Brain-based correlates of antidepressant response to ketamine: a comprehensive systematic review of neuroimaging studies

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Ketamine is an effective antidepressant, but there is substantial variability in patient response and the precise mechanism of action is unclear. Neuroimaging can provide predictive and mechanistic insights, but findings are limited by small sample sizes. This systematic review covers neuroimaging studies investigating baseline (pre-treatment) and longitudinal (post-treatment) biomarkers of responses to ketamine. All modalities were included. We performed searches of five electronic databases (from inception to April 26, 2022). 69 studies were included (with 1751 participants). There was substantial methodological heterogeneity and no well replicated biomarker. However, we found convergence across some significant results, particularly in longitudinal biomarkers. Response to ketamine was associated with post-treatment increases in gamma power in frontoparietal regions in electrophysiological studies, post-treatment increases in functional connectivity within the prefrontal cortex, and post-treatment increases in the functional activation of the striatum. Although a well replicated neuroimaging biomarker of ketamine response was not identified, there are biomarkers that warrant further investigation.

Introduction

Major depressive disorder and bipolar depression are associated with substantial disability and significantly reduced quality of life.[1] Conventional treatments for these disorders (such as selective serotonin reuptake inhibitors, and serotonin and norepinephrine inhibitors) are moderately effective but have substantial limitations including low rates of remission (particularly in people with treatment-resistant depression), a similar mechanism of action (modulation of monoamines), and a delayed onset of action requiring weeks to achieve significant therapeutic effects.[2,3] The discovery of rapid antidepressant effects from (R,S)-ketamine (ketamine) and its (S)-ketamine enantiomer (esketamine) can potentially overcome some of the limitations of conventional treatments as ketamine and esketamine have been shown to be effective even in individuals with treatment-resistant depression with an onset of action within hours.[2,3]

Nevertheless, there is substantial individual variability in the response to ketamine or esketamine, with most studies reporting response rates between 35% and 60%.[2,4] Currently, there are no established clinical or biological predictors of response to ketamine or esketamine and, as a result, clinical use of these rapid-acting agents still relies on a trial-and-error approach. Previous studies have investigated clinical variables and biomarkers associated with response to ketamine or esketamine but mostly with small sample sizes and methodological heterogeneity that have led to mixed and inconclusive results. For example, there is conflicting evidence whether clinical variables such as a history of alcohol use disorder (personal history, family history, or both),[5–8] higher BMI,[5,7,9–11] and the absence of a history of suicide attempt or psychiatric hospitalisation[5,8,10,12,13] are linked to better response to ketamine or esketamine. Similarly, blood-based biomarkers have not yet proven useful in predicting the treatment response to ketamine or esketamine.[4] A systematic review and meta-analysis found that the most consistent association in blood-based biomarkers was longitudinal treatment-associated increases in blood brain-derived neurotrophic factor (BDNF) and response to ketamine or esketamine,[4] albeit with a modest effect size (Cohen's d=0·26, 95% CI 0·03–0·48)[4] that, by itself, is unlikely to be clinically actionable.

The current limited ability to predict response to ketamine or esketamine with clinical variables and blood-based biomarkers provides further impetus to examine the usefulness of other predictive modalities that might more directly reflect illness-related dysfunction in the brain. Several neuroimaging modalities can be applied to study the structure and function of the CNS, each with intrinsic strengths, limitations, and a different specificity or sensitivity for investigating specific aspects of the CNS (table 1).[14] Structural neuroimaging, such as structural MRI (sMRI) and diffusion tensor imaging (DTI), obtains anatomical data with high spatial resolution, whereas functional MRI (fMRI) can measure brain activity as well as functional connectivity within and between brain regions. Molecular imaging, defined as "the use of neuroimaging techniques to detect and characterize molecular processes other than water",[15] include approaches such as PET and magnetic resonance spectroscopy (MRS), which enable the examination of specific molecules within the CNS and can provide unique neurochemical information but have limited spatial and temporal resolution. Finally, electrophysiological modalities, such as magnetoencephalography (MEG) and electroencephalography (EEG), measure the brain's electrical activity with high temporal resolution; however, these modalities have limited spatial resolution. A summary of the available studies on structural and functional neuroimaging correlates of

	Mechanism or measurement	Advantages	Disadvantages
Structural neuroimaging: modalities specialised in visualisation and analysis of static anatomical data			
Structural MRI	Produces a strong magnetic field that aligns the body's natural protons and then detects their magnetic properties; measures the amount of water in different tissues to produce anatomical images	High spatial resolution (millimetres), widely available, and does not expose patients to ionising radiation	Potential physiological and motion artifacts, contraindications (eg, metallic devices or dental devices and pacemakers), and potentially uncomfortable
Diffusion tensor imaging	Uses MRI techniques to detect the pattern of water diffusion, which is quantified by measures such as fractional anisotropy, radial diffusivity, and apparent diffusion coefficient	Comprehensive assessment of white matter organisation, high spatial resolution (millimetres), and does not expose patients to ionising radiation	Potential physiological and motion artifacts, contraindications (eg, metallic devices or dental devices and pacemakers), and potentially uncomfortable
fMRI: modalities that use MRI to estimate, at rest or during tasks, functional connectivity and activity of brain regions			
Resting-state or task-based fMRI	Detects changes in blood oxygenation (through measurement of deoxyhaemoglobin concentration) to estimate changes in neuronal activity	High spatial resolution (millimetres), widely available, and does not expose patients to ionising radiation	Potential physiological and motion artifacts, contraindications (eg, metallic devices or dental devices and pacemakers), and potentially uncomfortable
Arterial spin labelling	Uses fMRI techniques to label arterial blood water protons, a freely diffusible intrinsic tracer; primarily used to measure cerebral blood flow	Comprehensive assessment of cerebral blood flow, reliable and reproducible, no exposure to ionising radiation or other exogenous contrasts	Poor standardisation of arterial spin labelling techniques across studies, low signal-to-noise ratio, and contraindications (eg, metallic or dental devices and pacemakers)
Electrophysiological modalities: modalities that non-invasively examine neural electrical activity			
MEG	Detects magnetic fields generated by the electrical currents to study the brain electrical activity; one of the advantages of MEG over EEG is that MEG provides the tridimensional location of the electrical activity	High temporal resolution (milliseconds), not affected by signal distortion from the scalp and cerebrospinal fluid, no need to place electrodes on the scalp	Low spatial resolution (centimetres), high cost and low availability, and contraindications (eg, metallic or dental devices and pacemakers)
EEG	Detects the electrical activity of the brain through non-invasive electrodes placed on the scalp; the currents measured are divided into bands, which are believed to represent different functional components	High temporal resolution (milliseconds), low cost and widely available, and portable	Low spatial resolution (centimetres), does not accurately assess deep brain structures, and lengthy preparation time
Molecular modalities: modalities that detect and analyse specific molecules (other than water)			
Magnetic resonance spectroscopy	Detects radio frequency electromagnetic signals produced by the atomic nuclei within the molecules; different molecules can be examined and, as a result, tissue metabolites are identified and quantified in vivo	High sensitivity to specific molecules, provides metabolic data, and does not expose patients to ionising radiation	Low spatial resolution (centimetres), low temporal resolution (minutes), and contraindications (eg, metallic or dental devices and pacemakers
PET	Detects radiation issued by a radioactive substance (radiotracer) to visualise and measure intracellular biochemical change	High sensitivity to specific molecules, provides metabolic data, and measures variations in the course of the scan	Low temporal resolution (minutes), low spatial resolution, and ionising radiation exposure (injection of radioactive tracer)

EEG=electroencephalography. fMRI=funtional MRI. MEG=magnetoencephalography.

Table 1: **Overview of the main characteristics of structural and functional neuroimaging modalities**

response to ketamine or esketamine could not only allow a better prediction of response to these rapid-acting antidepressants, but also be particularly insightful about neurobiological therapeutic mechanisms of ketamine or esketamine.

Previous reviews partly summarised the available studies examining neural correlates of response to ketamine or esketamine.[16–19] However, some omitted certain neuroimaging modalities, such as electrophysiological studies,[17,19] structural neuroimaging,[18,19] or molecular neuroimaging,[18,19] and they have generally not addressed the convergence or replicability of the findings in independent samples.[16,18,19] As a result, there has not, to our knowledge, been a comprehensive systematic review, which is crucial given the frequently small and heterogeneous studies, often with overlapping samples.

Hence, in this report we have performed a systematic review of all neuroimaging data focused on ketamine or esketamine and response to treatment. In synthesising the data, we have focused on: (1) whether baseline (pre-treatment) neuroimaging biomarkers are associated with antidepressant response to ketamine or esketamine in individuals with major depressive disorder or bipolar depression; and (2) whether longitudinal (post-treatment) neuroimaging biomarkers are associated with antidepressant response to ketamine or esketamine in individuals with major depressive disorder or bipolar depression.

Methods

Search strategy and selection criteria

Searches were conducted in five electronic databases: MEDLINE (PubMed), Embase, PsycINFO, The Cochrane Library, and Web of Science. Searches (conducted by CT) were initially performed on April 8, 2020, and were updated on April 26, 2022. The search terms used are detailed in appendix 1 (p 11). Manual searches (conducted by GCM and MM) and studies obtained through personal communication complemented the electronic searches. Manual searching included the screening of review

See Online for appendix 1

articles, grey literature, included papers, and manuscripts that cited the included papers. This systematic review included studies that (1) examined adults who were aged 18 years or older, (2) included patients who were in a major depressive episode (ie, had active depressive symptoms) in major depressive disorder or bipolar disorder, (3) were published in English (there were no restrictions on dates), (4) reported on clinical trials (open label and randomised controlled) that administered at least one dose of intravenous ketamine, intranasal ketamine, intravenous esketamine, intranasal esketamine, or a combination of these treatments, (5) measured the depressive symptoms using a standardised depression instrument or scale, (6) investigated participants with any structural or functional neuroimaging modality, and (7) measured the association between change in depressive symptoms after ketamine or esketamine treatment, and pre-treatment or post-treatment neuroimaging findings or both (ie, manuscripts that measured pre-treatment or post-treatment neuroimaging findings but did not examine their relationship with changes in depressive symptoms were not included).

See Online for appendix 2

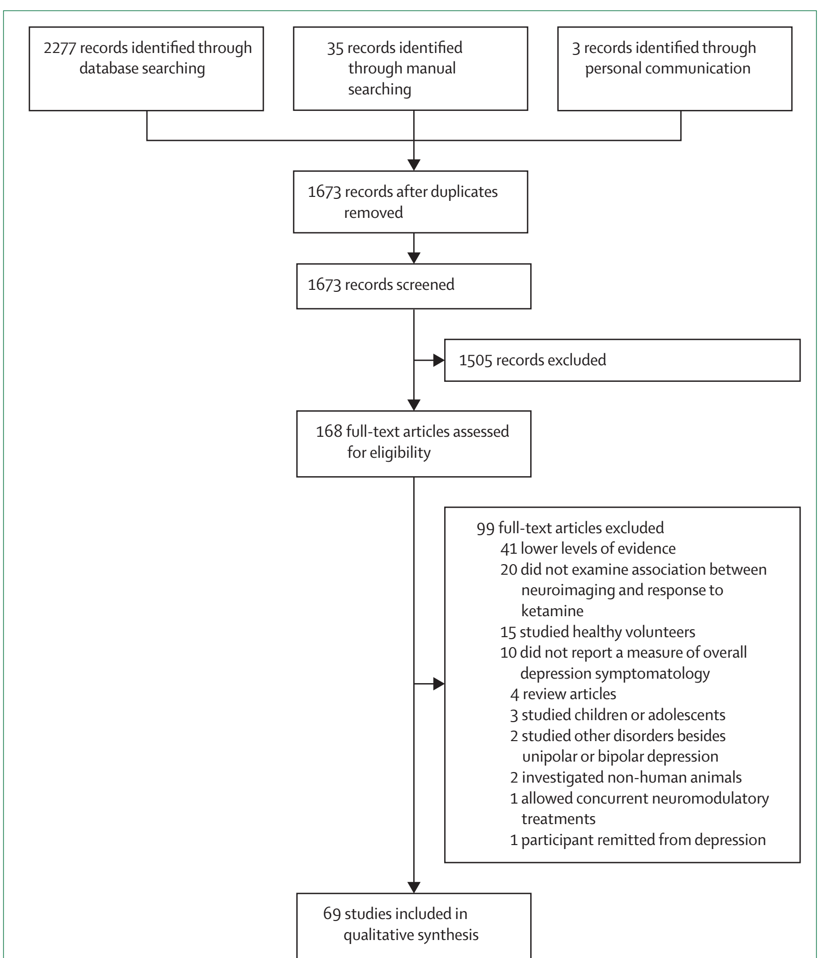

Figure: **Flow diagram of systematic searches for studies assessing neuroimaging biomarkers of antidepressant response to ketamine or esketamine**

We excluded studies that (1) investigated non-human animals, (2) were based solely on conference abstracts, case reports, or case series and editorials,[20] (3) assessed healthy volunteers or individuals with depressive symptoms due to other disorders besides major depressive disorder and bipolar disorder, (4) examined the association of pre-treatment and post-treatment neuroimaging findings with only a specific depressive symptom (eg, suicidality or anhedonia) and not an overall depression scale, (5) included concurrent neuromodulatory treatments including vagal nerve stimulation, electroconvulsive therapy, and repetitive transcranial magnetic stimulation (psychotherapy and concurrent medications were not exclusion criteria), (6) examined individuals with serious or unstable medical comorbidities, and (7) studied individuals in surgical or perioperative settings.

Manuscript selection

The manuscript selection process consisted of an initial screening of titles and abstracts to choose the articles warranting a full-text review, followed by a selection of the manuscripts that were ultimately included in this systematic review. The manuscript selection team consisted of four investigators (GCM, MM, SM, and FSG) and, in each of the two selection phases, a manuscript was independently reviewed by two investigators. Disagreements between the two independent reviewers were resolved by consensus discussion. If two or more manuscripts reported on the same results on the same dataset, we only included the most comprehensive report in this systematic review.

Data extraction and data report

The list of variables extracted for each manuscript and the database used are available in the appendices (appendix 1 pp 1–2; appendix 2 tab 1).

To answer our research questions, the main findings focused on the association between neuroimaging findings (baseline or longitudinal) and change in depressive symptoms in individuals who were treated with ketamine or esketamine. Improvement of depressive symptoms included continuous measures of improvement in depression scores (such as percentage and absolute changes in depression scores), categorical measures of improvement (such as response and remission), or both. The data extraction team consisted of three investigators (GCM, MM, and ID) and the data for each individual study were independently extracted by two investigators.

Results

Our search identified 2315 articles by database searching (2277 articles), manual searching (35 articles; appendix 1 p 1), and personal communication (three articles). After the screening of titles and abstracts, 168 were considered to be potentially eligible for inclusion in this systematic review and, therefore, underwent full-text review (figure).

	Studies (n=69)
Number of neuroimaging modalities used	
One	64 (93%)
Two or more	5 (7%)
Neuroimaging modality used	
Structural modalities	10 (15%)
Structural MRI	7 (10%)
Diffusion tensor imaging	3 (4%)
fMRI	29 (42%)
Resting-state fMRI	19 (28%)
Task-based fMRI	7 (10%)
Arterial spin labelling	3 (4%)
Electrophysiological modalities	20 (29%)
Resting-state MEG	4 (6%)
Task-based MEG	8 (12%)
Resting-state (awake) EEG	4 (6%)
Task-based EEG	2 (3%)
Sleep EEG	2 (3%)
Molecular modalities	15 (22%)
Magnetic resonance spectroscopy	8 (12%)
PET	7 (10%)
Medication used	
Only ketamine	67 (97%)
Both ketamine and esketamine	2 (3%)
Number of infusions	
Single	59 (86%)
Multiple (two or more)	10 (14%)
Number of participants	22 (16–32)
Age of participants (years; n=66 studies)	41·5 (36·1–45·0)
Percentage of women (n=66 studies)	56% (41·25–61·00)
Percentage of men (n=66 studies)	44% (39·00–58·75)
Primary diagnosis included	
Only major depressive disorder	64 (93%)
Only bipolar depression	3 (4%)
Combination of individuals with major depressive disorder and bipolar depression	2 (3%)
(Continued from previous column)	
Association studied	
Only longitudinal neuroimaging findings	36 (52%)
Both baseline and longitudinal neuroimaging findings	23 (33%)
Only baseline neuroimaging findings	10 (15%)
Reported statistically significant associations*	
Yes	55 (80%)
No	14 (20%)
Clinical trial design	
Randomised controlled trial	35 (51%)
Open-label trial	32 (46%)
Combination of different designs	2 (3%)
Primary depression outcome measure	
Montgomery-Asberg Depression Rating Scale	49 (71%)
Hamilton Depression Rating Scale	14 (20%)
More than one measure	4 (6%)
Beck Depression Inventory	2 (3%)
Allowed concurrent antidepressants	
Yes	27 (39%)
No	42 (61%)
Number of previous antidepressant trials in which participants were required to have not met inclusion criteria	2 (1–2)
Current prevalence of any anxiety disorder in individual studies (n=15 studies)	70% (55–75)

(Table 2 continues in next column)

Data are n (%) or median (IQR). EEG=electroencephalography. fMRI=funtional MRI. MEG=magnetoencephalography. *Associations between response to ketamine or esketamine (analysed categorically or continuously), and baseline or longitudinal neuroimaging findings in the total sample (ie, statistically significant associations in subsamples were not included).

Table 2: **Main characteristics of studies using neuroimaging to examine ketamine or esketamine antidepressant effects**

69 manuscripts were ultimately included, yielding a combined sample of 1751 participants. Most of the included studies used only one neuroimaging modality (64 [93%] of 69 studies) and investigated only individuals with major depressive disorder (64 [93%]). All 69 studies treated individuals with intravenous racemic ketamine and two (3%) of these studies had a subsample of participants who were treated with intravenous esketamine.[21,22] Since the two studies that included individuals treated with esketamine did not conduct separate analyses for participants who received only esketamine, this systematic review mostly consists of evidence on neuroimaging correlates of antidepressant response to racemic ketamine.

Ten (15%) studies investigated structural neuroimaging (sMRI and DTI), 29 (42%) studies reported on fMRI (resting-state fMRI, task-based fMRI, and arterial spin labelling, which measures cerebral blood flow and is hypothesised to be correlated with brain activation), 20 (29%) studies examined electrophysiological modalities (MEG and EEG), and 15 (22%) studies used molecular modalities (PET and MRS). 33 (48%) articles reported on baseline (pre-treatment) neuroimaging findings and 59 (86%) articles reported on longitudinal (post-treatment) neuroimaging findings. 55 (80%) articles reported statistically significant associations between neuroimaging findings and response to ketamine. The main brain regions involved in statistically significant findings were the prefrontal cortex (16 studies),[21,23–37] the anterior cingulate cortex (12 studies),[21,28,34,38–46] and the striatum (nine studies).[23,27,29,37,47–51] Table 2 describes the main characteristics of the included studies.

Structural neuroimaging (sMRI and DTI)

Ten studies examined structural neuroimaging biomarkers of response to ketamine (appendix 1 p 12). Seven studies used sMRI[40,44,47,52–55] and three studies used DTI.[41,56,57] Eight of the ten studies reported statistically significant associations between neuroimaging findings and response to ketamine.

Nine studies reported on baseline (pre-treatment) structural neuroimaging biomarkers of response to ketamine,[40,41,44,52–57] six using sMRI and three using DTI. There was convergence in two types of findings. In sMRI studies, there was convergence between two studies that found an association between smaller baseline hippocampal volume and greater improvement of depressive symptoms.[44,52] In DTI studies, there was convergence in the results of two studies that found an association between greater baseline fractional anisotropy in the cingulum[56,57] and greater improvement of depressive symptoms (appendix 1 pp 2–4).

Six studies reported on longitudinal (post-treatment) structural biomarkers of response to ketamine, five using sMRI and one using DTI.[40,44,47,53,55,57] Three studies reported statistically significant findings,[47,55,57] two of them (using two independent samples) involving the hippocampus.[47,55] However, there was no significant convergence between positive findings (appendix 1 p 4).

fMRI (resting-state fMRI, task-based MRI, and arterial spin labelling)

29 studies examined the correlates of response to ketamine using fMRI (appendix 1 pp 13–15),[21–25,27,29,35,37,38,41,44,48,50,58–72] of which 19 studies used blood-oxygenation-level dependent (BOLD) resting-state fMRI,[21,23–25,27,35,38,41,44,50,58–66] seven studies used task-based BOLD fMRI,[37,48,67–71] and three studies used arterial spin labelling during resting state.[22,29,72] 20 studies investigated functional connectivity and 11 studies examined measures of fMRI brain activation. The tasks used varied substantially, with two studies using the same task (No Go/Go task) and each of the other five studies using a distinct task (appendix 1 p 14).[70,71] 22 (76%) of the 29 studies using fMRI-based modalities reported statistically significant associations between neuroimaging findings and response to ketamine.

14 studies reported baseline neural correlates of response to ketamine,[21,22,24,27,41,44,48,50,64,66,68,70–72] of which ten studies examined resting state and four investigated neural correlates during tasks. Ten studies investigated functional connectivity, of which eight had statistically significant findings. Five studies investigated brain activation, of which three had statistically significant findings. There was no significant convergence between positive findings relating to functional connectivity or brain activation.

27 studies examined the association between longitudinal neuroimaging findings and response to ketamine,[21–25,29,35,37,38,44,48,50,58–72] of which 20 studies examined resting state and seven investigated neural correlates during tasks. 20 studies investigated longitudinal changes in functional connectivity, of which nine (45%) had statistically significant findings. 11 studies examined the association between longitudinal changes in brain activation and response to ketamine, of which eight (73%) found statistically significant associations. In resting-state studies, there was convergence in findings associating response to ketamine with post-ketamine increases in functional connectivity in the prefrontal cortex (appendix 1 pp 4–5).[23,25] Six of the seven task-based studies reported statistically significant findings. However, there was no significant convergence between the positive results.

Electrophysiological modalities

20 studies investigated the neural correlates of response to ketamine with electrophysiological neuroimaging modalities (appendix 1 pp 16–17).[26,28,31,33,34,39,42,43,61,73–83] 12 studies used MEG, of which four used resting-state MEG[33,34,39,79] and eight used task-based MEG,[42,43,73–78] and eight studies used EEG, of which four used wake resting-state EEG,[26,28,31,61] two used sleep EEG,[81,82] and two used task-based EEG.[80,83] In the ten task-based studies (eight using MEG and two using EEG), the task used varied substantially, with four studies using a passive somatosensory stimulation task and each of the other six studies using a distinct task (appendix 1 pp 16–17). 17 (85%) of the 20 studies using electrophysiological modalities reported statistically significant associations between neuroimaging findings and response to ketamine. There was substantial sample overlap between the studies that used MEG, with all 12 studies ultimately coming from two independent samples. The eight EEG studies comprised five independent samples.

Six electrophysiological studies reported on baseline biomarkers of response to ketamine.[26,28,33,42,43,82] All six studies reported statistically significant findings but the specific electrophysiological correlates highlighted were variable, and there was no significant convergence between positive results.

17 studies investigated the association between longitudinal changes in electrophysiological parameters and response to ketamine.[26,28,31,33,34,39,61,71–81,83,84] All studies used distinct analytical approaches, complicating comparisons between studies. With this caveat in mind, there was convergence in two types of findings: (1) response to ketamine was associated with post-ketamine increases in power in the gamma band in frontoparietal regions,[28,31,75] an EEG frequency range (typically between 30 Hz and 50 Hz) that is closely related to the generation of action potential by cortical neurons[85,86] (observed in three studies using three independent samples), and (2) response to ketamine was associated with post-ketamine decreases in theta cordance, an electrophysiological measure that correlates with brain consumption of energy[87] (observed in two studies with two independent samples; appendix 1 pp 5–6).[26,28]

Molecular modalities

15 studies examined the neural correlates of response to ketamine with molecular neuroimaging modalities

(appendix 1 pp 18–19).[30,32,36,41,45,46,49,51,53,88–93] Eight studies used molecular resonance spectroscopy[32,36,41,45,46,88–90] and seven studies used PET.[30,49,51,53,91–93] Nine studies investigated glutamatergic function,[32,36,41,45,46,88–90,93] six studies investigated GABAergic function,[32,36,45,46,88,90] five studies (all using PET) examined [^{18}F]-fluorodeoxyglucose[30,49,53,91,92] to measure cerebral glucose metabolism, and one study examined serotonergic function (changes in 5-HT$_{1B}$ receptor availability).[51] 11 (73%) of the 15 studies using molecular modalities reported statistically significant associations between molecular or biochemical function and response to ketamine.

Eight studies using molecular neuroimaging reported on baseline biomarkers of response to ketamine.[36,41,46,51,53,88,89,92] Four studies reported statistical significance but there was no significant convergence in positive results.

12 studies examined the association between longitudinal changes in molecular or biochemical function and response to ketamine.[30,32,45,49,51,53,88–93] Eight studies reported statistically significant results but there was no significant convergence between the positive findings (appendix 1 pp 6–7).

Convergence in findings across neuroimaging modalities

A cross-modality comparison (including structural, fMRI-based, electrophysiological, and molecular modalities) revealed substantial disparities across the results, with no strict convergence (replication) between study-specific positive findings. However, at a broader level, some findings showed convergence in two or more studies, warranting further consideration (table 3).

In the baseline (pre-treatment) neuroimaging analyses, there were associations between response to ketamine and smaller baseline hippocampal volume in sMRI studies,[44,52] and between response to ketamine and greater baseline fractional anisotropy in the cingulum in DTI studies.[56,57] However, an important caveat is that although these results showed convergence in two independent samples, the association with smaller baseline hippocampal volume was much less consistent since there were four negative studies[40,53–55] and there were no negative studies for the association with greater baseline fractional anisotropy in the cingulum.

Six longitudinal (post-treatment) neuroimaging biomarkers showed convergence in independent samples, of which three biomarkers were observed

	Number of independent samples for which the finding was observed	Number of independent samples for which the finding was not observed
Baseline (pre-treatment) findings		
Response to ketamine was associated with greater baseline fractional anisotropy in the cingulum	Two independent samples: Vasavada et al (2016[56]; DTI) and Sydnor et al (2020[57]; DTI)	None
Response to ketamine was associated with smaller baseline hippocampal volume	Two independent samples: Abdallah et al (2015[52]; sMRI) and Sydnor et al (2020[57]; sMRI)	Four independent samples: Ortiz et al (2015)[53] (sMRI), Niciu et al (2017[54]; sMRI), Zhou et al (2020[55]; sMRI), and Herrera-Melendez et al (2021[40]; sMRI)
Longitudinal (post-treatment) findings		
Response to ketamine was associated with post-ketamine increases in gamma power	Three independent samples: Nugent et al (2019[75]; MEG), de la Salle et al (2022[28]; EEG), and Lijffijt et al (2022[31]; EEG)	One independent sample: McMillan et al (2020[61]; EEG)
Response to ketamine was associated with post-ketamine increases in functional connectivity within the prefrontal cortex	Three independent samples: Abdallah et al (2017[23]; rs-fMRI), Abdallah et al (2018[25]; rs-fMRI), and Nugent et al (2020[34]; MEG)	Three independent samples: Nugent et al (2016[79]; MEG), Kraus et al (2020[60]; rs-fMRI), and McMillan et al (2020[61]; rs-fMRI)
Response to ketamine was associated with post-ketamine increases in activation within the striatum	Three independent samples: Nugent et al (2014[49]; PET), Sterpenich et al (2019[37]; tb-fMRI), and Gonzalez et al (2020[29]; ASL)	Two independent samples: Murrough et al (2015[48]; tb-fMRI) and Downey et al (2016[38]; rs-fMRI)
Response to ketamine was associated with post-ketamine increases in functional connectivity within the striatum	Two independent samples: Murrough et al (2015[48]; tb-fMRI) and Abdallah et al (2017[23]; rs-fMRI)	One independent sample: Nugent et al (2016[79]; MEG)
Response to ketamine was associated with post-ketamine increases in activation within the prefrontal cortex	Two independent samples: Li et al (2016[30]; PET) and Sterpenich et al (2019[37]; tb-fMRI)	Three independent samples: Carlson et al (2013[91]; PET), Gonzalez et al (2020[29]; ASL), and Loureiro et al (2020[68]; tb-fMRI)
Response to ketamine was associated with post-ketamine decreases in theta cordance in the prefrontal cortex	Two independent samples: Cao et al (2019[26]; EEG) and de la Salle et al (2022[28]; EEG)	None

ASL=arterial spin labelling. DTI=diffusion tensor imaging. EEG=electroencephalography. MEG=magnetoencephalography. rs-fMRI=resting-state functional MRI. sMRI=structural MRI. tb-fMRI=task-based functional MRI.

Table 3: **Convergence between neuroimaging biomarkers of antidepressant response to ketamine**

in three independent samples and the other three biomarkers were observed only in two independent samples. All convergent longitudinal findings were related to functional neuroimaging studies. Findings that broadly replicated in three independent samples included: (1) post-treatment increases in gamma power in frontoparietal regions, a putative marker of cortical excitability and synaptic potentiation, in electrophysiological studies (observed in two EEG studies[28,31] and one MEG study,[75] with only one negative study[61]); (2) post-treatment increases in functional connectivity within the prefrontal cortex (observed in two fMRI-based studies[23,25] and one MEG study,[34] with three negative studies[60,61,79]); and (3) post-treatment increases in activation within the striatum (observed in two fMRI-based studies[29,37] and one PET study,[49] with two negative studies[38,48]). The other three convergent associations (that were observed in two independent samples) were the relationship between response to ketamine and the following findings: (1) post-treatment increases in functional connectivity within the striatum (observed in two fMRI-based studies,[23,48] with one negative study[79]); (2) post-treatment increases in activation within the prefrontal cortex (one fMRI-based study[37] and one PET study,[30] with three negative studies[29,68,91]); and (3) decreases in theta cordance (observed in two EEG studies,[26,28] with no negative studies).

For findings that were convergent in at least two independent samples (26 studies), we compared the characteristics of the studies that had convergent findings (18 studies) with those without convergent findings (eight studies). There were no statistical differences in any characteristics including number of ketamine infusions, ketamine dose, study design, and primary diagnosis (appendix 1 p 20).

Discussion

We performed a systematic review of 69 studies that examined baseline (pre-treatment) and longitudinal (post-treatment) neuroimaging biomarkers. Ketamine and esketamine might have overlapping mechanisms of action, however, the number of studies investigating esketamine was small (n=2), therefore, this systematic review mainly summarised the evidence relating to racemic ketamine. Although we found no systematically replicated results due to the substantial methodological heterogeneity across studies, promising convergence was seen in longitudinal (post-treatment) biomarkers, including the association between response to ketamine and the following outcomes: (1) post-treatment increases in gamma power in frontoparietal regions, (2) post-treatment increases in functional connectivity within the prefrontal cortex, and (3) post-treatment increases in activation within the striatum. Each of these three associations was observed in three independent samples; however, the most consistency was seen in studies of increased gamma power in frontoparietal regions.

The heterogeneity in the findings included in this systematic review might be explained by several factors. First, most studies had relatively small sample sizes with the median sample size being 22 participants (IQR 16–32). Small samples are both statistically underpowered[94] and susceptible to yielding inaccurate effect sizes that replicate poorly.[95] Second, the fact that 55 (80%) of the 69 studies included in this systematic review reported statistically significant findings together with the inconsistency of results and the small sample sizes suggests the likelihood of publication bias. Third, there was substantial heterogeneity of analytical methods and statistical strategy, including variable approaches to correction for potential confounders (eg, age, sex, and BMI; appendix 1 p 7).[94] Fourth, there was substantial variability in study characteristics, including factors such as inclusion criteria, sample characteristics such as prevalence of concurrent psychiatric disorders, treatment schedule, and timepoints when neuroimaging outcomes were obtained. Fifth, major depressive disorder is an intrinsically heterogeneous disorder.

In addition, this systematic review has several limitations that need to be taken into account. In particular, details of each study's statistical analyses (specific tests used and adjustment for multiple comparisons) were not always thoroughly described and limited our ability to perform a more quantitative comparison of the literature. Similarly, given the scarcity of individual-level data, we were not able to conduct reliable meta-analytical calculations. We reported the brain regions as named in the original studies, which does not necessarily mean they have the exact same brain coordinates. Finally, neuroimaging studies usually do not include individuals with severe active symptoms (such as acute suicidality), which limits the generalisability of our findings.

Despite these caveats, an encouraging finding was the association between post-ketamine increased gamma power in frontoparietal regions and response to ketamine. This association was investigated in four independent samples and, in three of them, this association was statistically significant in individuals receiving the standard antidepressant dose of ketamine (0·5 mg/kg). Increases in gamma power have a strong translational potential since they can be captured by EEG, a widely available neuroimaging modality, and are observed in early stages of antidepressant response (within minutes to hours after treatment with ketamine). Another result seen broadly in three independent samples was the association between response to ketamine and post-treatment increases in functional connectivity within the prefrontal cortex, which could counteract the hypoconnectivity of the prefrontal cortex previously found in major depressive disorder and bipolar depression.[3,96] Finally, post-treatment increases in the activity within the striatum, a brain region involved in reward processing, is consistent with previous findings that individuals with depression have hypoactive striatum and that ketamine, a medication with substantial anti-anhedonic action, could normalise this hypoactivity.[97]

The three brain-based correlates of response to ketamine that were most widely convergent are broadly consistent with ketamine's proposed main mechanisms of action, which could underlie our findings. Preclinical studies conclude that ketamine is an N-methyl-D-aspartate receptor antagonist that preferentially blocks γ-aminobutyric-acid-containing (GABAergic) inhibitory interneurons.[98] This blockage in GABA transmission results in a downstream increase of neuronal firing, resulting in glutamate release (disinhibition hypothesis). As the EEG gamma band is closely related to the generation of action potentials by cortical neurons,[85,86] increases in gamma power could reflect the strengthening of glutamatergic neurotransmission as a result of ketamine. In addition, this increase in glutamatergic transmission triggers intracellular pathways that ultimately increase concentrations of neurotrophins, such as BDNF, which leads to synaptogenesis.[98] This increase in synaptic strength can be seen in functional neuroimaging as increases in functional connectivity, such as the one observed within the prefrontal cortex in three independent samples.[23,25,34] The strengthening of glutamatergic transmission and increased synaptogenesis, as well as ketamine's potential effect on dopamine, either direct or via glutamatergic connections, could also explain the increases in the activity within the striatum.

Interestingly, six of the eight replicated neuroimaging biomarkers were longitudinal (post-treatment), which raises the question as to why there were fewer replicated baseline (pre-treatment) neuroimaging biomarkers. First, there were fewer publications that addressed baseline neuroimaging biomarkers than longitudinal studies. Although data on baseline neuroimaging biomarkers were obtained in all 69 studies included in this systematic review, less than half of the studies (33 [48%] of 69) reported on them, whereas 86% (59 of 69) reported on longitudinal neuroimaging biomarkers. In addition, baseline biomarkers could be intrinsically more difficult to identify due to prominent interindividual heterogeneity when compared with longitudinal biomarkers, for which each individual can effectively act as their own control in a more controlled analytical framework. As a result, the identification of interindividual (baseline) biomarkers will probably require larger sample sizes and more effective subtyping than for longitudinal biomarkers to reduce heterogeneity.

Given the inconsistencies and possible publication bias of the current literature, future studies investigating brain-based biomarkers of response to ketamine should address the limitations of previous studies (appendix 1 pp 7, 21). Table 4 summarises some recommendations for improving the reproducibility or replicability and the clinical use of neuroimaging studies. First, it is important to investigate larger samples to reduce the noise due to sampling variability, which could be particularly pronounced when studying a highly heterogeneous condition such as depression. Recruitment of larger samples could be achieved with development of multisite collaborations and open sharing of neuroimaging data. Second, preregistration in publicly available repositories can improve research transparency, accountability, and credibility of the results, and decrease multiple testing and selective reporting. Third, it is crucial to control appropriately for common confounders (appendix 1 p 21). Finally, modalities with good temporal resolution, such as EEG and MEG, might be particularly useful to examine rapid-changing phenomena such as those during ketamine treatment or immediately after ketamine infusion. Studies using modalities highly susceptible to physiological and motion artifacts, such as sMRI and fMRI, should incorporate protocols that predefine exclusion motion thresholds and conduct post-hoc corrections.

	Rationale	Actions that facilitate the implementation of the recommendations
Investigation of larger samples	Most neuroimaging studies examine small samples, which are underpowered, and more likely to provide inaccurate or inflated effect sizes and false-positive findings; larger samples decrease the noise due to sampling variability, which could be particularly pronounced when studying a highly heterogeneous condition such as depression	Development of neuroimaging consortia and multisite collaborations; open sharing of neuroimaging data (eg, free and open-source platforms)
Preregistration in publicly available repositories	Most neuroimaging studies are not preregistered, which might facilitate the use of inappropriate analytical designs and of multiple testing; preregistration allows for a better distinction between exploratory and confirmatory studies, improves research transparency, accountability, and credibility of the results, and could decrease selective reporting	Use of free and open-source platforms that allow the researchers to register and share their studies (eg, Open Science Framework and the AsPredicted platform); journal or editorial policies that require or prioritise preregistered neuroimaging studies such as publishing preregistered studies even if the results are negative
Appropriate controlling of confounders	Most studies do not describe or perform controlling for confounders; procedural (such as motion) and patient-related confounders (such as age, gender, BMI, other medications or substances, and other psychiatric comorbidities) could substantially affect neuroimaging results	Implement study protocols that decrease motion by minimising time, increasing comfort and familiarisation in the scanner; predefine exclusion motion thresholds and conduct post-hoc corrections; conduct and describe controlling for main patient-related confounders; research design that minimises the effect of medications and substances; when combining distinct samples, use harmonisation techniques such as the ComBat algorithm

Table 4: **Recommendations to improve the reproducibility and replicability of neuroimaging studies investigating neural correlates of antidepressant response to ketamine or esketamine**

Conclusion

A well replicated neuroimaging biomarker of ketamine response was not identified in this systematic review. However, we found convergence across some significant results, particularly in longitudinal (post-treatment) biomarkers, that warrants further investigation. Post-treatment increases in gamma power in fronto-parietal regions are particularly promising given their consistency, strong translational potential, and occurrence in early stages of antidepressant response.

Contributors

GCM wrote the first draft of the report, set up the database, conducted manual searches, selected included studies, and extracted, verified, analysed, and interpreted the data. MM assisted in the writing of the first draft of the report, conducted manual searches, selected included studies, extracted and verified the data, interpreted the data, and critically reviewed and edited the report for important intellectual content. ID assisted in the writing of the first draft of the report, participated in the data extraction, interpreted the data, and critically reviewed and edited the report for important intellectual content. MJR interpreted the data and critically reviewed and edited the report for important intellectual content. SM selected included studies, interpreted the data, and critically reviewed and edited the report for important intellectual content. CT conducted the systematic searches in the electronic databases, interpreted the data, and critically reviewed and edited the report for important intellectual content. GSS interpreted the data, and critically reviewed and edited the report for important intellectual content. TDG assisted in the writing of the first draft of the report, interpreted the data, and critically reviewed and edited the report for important intellectual content. CAZ interpreted the data and critically reviewed and edited the report for important intellectual content. FSB provided input into the design and conceptualisation of the study, interpreted the data, and critically reviewed and edited the report for important intellectual content. FSG designed and conceptualised the study, provided supervision, assisted in the writing of the first draft of the report, verified the data, interpreted the data, and critically reviewed and edited the report for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

GSS conducted an investigator-initiated study that used medication (vortioxetine) provided without charge by Lundbeck. TDG is listed as coauthor on patent and patent applications related to the pharmacology and use of (2R,6R)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorder. He has assigned his patent rights to the University of Maryland, Baltimore, but will share a percentage of any royalties that might be received. TDG has also received research funding from Allergan and Roche Pharmaceuticals. CAZ is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2R,6R)-hydroxynorketamine, (S)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the US Government but will share a percentage of any royalties that might be received. FSB is a scientific adviser for WavePaths, and MindState Design Labs. FSG has received research grant support from Janssen Therapeutics. All other authors declare no competing interests.

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