbal task.	Male healthy volunteers (n=8) Racemic ketamine; 0.23mg/kg bolus, then 0.64mg/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 and instead measures glutamine, which is an index of turnover of synaptic glutamate involved in neurotransmission. No female participants
Fu 2005[78]	1.5T fMRI BOLD DB, PBO-controlled, crossover study. Infusions and scans were separated by at least 1 day. Subjects completed	Male healthy volunteers (n=10) Racemic ketamine; bolus of 0.23 mg/kg over 30 seconds, then	Ketamine did not significantly impair task performance compared to PBO. However, during ketamine, greater activations occurred in areas related to verbal fluency	Small *n*; No female participants.

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all p<0.05 unless otherwise noted)	Significant Limitations
	a verbal fluency task with two conditions: easy and hard.	0.65mg/kg for approximately 1 hour	(ACC, prefrontal, and striatal regions) during the easy vs. hard condition.	
Honey 2004[56] (working memory) Honey 2005[56] (episodic memory)	3T fMRI BOLD DB, PBO controlled, randomized, within subjects comparison study. Three sessions occurred: one was PBO and two were at different doses of IV ketamine (7 days apart). Subjects completed a memory tasks	Healthy volunteers (n=12) Racemic ketamine; infusions was done to reach a ketamine level of 50ng/ml or 100ng/ml, depending on which randomization day. 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 PBO 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 PBO.	
Rogers 2004[79]	3T fMRI BOLD Ketamine was administered at subanalgesic (50ng/mL) and analgesic/ subanesthetic (200ng/mL) concentrations to subjects in the MRI scanner compared to PBO. Each infusion was 24 minutes and was administered as saline-ketamine-ketamine. Subjects experienced noxious stimuli spread throughout the experiment.	Male healthy volunteers (n=8); average age was 28 years old Racemic ketamine; Ketamine was administered at increasing doses in a stepwise manner following PBO as follows: 50 ng/mL was administered at a rate of 0.18mg/kg/hr over 24 minutes; 200ng/mL was administered at a rate of 0.71mg/kg/hr over 24 minutes	High doses of ketamine produced a significant decrease in pain scores compared to PBO. This decrease correlated with significantly 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.
Musso 2011[77]	3T fMRI BOLD with simultaneous EEG Randomized, DB, PBO 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; 0.1mg/kg over the first 5 minutes, then 0.015625mg/kg/min for up to 1 hour in the scanner (with reductions in admin 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 PBO.	No female participants.
Shaw 2015[76]	MEG Single blind, PBO controlled, crossover study. Infusions scheduled at least 2 weeks apart to allow for washout. 90 minute MEG scan with visuomotor task was completed during pre-	Male healthy volunteers (n=18 with data available); ages ranged from 18–45 years old Racemic ketamine; 0.25mg/kg bolus for the first minute, then 0.25mg/kg over 40 minutes	Ketamine-mediated NMDAR antagonism reduced peak gamma frequency in the visual cortex and increased the amplitude of gamma oscillation in the motor and visual cortices. Furthermore, beta frequency event related desynchronization was reduced in both motor and visual cortices.	No female participants.

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all p<0.05 unless otherwise noted)	Significant Limitations
	ketamine and ketamine infusion in order to measure changes in oscillatory dynamics.			

Table 4

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

Author(s)	Scanning Details and Study Design	Subjects and Ketamine Details	Significant Findings* (all $p<0.05$ unless otherwise noted)
Lehmann 2016[42]	3T fMRI – 1 scan with IAPS task, and rsfMRI DB, PBO-controlled, two-arm study. Arm 1: Baseline scan and 24-hour follow-up scan post-PBO. 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; 0.25mg/kg	Resting State: Ketamine reduced functional connectivity between the pACC and the dPCC; this reduction in connectivity correlated significantly with increased psychotomimetic effects during the infusion. IAPS task: Increased BOLD reactivity in the pgACC (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[50]	3T fMRI during task and rsfMRI One baseline scan and one scan during an OL 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; 0.12mg/kg bolus followed by continuous 0.25mg/kg/hr infusion	Ketamine attenuated task-induced activation in the amygdalo-hippocampal complex during the emotional 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[7] 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.
Abel 2003[52] and Abel 2003[53]	1.5T fMRI during task and rsfMRI Randomized, DB, PBO controlled; 2 scans separated by at least 1 week during resting state and cognitive/emotional facial recognition task	Male healthy volunteers (n=8) Racemic ketamine; 0.23mg/kg bolus over 5 minutes, then 0.5mg/kg for 40 more minutes	Ketamine significantly decreased activation in the middle occipital gyrus and precentral gyrus compared to PBO. In the PBO group, several brain areas (amygdala, visual processing areas and cerebellum) were significantly activated during fearful faces; ketamine only significantly activated the left superior occipital gyrus during fearful faces.