SYSTEMATIC REVIEW OPEN

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Psychedelics and ketamine/esketamine in depressive disorders: biological mechanisms and associated neuroimaging and clinical changes

Giacomo d'Andrea[1,2,7]✉, Stefania Chiappini[1,3,7], Laura Ciavoni[1], Rolando Tucci[1], Fabrizio Martino[1], Francesco Maria Semeraro[1], Daniele Di Battista[1], Alessio Mosca[1], Andrea Miuli[2], Francesco Di Carlo[1], Mirella Russo[1], Gilberto Di Petta[4], Michele Fornaro[5], Mauro Pettorruso[1,2], Stefano L. Sensi[1,6] and Giovanni Martinotti[1,2]

BACKGROUND: Over the past ten years, several psychedelic compounds, including tryptamines like lysergic acid diethylamide/LSD, psilocybin, ayahuasca, and dimethyltryptamine/DMT, have been tested in clinical trials for a range of psychiatric conditions, such as anxiety and depression. While these compounds are relatively available for treatment, ketamine and its S(+) enantiomer, esketamine, are increasingly used to manage treatment-resistant depression. The biological mechanisms set in motion by these compounds are still largely unexplored. Preliminary data indicate modulatory activity of distinct brain networks and selected neurotransmitter pathways (i.e., glutamate, serotonin).
OBJECTIVE: This systematic review investigates functional changes in neural activity generated by these compounds (i.e., LSD, psilocybin, ayahuasca, and DMT or ketamine/esketamine) in depressive disorders. Studies involving different techniques (i.e. Positron Emission Tomography/PET, Single Photon Emission Computed Tomography/SPECT, functional Magnetic Resonance Imaging/fMRI and MRI) were included.
METHOD: A literature search was conducted following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines of 2015. The search was performed using PubMed Web of Science and Scopus databases, taking into consideration publications up to March 2022, without any time restrictions.
RESULTS: The search produced a final set of 49 articles. Most were related to ketamine/esketamine (n = 44). A smaller number (n = 5) pertained to psychedelic tryptamines (one on ayahuasca and four on psilocybin). From the total of 49 studies, 9 were randomized-controlled trials, 25 were open-label studies, 4 were double-blind trials, 8 were observational studies, and 3 cross-over studies.
CONCLUSIONS: Psylocibin seems to reset Default Mode Network (DMN) activity, thereby reducing depressive symptoms with long-term and sustainable antidepressant efficacy. Compared to psychedelics, ketamine exhibits a more specific action on networks involving prefrontal areas that act indirectly on the DMN. This effect may help explain ketamine's anti-anhedonic activity and its critical role in increasing cognitive control over emotional stimuli, thus reducing negative mood stages.

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INTRODUCTION

Depressive disorders and available treatments

Depression is a common pathological condition affecting approximately 280 million people globally, constituting the second leading cause of disability worldwide due to its substantial occupational and economic impacts. It may clinically manifest through severe symptoms affecting various functional areas and can be particularly acute in recurrent or severe cases, potentially leading to suicide, especially among youths aged 15-29 [1]. The Diagnostic and Statistical Manual of Mental Disorders-Fifth edition Text Revision (DSM-5-TR) [2] removed the broad category of mood disorders and classified depressive disorders separately from bipolar disorders. Nonetheless, from a phenomenological point of view, depression can present with i) a single episode depressive disorder; ii) a recurrent depressive disorder; and iii) bipolar disorder. Furthermore, other related conditions are: a depressed mood lasting at least two years in persistent depressive disorder (or dysthymia); postpartum depression and psychotic depression, occurring in cases of severe depression, associated with psychotic features like disturbing false fixed beliefs

[1]Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti-Pescara, Italy. [2]Department of Mental Health, ASL 2 Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy. [3]UniCamillus International Medical University, Rome, Italy. [4]SPDC, Mental Health Department, Santa Maria delle Grazie Hospital, Naples, Italy. [5]Department of Psychiatry, Federico II University of Naples, Naples, Italy. [6]Institute for Mind Impairments and Neurological Disorders - iMIND, University of California - Irvine, Irvine, CA, USA. [7]These authors contributed equally: Giacomo d'Andrea, Stefania Chiappini. PRISMA guideline has been followed in this study. Moreover, the systematic review was registered in PROSPERO on March 21, 2022 (PROSPERO ID: CRD42022311020). ✉email: giacomo.dandrea1993@gmail.com

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(delusions) hallucinations [2]. This underscores the enormous eterogeneity of depressive disorders, which are probably related to different neurobiological underpinnings.

First-line non-pharmacological treatments for mild cases include psychoeducation, self-management, and psychological therapies, such as cognitive behavioural therapy or interpersonal psychotherapy [3].

Pharmacological treatments should be considered for mild depression, considering the patient's preference, previous response to antidepressants, or lack of response to non-pharmacological interventions [3]. Other factors include the patient's clinical features and dimensions, any comorbid conditions, and intrinsic drug-related factors (e.g., comparative efficacy/tolerability and interactions with other medications). Currently, the first-line recommendations for pharmacotherapy for Major Depressive Disorder (MDD) include: selective Serotonin Reuptake Inhibitors (SSRIs); Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) like venlafaxine, and duloxetine; the Noradrenaline and Dopamine Reuptake Inhibitor (NDRI) bupropion; the Noradrenergic and Specific Serotonergic Antidepressant (NaSSA) mirtazapine; and the Serotonin Modulator and Stimulator (SMS) vortioxetine [3]. Recommended second-line agents include Tricyclic Antidepressants (TCAs) and the Serotonin Antagonist and the Reuptake Inhibitor Antidepressant (SARI) trazodone, which show all more side effects compared to first-line treatments [3]. Finally, due to the higher side-effect burden and potentially severe drug and dietary interactions, third-line recommendations include monoamine oxidase inhibitors (MAOIs) [3]. 'Adjunctive strategies' refers to the addition of a second medication to the initial medication, i.e., adding a second antidepressant to the first or adding another medication that is not an antidepressant (i.e., aripiprazole, lithium, or quetiapine, etc.), taking into consideration both efficacy and tolerability [4].

Despite the availability of various therapeutic options, approximately 30-50% of patients with depression do not achieve complete symptom remission even after multiple treatment steps [5]. This has led to a significant 'revolution' in the field of antidepressant therapies over recent years, with the exploration of new, rapid-acting treatments based on pharmacodynamic mechanisms that differ from conventional monoaminergic treatments.

The "antidepressant revolution": ketamine/esketamine and psychedelics renaissance

Despite structural and pharmacological differences, arylcyclohexamines (i.e. ketamine/esketamine) and tryptamines (e.g., LSD, psilocybin, ayahuasca, and dimethyltryptamine/DMT) have high evidence for treating depressive disorders. Their respective pharmacodynamic mechanisms goes beyond the monoaminergic theory of conventional antidepressants, involving either glutamatergic, opioidergic, dopaminergic and serotoninergic systems [6, 7], but resulting in a shared mechanism of increase brain plasticity via BDNF/mTOR pathways [8].

The non-competitive N-methyl-D-aspartate receptor (NMDAr) antagonist ketamine, which has long been used as a general anaesthetic, produces remarkable results in patients with treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD), bipolar disorder, obsessive-compulsive disorders [9–11]. An intranasal formulation of esketamine, currently branded as Spravato®, has been approved by the Food and Drug Administration (FDA) in the United States in March 2019 and by the European Medical Agency (EMA) in December 2019 for TRD [12, 13], and seems to be effective also in complicated populations with multiple comorbidities [14–16]. Despite the broad efficacy of ketamine/esketamine in clinically heterogeneous samples, there remains an absence of definitive indicators regarding clinical and biological markers of efficacy [17], with only preliminary data available from retrospective studies [18].

Classical psychedelic drugs, including psilocybin, lysergic acid diethylamide (LSD), and mescaline, have been extensively used in psychiatry before being banned as compounds listed in Schedule I of the United Nations Convention on Drugs in 1967 [19–21]. In the current resurgence of research into psychedelics, these substances are re-emerging as potential clinical therapies for treating various disorders. They present a model of single-dose, rapid-effect interventions that demonstrate substantial efficacy in treatment-resistant mental disorders, offering a distinct benefit as a potential monotherapy for mental illnesses [22]. Since 2006, there have been several trials using psychedelics (especially psilocybin) in non-psychotic psychiatric disorders, such as depression, anxiety, PTSD, and addiction, showing initial evidence of safety and efficacy, especially in the context of extensive psychological support, i.e., assisted psychotherapy [20, 23–25].

Some studies have suggested that psilocybin may induce profound psychological and spiritual effects, referred to as 'mystical experiences', such as high empathy, a sense of connection with the universe, and temporary alterations of thought patterns, mood, and time/space perception. These effects are considered potential facilitators of the antidepressant effects of psychedelics like psilocybin [26]. Nonetheless, this approach would be limited by several factors, including i) personal patients' expectancies which might condition primary outcomes of drug response; ii) generalisability; iii) legal and regulatory barriers; iv) long-term effects of psychedelics; and v) ethical issues [19, 20].

Macroscopic and microscopic structural changes in MDD

Magnetic resonance imaging (MRI) and neuroimaging in general, have been used to investigate the neurophysiological changes associated with MDD. These approaches have the advantage of being non-invasive and allow repeated measures. Gray matter changes have been identified in several areas involved in depressive disorders (i.e., increased cortical thickness of frontal and parietal lobes, as well as decreased thalamic, caudate, pallidum, and putamina volumes) (see Table 1 for details) [27]. Furthermore, neuroplasticity, i.e., the capacity of the nervous system to adapt its activity in response to intrinsic and extrinsic stimuli, resulting in structural and functional reorganization of its connections, is thought to be involved in the pathophysiology of depression. The enhancement of neuroplasticity in the hippocampus and prefrontal cortex and the modulation of glutamate transmission are two antidepressant mechanisms activated by rapidly-acting compounds like ketamine, esketamine, and tryptamines [28].

Brain networks involved in depressive disorders

A growing body of evidence supports the notion that depressive disorders are associated with widespread network dysconnectivity rather than aberrant alterations of individual brain regions [29] (Table 2). Different studies have coupled neuroimaging data on functional brain connectivity with specific clinical features of MDD to phenotype depressed patients based on clinical and neurobiological markers [30, 31].

Four core networks have been frequently implicated in depressive disorders: the Affective Network (AN), the Reward Network (RN) - both part of the so-called Salience Network of the Triple Network Model - (Menon, 2020), the Default Mode Network (DMN), and the Central Executive Network (CEN) [29]. The role of these networks in depressive disorders is depicted in Table 2. Overall, aberrant connectivity of the AN has been liked to negative affection and dysphoria [32, 33], while enhanced DMN activity has been related to self-referential thoughts and depressive ruminations [34], frequently related to a prior history of trauma exposure [35]. The hypoactivation of the RN has been associated with anhedonia, lack of interests and reduced motivation [36, 37]. Finally, diminished brain connectivity of the CEN seems to underlie inadequate cognitive control, particularly regarding negative thoughts and emotions [38, 39].

Table 1. Brain region involved in Major Depressive Disorder (MDD).

REGION	ROLE	ALTERATIONS DETECTED IN NEUROIMAGING STUDIES	CLINICAL CORRELATIONS
Frontal lobe[a]	-The ACC has an anatomical connection with dorsal neocortical and ventral paralimbic regions and plays a role in cognitive processes and mood regulation -The OFC is involved in inhibiting background-independent, redundant, or uncomfortable neural activity, feelings, and behaviours and also plays a crucial role in emotional/motivational management and decision making -The DLPFC plays an essential role in emotional, motivational, attentional, and executive functions	-Decreased magnetization transfer ratio in the right ACC in patients with treatment-refractory MDD, which increased after electroconvulsive therapy -Reduction in thickness of prefrontal areas are associated with poor clinical outcomes -The ACC has increased functional correlations with the DLPFC and the amygdala in MDD patients -Structural (reduced thickness of the right medial orbital cortex, and during treatment increased cortical thickness in the OFC in MDD patients) and functional changes (reduced brain activity) in the bilateral OFC may contribute to the reduced inhibition of negative stimuli in depressive patients -The volume of grey matter in the left middle frontal gyrus was found to be decreased in untreated depressive patients and to increase after drug treatment (and associated with emotional bias, apathy, and loss of motivation) -Reduced grey matter volume and brain activity in the DLPFC of depressed patients; they could be increased to the average level after antidepressant treatment	-The fibres in the medial frontal cortex are part of the DMN and play an essential role in the execution of long-term mental plans from immediate environmental or internal demands -Transcranial magnetic stimulation of the left DLPFC induces morphological increases in the left ACC and the middle frontal OFC, indicating that the DLPFC has connections with the ACC and the OFC
Hippocampus	-It is associated with memory recall and the rules of reward	-Volume reduction in depressed patients; on the other side, after antidepressant treatment and electroconvulsive therapy an increased grey matter volume in the hippocampus in MDD patients were found -Reduced volume of hippocampus may be associated with illness duration in MDD -Reduced functional activity in the hippocampus would lead to negative emotion and the inability of cognitive processing in depressive patients	-Stress via the hypothalamic-pituitary-adrenal axis can result in elevated glucocorticoid levels in patients with MDD and can act on the glucocorticoid receptors in the hippocampus, resulting in its atrophy, while increased hippocampal volume was associated with clinical improvement
Parietal lobe	-Parietal lobe is involved in the organization, decision making, and predictions of rewards during conditioning that evaluates outcomes for future response choices that are uncertain. It is also related to emotional processing and cognitive changes and is part of the DMN[b] which has a functional connection with the caudate via dopaminergic projections (striatal dopaminergic circuits may regulate cognition and emotion by modulating the DMN in MDD)	-Increased cortical thickness in the left inferior parietal gyrus and in the left superior parietal lobule and increased grey matter volume in the right postcentral gyrus in MDD patients	-Increased thickness and correlations indicate compensatory mechanisms associated with inflammation or other aspects of the pathophysiology of depression

Table 1. continued

REGION	ROLE	ALTERATIONS DETECTED IN NEUROIMAGING STUDIES	CLINICAL CORRELATIONS
Striatum[a] (basal ganglia): it contains the putamen, the caudate, and the VST	-Putamen plays a key role in mood, cognitive processes, motivation, and regulation of movement -The caudate nucleus is a critical component of the reward system in the brain	-Decreased grey matter intensity in the VST -Decreased volume of the bilateral putamen in MDD patients -Reduced volume and activity of the caudate in MDD patients	-Disruptions in striatal output may lead to impulsive and suicidal behaviour -Striatal activity plays an essential role in disease progression: it is reduced in reward system defects, and decreased reward network connections were found to be associated with depression severity -Dysfunction of the caudate nucleus may lead to a disruption in dopaminergic signalling in MDD patients, explaining the core features of depression or even the lack of responsiveness to positive stimuli or reward constituents
Thalamus[a]: the subthalamic nuclei accept fibres from the pallidum and motor cortex and send out fibres to the substantia nigra. The lateral dorsal thalamic nucleus sends out fibres to the parietal lobe, and the ventral lateral thalamic nucleus has connections with the cerebellum and the brainstem.	-It is considered a complicated sensory information node that controls emotion, memory, and arousal	-Volume reductions and changes in shape in the both the right and left thalamus of patients with MDD	-Dysfunction and structural disruptions in the thalamus can lead to an amnestic syndrome due to impairments in recall and recognition -As the anterior thalamic nuclei form a key region involved in emotional regulation, the decreased functional activity in these regions in MDD might contribute to emotional deregulation and could be a target for diagnostic assessments and therapies

ACC, anterior cingulate cortex; *DLPFC*, dorsolateral prefrontal cortex; *DMN*, default-mode network; *MDD*, Major Depressive Disorder; *OFC*, orbito-frontal cortex; *PFC*, prefrontal cortex; *PC*, parietal cortex; *PCC*, posterior cingulate cortex; *VMPFC*, ventromedial prefrontal cortex; *VST*, Ventral Striatum.
[a]The striatum, thalamus, and PFC constitute the prefrontal-subcortical circuit.
[b]The DMN is composed of the VMPFC, the PCC, bilateral inferior PC, and the middle temporal lobe.

Aim of the study

Overall, there is still a lack of evidence on the use of tryptamines and ketamine/esketamine as therapy concerning changes in functional connectivity (FC) and brain networks, their safety, outcomes, and duration of treatment. Therefore, this systematic review investigates changes in neuroimaging features in MDD, TRD, or bipolar disorder patients treated with tryptamines (e.g., LSD, psilocybin, ayahuasca, and dimethyltryptamine/DMT) or arylcyclohexamines (ketamine/esketamine).

Finally, the study analyses existing protocols, treatment outcomes, and the safety of these treatments, describing any recorded efficacy/tolerability problems.

MATERIALS AND METHODS

Data extraction

The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of 2015 [40, 41]. A literature search was performed using Pubmed (via Medline), Web of Science and Scopus databases on March 1st, 2022, without any time restrictions. We used the following search string: (fMRI or MRI or functional magnetic resonance or neuroimaging or magnetic resonance or PET or positron emission tomography or SPECT or single photon emission computed tomography) and (psychedelics or psilocybin or ayahuasca or LSD or lysergic acid diethylamide or dimethyltryptamine or DMT or tryptamines or ketamine or esketamine) and (treatment-resistant depression or depression or MDD or depressive symptoms) not review not meta-analysis not animal not in vitro. only original articles reporting data in patients affected from depression (i.e. MDD, Bipolar Depression and TRD) and treated with tryptamines (i.e., LSD, psilocybin, ayahuasca, and DMT) or ketamine/esketamine written in English were selected. In addition, only studies evaluating brain circuit alterations through specific neuroimaging techniques (i.e., Positron Emission Tomography/PET, Single Photon Emission Computed Tomography/SPECT, MRI, functional magnetic resonance imaging/fMRI) were included. Experimental and observational studies, post-marketing surveillance reports, case reports, case series, and fatality reports were included. the exclusion criteria included non-original research (e.g., reviews, commentaries, editorials, book chapters, and letters to the editor), non-full-text articles (e.g., meeting abstracts), works in a language other than English, and studies involving animal/in vitro experiments. Furthermore, articles not assessing post-treatment variation through PET/SPECT/MRI investigation were excluded. Although letters to the editor, conference proceedings, and book chapters were excluded from the literature review, they were still considered to retrieve further secondary references. We also performed secondary searches using the reference lists of all eligible papers.

Data synthesis strategy

The search for results was carried out individually by six investigators (L.C., F.M.S., R.T., F.M., D.D.B., and A.M.) and supervised by S.C., G.D.A, F.D.C., A.MI., and M.P., while G.M. and M.D.G. discussed unclear cases. The selection and eligibility phases

Table 2. Brain networks involved in Major Depressive Disorder (MDD) and their clinical correlates.

NETWORK	ANATOMICAL STRUCTURES	ROLE	CLINICAL OUTCOME
Central Executive Network (CEN)	-parietal cortex -dACC -PFC (VMPFC, DLPFC)	- cognitive processing: VMPFC has the functions of generating normal emotions, especially those with social connotations and for the regulation of autonomous and neuroendocrine responses, for the modulation of pain, for the expression of aggression, as well as for sexual and eating behaviours DLPFC is involved in cognitive control, in solving complex tasks, in maintaining information in the buffer and manipulating it in working memory	-MDD patients with impaired dorsolateral prefrontal circuits may exhibit executive dysfunction, -Dysconnectivity of regions involved in the ECN has been reported in MDD subjects during tasks involving working memory, executive-control, and affective interference, as well as during rest. -Reduced cognitive control of ECN areas (PFC, ACC) over AN areas (hippocampus, amygdala, insula) is related to increase of negative affective mood stages.
Affective Network (AN)	-OFC -ACC -Amygdala -Hyppocampus -Insula	- AN is associate with regulation and control of affective processing. - Orbital PFC corrects the emotional or behavioural responses generated partially by the amygdala, which is involved in memory processes and learning through emotions	- enhanced OFC connectivity with the precuneus and angular gyrus was related to affectively negative sense of the self in MDD - Amygdala -sgACC connectivity is related with increase in negative affectivity - increase susceptibility tu negative stimuli and dysphoria have been related to elevated connectivity in the AN
Fronto-Striatal Reward Network (RN)	-PFC -Nac -Cau -Put -VTA	- Fronto-striatal networks are involved in reward processing and hedonic function - RN is responsible for incentive salience and positively valanced emotions. - Positive valanced stimuli determined a rapid and sustained firing of dopaminergic neurons in VTA, thus determining increasing of positive feelings stimulus related. - VTA projection are related to mesocorticolimbic dopaminergic patways which involves Nac, Cau and Put. - PFC act as a modulator of reward system activity, giving a cognitive control on reward stimuli.	- When exposed to positive stimuli, depressed patients demonstrated reduced magnitude and duration of positive affect. - Anhedonia have been frequently related to a decrease of RN activity. - Aberrant activation and connectivity of the RN is associated with depression-related appetite loss/increase.
Default Mode Network (DMN)	- precuneus - PCC - VMPFC - parietal cortex	- DMN is involved in self-referential thoughts and mind wandering. - DMN has been defined as a task-negative network as its regions generally demonstrate deactivation during performance of cognitive task.	- DMN hyperactivation seems to be a "trait" feature of MDD, evident even in remitters patients. - Elevated functional connectivity within DMN has been related maladaptive rumination in MDD - Hyperactive DMN in frequently related to a longer history of trauma-exposure and history of pre-school onset of depression in children.

dACC dorsal anterior cingulate cortex, *Cau* caudate, *DLPFC*, dorsolateral prefrontal cortex, *MDD* major depressive disorder, *OFC* orbitofrontal prefrontal cortex, *PCC*, posterior cingulate cortex, *PFC*, prefrontal cortex, *Put* PUTAMEN, *SN* substantia nigra, *VMPFC* ventromedial prefrontal cortex, *VTA* Ventral Tegmental Area.

of the articles were carried out independently by the two selected members, and afterward, the papers were subjected to a final cross-check. Any questions not solved by the team related to understanding the topic covered in the articles were requested directly from the authors if they were contactable. Data were collected in a word table containing the first names and year of publication of the study, the design, demographic variables (e.g., gender, age, and psychiatric history), details on the intervention drug (dosage and route of administration), and any other drug in combination, as well as the drugs' antidepressant effect (i.e. clinical outcome), neuroimaging findings, as well as any adverse event recorded. Data synthesis was carried out by five independent members of the team (F.M.S., R.T., F.M., D.D.B., and A.M.) and compared at the end of the extraction process. All titles/abstracts were examined in the first selection phase, and full texts of potentially relevant papers were obtained and evaluated. Relevant works were selected to obtain a full representation of the available literature data on the chosen topic.

From an initial list of 890 studies (PubMed = 369; Scopus = 252; WOS = 269), duplicates (n = 256) were eliminated, as were papers unrelated to the topic (n = 411) and those that did not meet the inclusion criteria (e.g., non-original articles, n = 131, non-English papers n = 11). This yielded records relevant for screening. Studies deemed irrelevant to the topic considering the title and abstract (e.g., animal/in vitro studies; articles that did not deal with diagnosis of depression, specific neuroimaging techniques, e.g. PET, SPECT, fMRI, MRI, and the therapeutic use of tryptamines or ketamine/esketamine). Of the 81 full-text articles assessed for eligibility, 28 articles did not meet the inclusion criteria, and 4 were unavailable. Therefore, 49 articles were eventually considered and analysed (Fig. 1).

RESULTS

Findings are reported according to the class of substance, type of study, and alphabetical order (see Table 3). Of the selected articles, the majority were related to ketamine/esketamine (n = 44), while

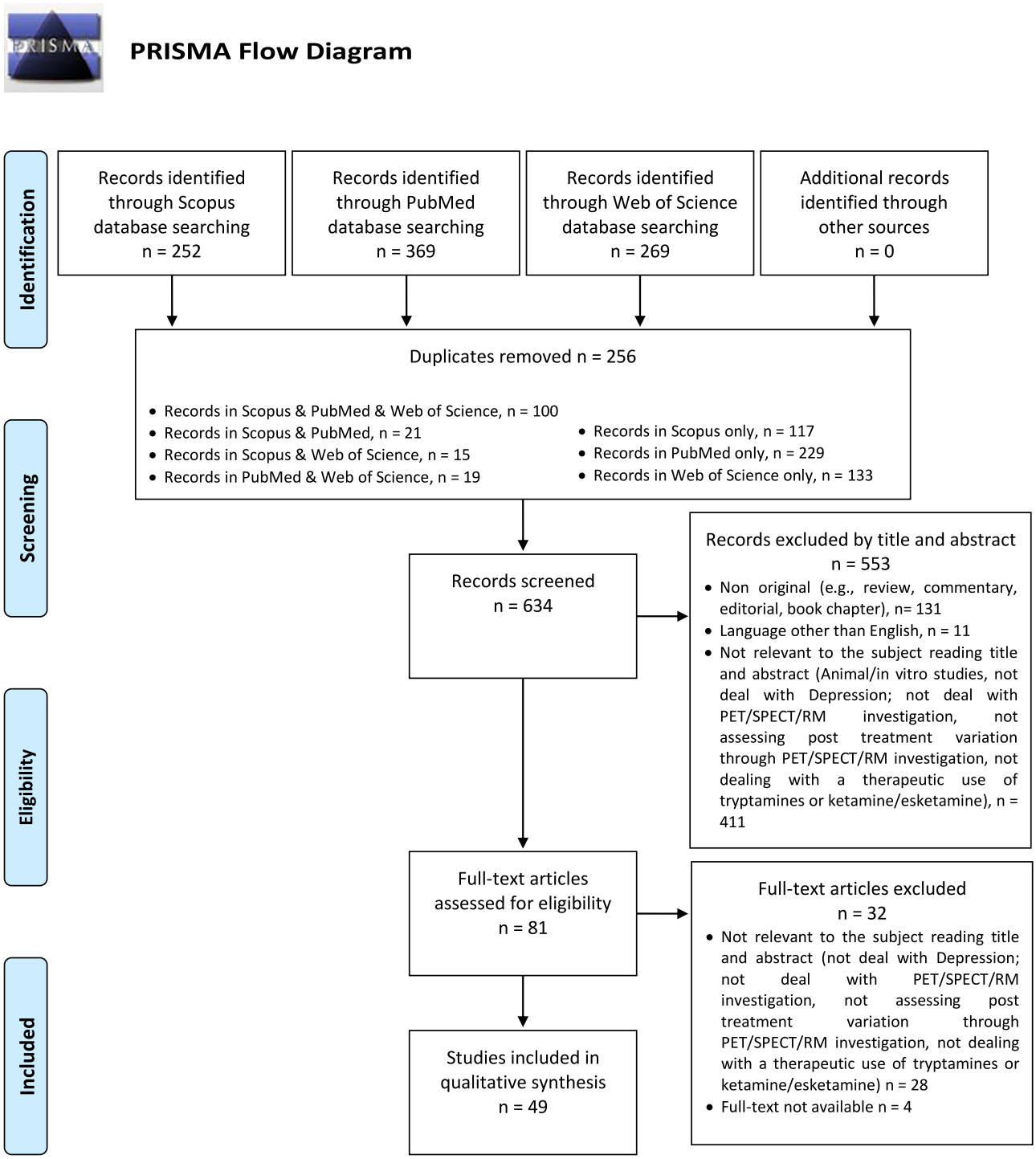

Fig. 1 Prisma Flow Diagram.

fewer (n = 5) were related to psychedelic tryptamines, specifically one to ayahuasca and four to psilocybin. From the total 49 studies, 9 were randomized-controlled trials (RCT), 25 were open-label studies, 4 were double-blind trials, 8 were observational studies, and 3 cross-over studies.

Specifically, the sample consisted of 687 patients suffering from MDD, 598 from TRD and 95 from bipolar disorder. All the study cohorts included adult subjects (mean age ranged from 30.2 to 51.13 years) except for one study, which included an adolescent cohort [42].

Most studies (n = 24) employed fMRI to investigate ketamine-related neural changes, while a few reported by magnetic resonance spectroscopy data [43–47], SPECT [48], or PET [49–57]. Seven studies only evaluated structural brain changes (i.e., brain volumes, cortical thickness, grey- or white-matter changes) [58–63].

Clinical measures included the Montgomery-Asberg Depression Rating Scale (MADRS) in n = 21 studies, the Hamilton Depression Scale (HAM-D) in n = 19 studies, the BDI in n = 8 studies, the Quick Inventory of Depressive Symptomatology-self-report (QIDS-SR) in

Table 3. Main findings of retrieved studies.

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
		PSYCHEDELIC TRYPTAMINES								
		AYAHUASCA								
		Open-label studies								
Sanches et al., [48]	17 MDD subjects	42.71 (12.11)	Ayahuasca	Single dose of 120 to 200 mL (2.2 ml/kg)	No psychiatric medication or other recreational drugs	-HAM-D and MADRS score significantly ↓ from 80 min to day 21 -BPRS score ↓ in Anxious-Depression, Thinking Disorder, Withdrawal-Retardation subscales	SPECT	2 scans: 1. before treatment 2. 8 h after drug administration	-↑ blood perfusion in left NAc, right INS and left Sg after ayahuasca intake	-vomiting (47%); -significant ↑ of dissociative symptoms (CADSS) from 40 to 80 min
		PSILOCYBIN								
		Open-label studies								
Carhart-Harris et al., [64]	16 TRD subjects	42.8 (10.1)	Psilocybin	Two psylocibin sessions (10 mg followed by 25 mg one-week apart)	ND	Depression symptoms improved from baseline (18.9 ± 3) to week 5 (10.9 ± 4.8), resulting in 6/16 responders (QIDS-SR)	fMRI	2 scans: 1. before treatment 2. one day after second treatment session	-↓ CBF post treatment in left areas (HeGyr, TGyr, PCGyr, left Am) -significant relationship between ↓ CBF in left Am and reduction of depressive symptoms -↑ RSFC between sgACC and the PCC, not correlated with treatment response -↑ RSFC between VMPFC and bilateral ilPC, which predict treatment response at week 5 -↑ RSFC of DMN, DAN and parietal Op, not correlated with treatment response -↓ RSFC between DMN and RFPN -↑ RSFC SMN and RFPN, not correlated with treatment response -mystical experiences were related to higher ↓ RSFC in Am and DMN-related cortical regions	ND
Doss et al., [65]	24 MDD subjects	39.83 (12.23)	Psilocybin	Two psilocybin sessions, separated by ~1.6 weeks (first session at a moderately high dose, i.e. 20 mg/70 kg, and second session at a high dose of psilocybin, i.e. 30 mg/70 kg)	ND	-Significant reduction of depressive symptoms (HAM-D) from baseline to 1 week and 4 weeks post-treatment; significant improvement of cognitive flexibility	fMRI-BOLD [1]HRMS	2 scans: 1. before treatment 2. 1 week after second treatment session	-↑ dFC between the ACC and PCC 1 week after psilocybin therapy -↑ baseline dFC was associated with better baseline cognitive flexibility but less improvement in cognitive flexibility - ↓ glutamate and N-acetylaspartate in ACC one week after psilocybin therapy	ND
Mertens et al., [66]	19 TRD subjects	44.7 (10.9)	Psilocybin	Two psilocybin sessions, separated by one week, including a first session at 10 mg and second session at 25 mg	-One patient continued taking venlafaxine -No other drugs	-63.2% responders (50% drop in BDI score) at week-1; 57.9% were remitters at week-1 -Rumination (RRS) significantly reduced at 1 week and three-months time-points when compared to baseline scores	fMRI with a face/emotion perception task	2 scans: 1. before treatment 2. one day after second treatment session	-↓ FC between VMPFC and right Am during face processing, with lower connectivity being linked to lower rumination levels (RRS) -↑ FC between Am and visual areas and OC during face processing -↑ FC between the VMPFC and areas in the left occipital and parietal lobes (supracalcarine and intracalcarine cortex, precuneus and lingual gyrus) during face processing -↑ FC between the VMPFC and occipital-parietal cluster was related to decrease of depressive symptoms at one week. Remitters had significant higher FC than responders	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Roseman et al., 2018	19 TRD subjects	44.7 (10.9)	Psilocybin	Two sessions, separated by one week, including a first session at 10 mg and a second one at 25 mg	Participants were antidepressants-free for at least two weeks before the study	Response (63.2%) and remission (57.9%) in BDI scores at 1-week; 47% were responders at 5 weeks	fMRI	2 scans: 1. before treatment 2. one day after second treatment session	-↑ right Am FC during fearful faces task -change, response and remission of BDI scores significantly related to ↑ right Am FC	ND
		KETAMINE								
		Randomised-controlled trials (RCT)								
Abdallah et al., [78]	22 TRD subjects and 29 HC subjects	TRD: 44,8 (2.3); HC: 44,4 (1.8)	Ketamine or midazolam as active placebo	Ketamine 0.5 mg/kg over 40 min and active placebo 0.045 mg/kg over 40 min	ND	- Response and remission data after ketamine infusion not reported - baseline GBCr in the altered clusters significantly predicted MADRS improvement	fMRI	2 scans: 1. baseline 2. one day after treatment	-↓ GBCr in bilateral DMPFC and right DLPFC in TRD compared to HC -GBCr abnormalities overlapped with the ventral attention and frontoparietal networks -ketamine, but not midazolam, ↑ GBCr in the altered areas	ND
Abdallah et al., [43]	56 MDD subjects randomized to placebo (n = 18), ketamine (n = 19), and lanicemine (n = 19)	Placebo group: 25.7 years; ketamine group: 27.1 years; lanicemine group: 26.7 years	Ketamine or placebo or lanicemine	Ketamine 0.5 mg/kg IV infused over 60 min; lanicemine 100 mg in a single administration and placebo administered in saline infusion	Not recorded	-↓ BDI scores following ketamine (32%), placebo (27%), and lanicemine treatments (26%) -No differences in BDI improvement between treatment groups	fMRI	3 scans: 1. baseline, 2. during infusion 3. one day post treatment	-ketamine ↑ PFC GBFCr during infusion and 24 h post treatment - no significant change of lanicemine compared to placebo -delta PFC GBFCr positively predicted depression improvement in ketamine and lanicemine group, but not placebo -in ketamine group, GBFCr ↑ in DLPFC, DMPFC, and FMPFC during infusion and in the DLPFC and DMPFC at 24 h post treatment	ND
Chen et al., [51]	24 TRD subjects randomized to 0.5 mg/kg ketamine (n = 8), 0.2 mg/kg ketamine (n = 8), and placebo (n = 8)	0.5 mg/kg ketamine group: 51.13 (13.59); 0.2 mg/kg ketamine group: 49.75 (11.08); placebo group: 46.25 (8.14)	Ketamine or placebo	Ketamine 0.5 mg/kg, ketamine 0.2 mg/kg, and normal saline as placebo IV infused for 40 min	ND	-↓ in HAM-D in the 0.5 mg/kg ketamine group compared to the other groups at 240 min (-42.7% vs. -15.9% vs. -16.1%) and 1 day after infusion (-50.0% vs. -25.3% vs. -11.5%) -treatment response at 240 min (37.5% vs. 0% vs. 0%) and 1 day later (50% vs. 12.5% vs. 0%) after ketamine infusion compared with other groups	^{18}F-FDG PET	2 scans: 1. baseline 2. one day after treatment	-↑ activation of SMA and dorsal ACC higher in 0.5 mg/kg ketamine group than 0.2 mg/kg group and placebo -↑dorsal ACC activation is negatively correlated with depressive symptoms at 1 day later after ketamine	ND
Chen et al., [70]	48 TRD subjects randomized to standard ketamine dose (n = 16), low ketamine dose (n = 16), and placebo (n = 16)	Standard dose 43.3 (11.9); low dose 44.4 (10.8); placebo infusion 49.9 (8.1)	Ketamine or placebo	Ketamine 0.5 mg/kg (standard dose), ketamine 0.2 mg/kg (low dose), and normal saline as placebo infused for 40 min	ND	-placebo and both ketamine (0.5 mg/kg, and 0.2 mg/kg) groups showed respectively a 23.7% and 32.5%-36.4% reduction in MADRS scores -the ketamine 0.2 mg/kg group had a lower score of item 10 of MADRS (suicidal ideation) compared with the placebo group	fMRI	2 scans: 1. baseline 2. three day after treatment	-standard dose group: ↓ FC between the left dorsal ACC and right ACC and between the right DLPFC and right frontal pole; ↓ of suicidal ideation was negative correlated and ↓ FC between left dorsal ACC and right ACC -low dose group: ↓ FC between bilateral dorsal ACC and several frontal and parietal regions. Positive correlation between ↓ of suicidal ideation and ↑ FC between right DLPFC and left superior parietal region	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Evans et al., [44]	20 MDD subjects and 17 HCs	MDD: 36.2 (2.5); HC: 34.7 (2.9)	Ketamine or placebo	-0.5 mg/kg ketamine - one infusion of 0.9% saline solution with 2 weeks between infusions	Not recorded	-↓ of MADRS, SHAPS and HAM-D scores only in the MDD group after ketamine treatment -↓ of all psychometric scales in MDD group between ketamine and placebo scans	[1]HMRS	2 scans: 1. baseline 2. one day post ketamine or placebo infusion	-no significant differences were found both at baseline and after placebo or ketamine infusion in the pgACC -antidepressant effect was not predicted by baseline glutamate levels	ND
Lally et al., [53]	36 BD treatment resistant subjects, with a ^{18}F-FDG PET subgroup (n = 21)	BD: 46.69 (11.09), subgroup: 45.33 (11.89)	Ketamine	-0.5 mg/kg ketamine -one infusion of 0.9% saline solution randomized order over a 4-week study period, and with 2 weeks between each infusion	Monotherapy with a mood stabilizer (lithium or valproate)	-ketamine caused a greater ↓ in levels of anhedonia (SHAPS) across time than placebo -antianhedonic effects of ketamine were significant at days 1, 3, 7 and 14 following ketamine infusion and was independent from ↓ in general depressive symptoms	^{18}F-FDG PET	2 scans: 1. baseline 2. 2 h post ketamine infusion	-↑ rCMRGlu in VST was related to the highest anti-anhedonic effect of ketamine -significant relationship between ↓ in SHAPS scores and rCMRGlu ↑ in the dorsal ACC	ND
Lally et al., [54]	52 patients diagnosed with treatment-refractory MDD without psychotic feature	48.29 (12.84), ^{18}F-FDG PET subgroup (n = 20): 47.80 (11.79)	Medication-free patients received a single open-label dose of IV ketamine followed by oral riluzole, a glutamate reuptake enhancer, or placebo for 28 days	-single IV infusion of ketamine hydrochloride (0.5 mg/kg) over 40 min -between 4- and 6-h post-infusion, patients were randomized to receive either riluzole or placebo (n in both groups=26) twice a day for 4 weeks -riluzole was initiated at 100 mg/day, with the dose increasing in increments of 50 mg to a maximum of 200 mg/day	Medication-free patients (2-week drug-free period or 5 weeks for fluoxetine)	-investigating the changes following ketamine and adjunctive riluzole specifically on anhedonia, as assessed by SHAPS -the anti-anhedonic effect was correlated with increases in glucose metabolism in the dorsal ACC -almost all patients (87%) reported clinically significant levels of anhedonia at baseline, with a significant positive correlation between total SHAPS score and MADRS score at baseline, indicating that patients with higher levels of	^{18}F-FDG PET	2 scans: 1. baseline 2. 2-3.5 h post-infusion	-no association between anhedonia and baseline glucose metabolism was found -negative association between increased rCMRGlu and decreased anhedonia was found in the VST -negative association between decreases in anhedonia and increases in rCMRGlu in dorsal ACC and hippocampus following ketamine	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
						anhedonia also exhibited higher depressive symptoms -↓ in SHAPS scores across the 28-day period following a single ketamine infusion with a substantial effect within 40 min remaining 3 days post-infusion (riluzole had no additional benefit) -significant main effect of family history of alcohol use disorder, with improved anti-anhedonic response to ketamine in subjects with a positive history				
Li et al., [55]	48 TRD subjects divided into: -Group A (n = 16) -Group B (n = 16) -Placebo (n = 16)	Group A: 43.3 (11.9); Group B: 44.4 (10.8); Group C (placebo): 49.9 (8.1)	Ketamine or placebo	-Group A: 0.5 mg/kg ketamine; -Group B: 0.2 mg/kg ketamine; -Group C: saline solution	Antidepressants + others (not specific)	-group A and B had a significant higher antidepressant (HAM-D) response than placebo group	^{18}F-FDG PET pre and post treatment session	2 scans: 1. baseline 2. 40 min post infusion	-active groups higher ↑ PFC SUV than placebo -all groups had a significant ↓ Am SUV after infusion -HAM-D scores correlated with differences in SUV in PFC but not in Am -PFC changes did not differ between those with and without floating sensations -↑ PFC SUV predicted antidepressant response, with ketamine groups showing ↑ SUV in PFC, SMA, dorsal ACC and PCgyr than placebo, and Group A ↑ dorsal ACC and bilateral PCgyr SUV than Group B	-floating sensations, dissociation, dizziness/nausea, chest tightness, and others (e.g., crying)
Milak et al., [46]	38 MDD subjects	38.6 (11.2)	Ketamine	Single infusion of 0.1, 0.2, 0.3, 0.4 or 0.5 mg/kg ketamine	ND	-ketamine dose correlated positively with improvement in the HAM-D score; -clinical response was related to a small increase in Glx	^{1}HMRS	2 scans: 1. baseline 2. one day post ketamine infusion	-↓ in medial PFC Glutamine level after ketamine infusion -ketamine effects on brain Glx were dose-dependent -Glx ↓ in medial PFC mediated the antidepressant effect of ketamine	1 suicide, 1 active suicidal ideation, 1 antidepressant misuse, and 1 unrelated medical illness
Tiger et al., [57]	30 TRD subjects, including a placebo group (n = 10) and ketamine group (n = 20)	Placebo group: 37.1; Ketamine group: 39.2	Ketamine or placebo	0.5 mg/kg single infusion of ketamine; placebo: saline infusion	SSRIs	-partial response was achieved by 75% treated with ketamine vs. 30% in the placebo group; 35% of the ketamine-treated patients and 20% of patients given placebo fulfilled the criterion for response	PET	2 scans: 1. baseline 2. 24-72 h post infusion	-16.7% ↑ of 5- HT1B receptor binding in the hippocampus after ketamine; -5- HT1B receptor binding in VST at baseline correlated with MDD symptom ratings and with ↓ of depressive symptoms with ketamine	Disturbing dissociative side effects

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
		Open-label studies								
Abdallah et al., [78]	18 MDD subjects and 25 HC	MDD: 43 (2.2); HC: 39 (3.1)	Ketamine	Ketamine 0.5 mg/kg single infusion to MDD subjects	ND	56% of MDD subjects achieved clinical response	fMRI	2 scans: 1. before treatment 2. 24 h post infusion	-↓ GBCr in PFC but ↑ GBCr in PCC, precuneus, lingual gyrus, and cerebellum in the MDD group compared to HC -MDD is associated with a functional dysconnectivity between PFC/subcortical regions -ketamine responders showed ↑ GBCr in the lateral PFC, caudate and INS -ketamine normalized the discontinuity pattern PFC/subcortical regions in responders	ND
Ballard et al., [49]	19 TRD subjects	48 (12)	Ketamine	Ketamine: 0.5 mg/kg single infusion	ND	7 on 12 patients showed a significant reduction of suicidal ideation 230 min after ketamine infusion	^{18}F-FDG PET	2 scans: 1. before treatment 2. 230 min post infusion	-At baseline, suicidal ideation was associated with ↑ infralimbic cortex rMRGlu. -suicidal ideation ↓ after ketamine infusion was associated with ↓ rMRGlu in the infralimbic cortex -suicidal ideation ↓ was associated with rMRGlu ↑ in a large posterior cluster from the left lingual gyrus to the left superior cerebellum and the lateral OC	ND
Carlson et al., [50]	20 TRD subjects	47.6 (12.2)	Ketamine	Ketamine 0.5 mg/kg single infusion	ND	-Mean MADRS scores ↓ between baseline and 230 min post-ketamine: 29.7% (+/− 28.0% SD) - 6/20 were responders 230 min post ketamine infusion	^{18}F-FDG PET	2 scans: 1. before treatment 2. 120 min post infusion	- ↓ rMRGlu in habenula, INS, right VLPFC and DLPFC post ketamine infusion - ↑ rMRGlu in bilateral occipital, right sensorimotor, left parahippocampal, and left inferior parietal cortices post ketamine infusion, conceivably related to illusory phenomena experienced with ketamine - ↓ rMRGlu in the right habenula and the extended medial and orbital prefrontal networks is related with the antidepressant response to ketamine	ND
Dai et al., [58]	21 MDD subjects including subjects with comorbid PTSD (n = 10) and 29 HCs	MDD group: 35.80 (2.7);HC 32.90 (2.3)	Ketamine	- 36 subjects had an initial bolus of 0.23 mg/kg over 1 minute followed by a constant infusion of 0.58 mg/kg over 1 h (23 HC, 9 MDD and 4 MDD/PTSD); - 14 subjects (6 HC, 2 MDD and 6 MDD/PTSD) had an infusion of 0.5 mg/kg over 40 mins.	ND	-ketamine had a significant effect on depression severity of MDD subjects and MDD/PTSD subjects -ketamine did not show significant effects on PTSD severity in MDD/PTSD subjects -24 h after ketamine infusion, 55% MDD subjects (6 out of 11) and 70% MDD/PTSD subjects (7 out of 10) met depression remission criteria -37.5% of MDD/PTSD subjects met PTSD remission criteria	MRI	2 scans: 1. before treatment 2. one day post infusion	-↓ volume of right dorsolateral SFGyr, right opercular IFGyr, left SMA in the MDD group compared to HC before ketamine administration -24 h after ketamine administration, ↑ volume of right opercular IFGyr in both MDD and MDD/PTSD groups -↓ volume in left lateral OFC after ketamine administration in the MDD group -ketamine administration normalized the structural alterations of opercular IFG in both MDD and MDD/PTSD groups -no group differences in the volume of right opercular IFG after ketamine administration	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Gärtner et al., [81]	24 MDD subjects	44.4 (11.8)	Racemic ketamine or S-ketamine	-One IV 0.5 mg/kg racemic ketamine infusion or S-ketamine 0.25 mg/kg	-SSRIs (n = 7) -SNRIs (n = 7) -tricyclic antidepressants (n = 4) -anticonvulsants (n = 3) -atypical neuroleptics (n = 9) -benzodiazepines (n = 6) -melatonin (n = 3)	-92% of the patients (22/24) showed a reduction of depressive symptoms 24 h after the ketamine infusion -33% (8/24) of the patients were classified as responders	fMRI pre and post treatment session	2 scans: 1. before treatment 2. one day post infusion	-↓ baseline FC values between the sgACC and the right lateral anterior PFC in ketamine responders more than in ketamine non-responders -↑ FC changes in ketamine responders after ketamine more than ketamine non-responders between the sgACC and the right anterior PFC -baseline ↓ FC of the sgACC to the right lateral anterior PFC is related to ↑ levels of symptom reduction 24 h after ketamine	ND
Gonzalez et al., [71]	11 TRD subjects	47.7 (11.90)	Ketamine	A single dose of 0.5 mg/kg of ketamine diluted in 60 cc normal saline IV administered over 40 min	ND	Depression scores decreased significantly 24 h after infusion (HAM-D values from 22.44 to 9.00; MADRS values from 34.89 to 16.00; QIDS-SR values from 17.78 to 10.40)	fMRI	4 scans : 1. baseline 2. 1 h 3. 6 h 4. one day post infusion	-regional CBF changes after ketamine infusion detected across all subjects (↑ CBF observed in the thalamus and ↓ in the lateral OC) -In ventral basal ganglia significant negative relationships noted between change in depression score (baseline vs 24 h post infusion) and change in CBF from baseline to 1 h and from baseline to 24 h post infusion (↓ CBF after ketamine infusion in non-responders) -positive associations noted in mPFC for CBF change from baseline to 6 h post infusion, where responders tended to have decreased CBF after 6 h	ND
Herrera-Melendez et al., [59]	33 TRD subjects (F:18; M: 15)	47 (12.67)	Racemic ketamine and s-ketamine	23 subjects received a 40-min IV infusion of 0.5 mg/kg of racemic ketamine and 10 subjects received 0.25 mg/kg of s-ketamine	-SSRIs (n = 7) -SNRIs (n = 8) -tri-/tetracyclic antidepressants (n = 4) -antiepileptics (n = 3) -atypical antipsychotics (n = 9) -benzodiazepines (n = 6) -melatonin (n = 3)	-the average MADRS score at baseline was 25.8 and 17.4 after 24 h. The mean symptom improvement was 32.3% in 24 h post-infusion -30.3% of the subjects were classified as responders (e.g., a PCB greater than 50% after 24 h), while 66.7% of the subjects reached at least a partial response (e.g., a PCB greater than 25% after 24 h) -no significant difference between sites regarding symptom improvement, number of responders or partial-responders -no difference in depression severity at baseline between responders and non-responders	MRI	2 scans: 1. baseline 2. one day post infusion	-greater GMV of the bilateral rACC significantly predicted rapid depressive symptom reduction -potential of the rACC as a biomarker for response prediction to different antidepressant treatments	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Milak et al., [45]	11 MDD subjects	38.8 (12.8)	Ketamine	0.5 mg/kg single infusion	ND	10/11 subjects met criteria for remission by 230 min post-infusion, 9/11 at 24 h post-infusion and 7/10 at three days. HAM-D and BDI scores declined dramatically 24 h post-ketamine	^{1}HMRS	3 scans : 1. baseline 2. during infusion 3. immediately after infusion	-the peak frame for each subject revealed a 38% ± 8% increase in Glx/W from baseline and a 38% ± 9% increase in GABA/W from baseline -the time points for these peak values, obtained by averaging the mid-time point of the frame of each peak, were 28 ± 8 and 26 ± 21 min from the start of infusion for Glx/W and GABA/W, respectively (W = unsuppressed voxel tissue water)	ND
Rivas-Grajales et al., [73]	35 TRD subjects	42.2 (SD 13.9)	Ketamine	0.5 mg/kg single infusion	As needed, benzodiazepines were allowed but withheld the day of each scan	24 h following ketamine treatment, 20 subjects (57%) achieved a response (reduction in the baseline MADRS score by 50% or more), and 14 subjects (40%) showed remission of symptoms (defined as a MADRS score ≤ 9 post treatment). There was a significant main effect of ketamine on depression severity. MADRS scores at 24 h did not differ as a function of site	fMRI	2 scans: 1. baseline 2. one day post infusion	-main effect of time in the FC between the right habenula and a cluster in the left hippocampus and left parahippocampal gyrus -↓ MADRS scores from baseline to 24 h after infusion associated with an increase in FC between the right habenula and a cluster in the right frontal pole -↓ QIDS-SR scores associated with increased FC between the right habenula and clusters in the right occipital pole, right temporal pole, right parahippocampal gyrus, and left lateral OC	ND
Roy et al., [42]	13 TRD subjects	12-18 (16.9)	Ketamine	Six sessions of ketamine (0.5 mg/kg) infusions over the course of 2 weeks	Insulin	Percentage change in CDRS-R; non-responders (n = 6), responders (n = 5)	fMRI	2 scans: 1. baseline 2. one day post the 6th infusion	Depression reduction correlated with increased right NAc entropy and physiological changes (↑) in insulin-stimulated phosphorylation of mammalian target of rapamycin (mTOR)-glycogen synthase-3-beta (GSkz3b) signaling were associated with treatment response	ND
Siegel et al., [74]	23 TRD subjects	40.0 (14.05)	Ketamine	96-hour infusion of IV ketamine (0.15 mg/kg/h titrated toward 0.6 mg/kg/h)	Clonidine (to reduce psychotomimetic effects)	MADRS scores improvement (29 pre-infusion to 9 at day one, 13 at 2 weeks, 15 at 8 weeks)	fMRI	2 scans: 1. baseline 2. two weeks post infusion	-↓ connectivity within the DMN and between sgACC and the remainder of the DMN 2 weeks after -↑ FC between sgACC bilateral caudal anterior cingulate and bilateral anterior INS -↓ FC within the limbic system of depressed individuals	Fatigue (14%), inattention (14%), sedation (14%), light-headedness (5%), restlessness (5%), and palpitations (5%)
Sterpenich et al., [69]	10 MDD subjects	38–58 (51.0)	Ketamine	Single dose of ketamine (0.5 mg/kg)	ND	Decrease in scores in MADRS, HAM-D, BDI both rapidly (day 1) and lastingly (day 7); scores improved in emotional judgment and reward tasks	fMRI	3 scans: 1. baseline 2. one day post infusion 3. 1 week post infusion	-INS and VST activation for positive cues presentations -VST and medial substantia nigra/ventral tegmental area activation for successful presentations - Am, INS, and medial substantia nigra/ventral tegmental area increased activity for positive pictures	Transiently altered vigilance lasting less than 15 min; transient increase in blood pressure not needing any pharmacologic intervention

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Sydnor et al., [61]	13 TRD subjects	42.0 (13.9)	Ketamine	- ketamine: 0.5 mg/kg single infusion	Stable psychotropic medication regimen (including an antidepressant or a mood stabilizer) for 28 days prior to the infusion	66.2% improvement on the HAM-D from pre-treatment to 24 h post-treatment	MRI	2 scans: 1. baseline 2. 4 h post infusion	-positive correlation between pre infusion FA in the left cingulum bundle hippocampal portion and the left SLF with HAM-D ↓ post ketamine infusion -white matter ↑ after ketamine infusion, with ↑ FA in right ILF and left SLF -higher ↑ in FA in left UF and right UF is associated with ↓ of depressive symptoms	ND
Thai et al., [103]	11 TRD subjects	17.02 years (1.18)	Ketamine	Six ketamine infusions across 2 weeks	Not recorded	CDRS-R change positively correlated with change in TEPS and MADRS	Word Face Stroop (WFS) fMRI task where they indicated the valence of affective words superimposed onto either congruent/ incongruent emotional faces before and after the ketamine infusions	2 scans: 1. baseline 2. after infusion	-following ketamine treatment, better WFS performance correlated with self-reported decreased depressive symptoms and increased pleasure -analyses of corticolimbic, corticostriatal and DMN showed that across networks ↓ activation during all conditions (congruent negative, congruent positive, incongruent negative, and incongruent positive) correlated with ↓ in depressive symptoms and with ↑ in pleasure	ND
Valentine et al., [47]	10 MDD Subjects	41.7 (12)	Ketamine	- ketamine : 0.5 mg/kg single infusion	ND	-↓ in HAM-D and BDI scores one-hour post-infusion -↓ in HAM-D scores at day 7	[1]HMRS scans:	3 scans: 1. baseline 2. 3 h 3. 48 h post-infusion	-baseline measures of glutamate, GABA and glutamine in OC were not correlated with changes in HAM-D scores at any time point -no significant differences pre and post ketamine infusion in glutamate, GABA and glutamine in OC	-↑ in systolic blood pressure -↑ dissociation (CADDS score) at 20 min post-ketamine infusion (dissociation did not correlate with changes in HAM-D scores at any time point)
Vasavada et al., [62]	44 MDD subjects, 50 HCs	MDD subjects: 38.2 (10.9); HCs: 32.3 (11.9)	Ketamine	40-minute IV infusions of a subanesthetic dose (0.5 mg/kg) of ketamine diluted in 60 mL of saline with continuous clinical and hemodynamic monitoring	ND	-54.9% decrease in HAM-D scores for all subjects at T3 -↓ SHAPS, DASS, and rumination scale, while the BIS scale did not significantly change	MRI	3 scans: 1. baseline 2. 24 h post 1st infusion 3. 24 h post 4th infusion	-ketamine ↑right Am FC to the right CEN, ↓ Am FC to the left CEN at T2 versus T1, which then increased at T3 versus T2, and ↓ left Am FC to the SN -↓ at T2 FC left Am to SN predicted improvements in anxiety at T3 -ketamine ↑right hippocampus FC to the left CEN, and this change at T2 predicted decreased anhedonia at T3 -ketamine therapy leads to neuroplasticity between limbic regions	ND
Zhou et al., [84]	44 MDD subjects	35.2 (12.2)	Ketamine	0.5 mg/kg of ketamine diluted in saline administered over 40 min via IV and six subanesthetic dose infusions of ketamine	ND	Twenty-seven subjects (61.4%) showed significant improvement (more than a 50% decrease in MADRS scores) after receiving six infusions of ketamine	MRI	2 scans: 1. baseline 2. one day post last infusion	-at baseline smaller volumes were observed in the bilateral thalamus, bilateral hippocampus, and bilateral Am of the MDD group compared with the HCs. No significant volume difference in any subcortical regions between responders/nonresponders -after six ketamine infusions, increases were observed in the volumes of the left Am; the cornu ammonis 4 body, granule cell and molecular layer of the dentate gyrus body in the left hippocampus; and the cornu ammonis 4 head and molecular layer head in the	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
									right hippocampus -positive correlations were found between symptom improvement and the pretreatment volumes of the right thalamus and left subiculum head of the hippocampus, and changes in the volumes of the left Am and the left cornu ammonis 4 body	
Zhou et al., [85]	44 MDD subjects	35.2 (12.2)	Ketamine	0.5 mg/kg of ketamine diluted in saline administered over 40 min via IV over 12 days	ND	Twenty-seven (61.4%) and twenty-two (56.4%) subjects had an antidepressant response at day 13 and day 26, respectively (response defined as a decrease in MADRS score of at least 50%)	MRI	2 scans: 1. baseline 2. one day post last infusion	-following ketamine, a significant improvement in depressive symptoms, a small increase in right hippocampal volume and alterations in inflammatory markers was found -no significant association was found between changes in inflammatory markers and changes in hippocampal volume from baseline to day 13, while a weak association was found between tryptophan metabolite changes and other cytokine changes from baseline to day 26	ND
Zhuo et al. [63]	38 Treatment Resistant BD subjects	43.10 (5.3)	Ketamine	-0.5 mg/kg ketamine for a total of 10 administrations	-Sodium valproate -Atypical antipsychotics - Lithium - Lamotrigine - Sertraline - Citalopram - Bupropion - Clonazepam - Diazepam	-↓ HAM-D scores of 49.8% after 1-week of ketamine infusion -21 days after starting treatment, patients reported depressive symptoms more severe than before starting ketamine treatment	5 MRI scans:	5 scans: 1. before the treatment 2. second day, 3. one week, 4. two weeks 5. three weeks after initiating ketamine treatment	-↓ gFCD in bilateral INS, right caudate nucleus, and bilateral IFGyr - ↑ gFCD in bilateral postcentral gyrus, Sg ACC, bilateral thalamus, and cerebellum - gFCD alterations were sustained for up to three weeks after the first ketamine infusion	13 patients stopped ketamine treatment due to side effects
		Double-blind trials								
Abdallah et al., [43]	7 MDD subjects and 14 HCs	30 years (1.2)	Ketamine	HCs received a subanaesthetic dose of the drug (0.23 mg/kg bolus followed by 0.58 mg/kg infusion over approximately 75 min), while MDD subjects received 0.5 mg/kg infused over 40 min	ND	-compared to placebo, ketamine induced significant ↑ in CADSS and BPRS Positive symptoms, but not BPRS Negative symptoms -During the ketamine infusion, the 13 C Glx enrichment ratio was negatively correlated with CADSS, but not with BPRS Positive or BPRS Negative symptoms -there were no significant correlation between Glutamine or 13 C Glutamate enrichment and	^{13}C MRS	2 scans: 1. baseline 2. one day post last infusion	-compared to placebo, ketamine ↑ prefrontal glutamate-glutamine cycling, as indicated by a 13% increase in 13 C glutamine enrichment -no evidence of ketamine effects on oxidative energy production, as reflected by 13 C glutamate enrichment -during ketamine infusion, the ratio of 13 C glutamate/glutamine enrichments, a putative measure of neurotransmission strength, was correlated with the CADSS (providing the most direct evidence in humans to date that ketamine increases glutamate release in the prefrontal cortex)	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
						any of CADSS, BPRS Positive, or BPRS Negative scores -during placebo infusion, no significant correlations between any of the metabolites and psychotomimetic measures				
Evans et al., [44]	33 MDD subjects and 25 HCs	MDD: 36 ± 10 years; HC: 33 ± 10 years	Ketamine	IV infusion of either ketamine (0.5 mg/kg) or placebo on two separate test days spaced two weeks apart	ND	-MDD subjects had significantly improved MADRS scores, a change that was maintained at the Day 2 time-point -no significant differences in MADRS score were observed for the HCs from baseline or placebo at either Day 2 or Day 10	fMRI	3 scans: 1. baseline 2. two days post infusion 3. ten days post infusion	-at baseline, the HCs had greater connectivity within the DMN than the MDD group in the right DLPFC and left post-central gyrus. The HCs showed greater connectivity within the DMN than the MDD group in the right precentral gyrus, as well as the left and right post-central gyrus. A smaller difference unique to the k2 scan was noted with regard to connectivity of the INS with the DMN between the MDD and HC groups. This normalization between the groups returned to baseline by Day 10 -In MDD subjects, connectivity between the INS and the DMN was normalized compared to HCs two days post-ketamine infusion. This change was reversed after 10 days and did not appear in either of the placebo scans -Group-specific connectivity differences in drug response were observed, most notably in the INS in MDD subjects and the thalamus in HCs	ND
Kraus et al., [68]	28 MDD subjects and 22 HCs	MDD: 33.9 years (10.6); HC: 36 years (9.7)	Ketamine	IV infusion of ketamine (0.5 mg/kg) or saline 2 weeks apart in randomized order	ND	MADRS scores improved in MDD subjects from baseline (33.1 (4.7)) after ketamine infusion (23.4 (10.7)); similarly, HAM-D and BDI scores reduced after ketamine infusion from baseline to T2 (respectively from 21.0 (4.4) to 14.1 (6.1) and 29.1 (7.8) to 20.4 (12.7))	fMRI	2 scans: 1. baseline 2. two or three days post infusion	-↓ GBC was observed in individuals with MDD only at baseline in the anterior and medial cingulate cortices, as well as in the PFC only after regressing the global signal. Ketamine had no effect compared to baseline or placebo in either group in any pipeline.	
Mkrtchian et al., [76]	33 TRD subjects and 21 HCs	TRD: 36 years (9.54); HCs: 34 years (10.97)	Ketamine versus placebo	ketamine: 0.5 mg/kg single infusion; placebo: 0.9% saline solution	All TRD participants were medication-free for at least 2 weeks (5 weeks for fluoxetine, 3 weeks for aripiprazole)	-no significant correlations were noted between ΔMADRS and ΔFC at Day 2 in TRD; however, a significant correlation was observed between post-ketamine improvement	fMRI	2 scans: 1. baseline 2. two days post infusion	-in TRD participants ketamine increased FC between the caudate and prefrontal regions (left DLPFC and right VLPFC) involved in cognitive processes and between the putamen and prefrontal regions (perigenual ACC and OFC) associated with affective processes. -increased frontostriatal connectivity post ketamine is associated with sustained improvements in anhedonia but not general depressive symptoms -no significant correlations were noted	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
						(SHAPS score) and post-ketamine increases in FC between dorsal caudate-right VLPFC -no significant correlations were observed between ΔMADRS and ΔFC at Day 10 in TRD participants; improvement in Day 10 SHAPS scores were associated with post-ketamine increases in dorsal caudate-perigenual ACC connectivity, and there was a trend toward a similar pattern for dorsal caudate-right VLPFC connectivity and ventral rostral putamen-right OFC -no significant main effects on C reactive protein levels were noted for group, treatment, or group-by-treatment interaction			between MADRS and FC at day 2 and 10 in TRD participants -a significant correlation was observed between post-ketamine improvement (SHAPS) and post-ketamine increases in dorsal caudate-right VLPFC functional connectivity on day 2 and 10 TRD participants	
		Observational Studies								
Esterlis et al., [52]	14 MDD and 13 HC	MDD: 35.6 years ±13.6; HC: 33.1 years ±13.1	Racemic ketamine	Initial bolus of 0.23 mg/kg over 1 minute, followed by a constant infusion of 0.58 mg/kg over 1 hour	ND	-↓ depression scores following ketamine administration (45 ± 70% on MADRS, 52 ± 29% on BDI; $p < 0,001$) and 24 h post ketamine (53 ± 69% on MADRS, 49 ± 35% on BDI; all $p < 0,001$) in the MDD group -↑ in CADSS scores during ketamine administration in both the HC and MDD groups (amnesia: $F(2,22) = 15.08$, $p < 0,001$)) which returned to	$^{[11C]}$ABP688-PET	3 scans: 1. baseline 2. during infusion 3. one day post infusion	-at baseline, significantly lower $^{[11C]}$ABP688 binding (ketamine-induced ↓ in mGluR5 availability) was detected in the MDD as compared with the control group -a significant ↓ in depressive symptoms was observed following ketamine administration in the MDD group, which was associated with the change in binding immediately after ketamine	Significant increases in blood pressure and heart rate were observed during the ketamine scan until ~30 min post ketamine

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
						baseline at 24 h -↓ MADRS scores in MDD subjects from 23.9 ± 8.7 to 11.5 ± 11.2 (post ketamine) and 11.9 ± 12.3 (24 h after the administration) -↓ BDI values from 24.2 ± 11.4 (baseline) to 13.2 ± 8.5 (post ketamine) and 14.3 ± 11.2 24 h after the administration				
Loureiro et al., [60]	44 MDD subjects and 32 HCs	ECT (n = 17): 36.8 years (11.0); Ketamine (n = 27): 37.3 years (10.8); HC (n = 32): 34.5 years (13.5)	Ketamine or ECT	Ketamine infusions 2–3 days apart (2–3× a week) for a total of four infusions: at each session a single subanaesthetic dose (0.5 mg/kg) of ketamine diluted in 60 cc normal saline was delivered IV over a 40-minute period. All subjects received right-unilateral ECT (pulse width: 0.3 ms, amplitude: 800 mA.) 48% of subjects were subsequently switched to bitemporal ECT (pulse width: 0.5 ms, amplitude: 8000 mA) - the length of the ECT index was individually prescribed (average number of sessions = 14)	-SSRI, SNRI, NDRI, and tricyclic antidepressants were continued during the study if unchanged for at least the preceding 6-weeks -Benzodiazepines were discontinued at least 24 h prior to all study visits	-ECT: HAM-D scores improved from 21.41 (8.33) to 15.35 (8.60); similarly, DASS scores changed from 7.82 (5.60) to 6.53 (4.38) and SHAPS from 6.76 (4.41) to 3.12 (3.89) -KET: HAM-D scores improved from 20.15 (4.70) to 8.93 (4.46), and similarly DASS from 5.52 (5.32) to 1.67 (2.20) and SHAPS from 8.07 (3.88) to 3.81(4.15) -No significant differences for either of the clinical scales were observed between the ECT and ketamine samples at baseline. HAM-D and SHAPS significantly decreased after both ketamine and ECT. However, DASS scores decreased significantly after ketamine only	fMRI	2 scans: 1. baseline 2. 24-72 h post last infusion	-↓ Am activity after both ECT and ketamine for positive and negative emotional face processing comparing baseline and post-treatment across all subjects -BOLD change for positive faces in the inferior parietal cortex significantly correlated with overall symptom improvement, and BOLD change in frontal regions correlated with anxiety for negative faces, and anhedonia for positive faces -in the ketamine sample only, post-treatment change in the fearful > objects contrast significantly correlated with %DASS and % SHAPS change in the right Am -BOLD activity change before and after treatment for the neutral faces condition revealed no significant effects of time -examining associations with change in clinical outcome measures in the emotional face processing network, a cluster in the posterior superior temporal cortex showed a significant positive correlation between %HAM-D change and BOLD change for the happy > objects contrast. Three clusters in the right INS, right DLPFC and right postcentral cortex revealed a significant negative correlation between %DASS change after treatment, and BOLD change for the fearful > objects contrast. Finally, a right DLPFC cluster showed a significant positive correlation between change in %SHAPS and BOLD response for the happy > objects contrast	Measures of ketamine side effects were acquired using the CADSS after 60 min of each infusion
Loureiro et al., [75]	46 TRD-MDD subjects and 32 HCs	TRD-MDD subjects: 39.2; HCs: 35.2	Racemic ketamine	Four serial IV infusions of racemic ketamine: for each session a single subanaesthetic dose (0.5 mg/kg) of ketamine, 2–3 times a week	Previous monoaminergic antidepressant therapy, if unchanged in the preceding 6-weeks. Benzodiazepines were discontinued >	HAM-D scores improved in MDD subjects from T1 (n = 42): 1957 (4,69), to T2 (n = 39): 1290 (4,28), to T3 (n = 40): 8,58 (4,76); similarly, QIDS scores	fMRI	3 scans: 1. baseline 2. 24 h after the first infusion 3. 24 - 72 h after the last infusion	-the average activation map for the NoGo > Go contrast revealed mostly right hemisphere ↑ in BOLD in the PFC, SMA, anterior INS, superior frontal cortex, ACC, PCC, precuneus, and in the left cerebellum-lobuleVIIb - low-dose ketamine therapy, served to decrease the connectivity between the posterior cerebellum and both the FPN and SMN in patient remitters, but not	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
					72 h prior to all study visits	improved: from T1 (n = 42): 1627 (4,58), to T2 (n = 39): 1126 (5,43), to T3 (n = 40): 6,55 (4,04); finally DASS scores reduced from T1 (n = 42): 5,10 (4,64), to T2 (n = 39): 3,38 (3,38), to T3 (n = 40): 1,68 (2,09) -two sample t-tests considering HCs and MDD subjects at T1, revealed no significant differences for age, and education, and a trending difference for sex			non-remitters; however, the connectivity between the cerebellum and the SN decreased for both remitters and non-remitters, though there was a greater mean decrease for the remitters in comparison to non-remitters after both single and serial infusion -cerebellar-frontoparietal network and cerebellar-salience connectivity at baseline (T1) was associated with subjective clinical outcome as measured by the QIDs, suggesting cortico-cerebellar connections during response inhibition are relevant to successful treatment response and may have utility as biomarkers for successful ketamine response	
Morris et al., [72]	Study 1: 28 MDD subjects and 20 HCs; Study 2: 14 MDD subjects	Study 1: 36.5 (11); Study 2: 44.69 (11.4)	Ketamine	Study 1: task-based fMRI using an established incentive-processing task; Study 2: same scanning protocol at baseline and following a 40 min infusion of ketamine (0.5 mg/kg)	Not recorded	There was a significant improvement in MDD symptoms following a single-dose IV ketamine (MADRS, $T(16) = 10.52$, $p < 0.0001$), as well as improvements in anhedonia ($T(16) = 5.52$, $p < 0.0001$)	fMRI	Study 2: 2 scans: 1. baseline 2. following ketamine infusion	-subjects with MDD showed higher sgACC activation to positive and negative monetary incentives compared to controls, associated with anhedonia and anxiety, respectively. In addition, subjects with MDD had higher resting-state FC between hippocampus and sgACC, associated with sgACC hyper-activation to positive incentives, but not negative incentives. Finally, ketamine reduced sgACC hyper-activation to positive incentives, but not negative incentives	ND
Murrough et al., [83]	18 TRD subjects and 20 HCs	TRD: 38.1 years (13.8); HCs: 35.0 years (8.9)	Ketamine	0.5 mg/kg single IV infusion	Not recorded	In the TRD group, baseline MADRS score 29.9 (6.8) improved to post treatment MADRS score 16.4 (11.1)	fMRI	2 scans: 1. baseline 2. one day post infusion	-during the positive emotion task, both groups demonstrated main effects of emotion and there was a significant group × emotion interaction within the left INS and right caudate. In both regions, the TRD group demonstrated hypoactivation for the emotion>neutral contrast compared with the HC group -in the right caudate, mean blood oxygen level dependent percent signal for each condition showed that responses to positive emotion are reduced in the TRD compared with healthy group, whereas the responses to neutral stimuli are similar. There were no significant results for the happy 50% >neutral contrast. During the negative emotion task, no main effects of emotion or group × emotion interactions survived correction	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Sahib et al., 2019	22 MDD subjects and 18 HCs	MDD: 35.2 years (9.95); HC: 36.11 (14.5)	Ketamine	IV infusions of ketamine (0.5 mg/kg)	Monoaminergic antidepressants and benzodiazepines (discontinued the night before and morning of all study visits)	13/22 TRD showed <50% improvement; 7/22 achieved remission (HAM-D < 7)	fMRI	3 scans: 1. baseline 2. one day post first infusion 3. one day post last infusion	-↑ in global CBF after the first infusion that decreased/normalized after the fourth infusion in the cingulate and primary and higher-order visual association regions -↓ in regional CBF in the bilateral hippocampus and right INS after serial infusion therapy	ND
Sahib et al., [60]	47 MDD subjects and 32 HCs	MDD: 34.75 years (13.5); HCs: 38.61 years (10.6)	Ketamine	IV infusions of ketamine (0.5 mg/kg)	Monoaminergic antidepressant medications and benzodiazepines (they were discontinued the night before and morning of all study visits)	15 subjects achieved remission (HAM-D < 7)	fMRI	3 scans: 1. baseline 2. one day post first infusion 3. one day post last infusion	-↓ in fMRI activity in brain regions associated with response inhibition, including the DLPFC along with areas in the superior and inferior parietal lobules -↓ activity across DMN, FPN, DAN, and the SN networks in the right hemisphere; activation of dorsal ACC; activation of INS	ND
Sahib et al., [86]	61 MDD subjects and 40 HCs	HC: 32.87 years (12.7) 38.96 years (10.7)	Ketamine	IV infusions of ketamine (0.5 mg/kg)	Monoaminergic antidepressant medications and benzodiazepines (they were discontinued the night before and morning of all study visits)	24 subjects achieved remission (HAM-D < 7)	fMRI	3 scans: 1. baseline 2. one day post first infusion 3. one day post last infusion	-FC within the somatomotor network was found significantly greater in HC as compared to MDD at baseline -FC between the ventral attention node and the visual node was significantly higher in MDD -higher FC between visual cortex and the DMN node in MDDs -FC between the cerebellum and the SN was positively correlated and significantly reduced	ND
		Crossover Studies								
McMillan et al. 2020	30 MDD subjects	30.2 (8.2)	Ketamine or active placebo	-Day 1: racemic ketamine (0.25 mg/kg bolus, 0.25 mg/kg infusion for 45 min) - After 3-weeks of wash-out: active placebo remifentanil (1.7 ng/mL target-controlled infusion)	-SSRI -SNRI -Tricyclic -Other antidepressants	-69% of responder (≥ 50% reduction in MADRS score at one day post infusion) after ketamine infusion -significant ↓ MADRS scores after ketamine infusion than active placebo -85% participants were able to correctly identify their ketamine session during a debrief	fMRI	3 scans: 1. baseline 2.during infusion (ketamine or remifentanil) 3. during infusion (ketamine or remifentanil)	-↑ in BOLD signal in ACC, paracingulate gyrus, left frontal pole, SFGyr, PH gyrus, right INS, ITG, IFG and the occipital pole after ketamine infusion -BOLD signal ↓ in sgACC, medial PFC, inferior thalamus, hippocampus, rAm, putamen, and the pre- and post-central gyri after ketamine infusion -None of these ketamine-induced changes were significantly related to antidepressant response	ketamine: ↑ in heart rate and systolic and diastolic blood pressure. No significant changes to end-tidal CO2 or respiratory volume per unit time (RVT) with the active placebo
Nugent et al., [56]	21 BD Subjects	46 (12)	Ketamine or placebo (2 weeks between the two treatments)	Ketamine: single infusion 0.5 mg/kg Placebo: Saline Infusion	5 subjects: valproic acid (50–125 μg/mL) 16 subject: lithium (0.6–1.2 mEq/L)	-Significant ↓ MADRS score after Ketamine than placebo (nine subjects showed a reduction of at least 50% in MADRS score after ketamine infusions)	^{18}F-FDG PET	3 scans: 1. baseline 2. 120 min after infusion (placebo or ketamine) 3. 120 min after infusion (placebo or ketamine)	-↑ in rMRGlu in right VST after ketamine infusion - subjects with higher ↓ MADRS score had the largest metabolic increase after ketamine infusion in right VST -↑ rMRGlu under placebo in sgACC is related to a higher clinical improvement following ketamine administration -lower metabolism in left hippocampus is related to more depressive symptoms	ND

Table 3. continued

REF.	POPULATION	MEAN AGE (years) (SD)	TREATMENT	DOSE AND DURATION	CONCOMITANT DRUG	CLINICAL OUTCOME	IMAGING TECHNIQUE	TIMING	RADIOIMAGING FINDINGS	ADVERSE EVENTS RECORDED
Reed et al., 2019	33 MDD Subjects 24 HC	MDD: Mean age 35.9 (9.8) HC: 34.4 (10.7)	Ketamine or placebo. Every group received the other treatment condition two weeks later	Ketamine: 0.5 mg/kg single infusion Placebo: saline infusion	no	-MADRS scores ↓ significantly post ketamine infusion in MDD group, while there were no differences in placebo group	fMRI scan pre and post each treatment session	3 scans: 1. baseline 2. two days after infusion (placebo or ketamine) 3. two days after infusion (placebo or ketamine)	-in MDD group, ↓ of BOLD signal in bilateral frontal, temporal, precuneus, and posterior cingulate regions during the emotional task after ketamine infusion than placebo -Significant deactivation of areas involved in DMN after ketamine infusion (medial PFC, PCC) -MDD group has ↑ BOLD activation of INS and ACC than HC group during emotional processing -post-ketamine, MDD group shows a ↓ of BOLD activation in those areas, similar to HC participants	ND

ACC anterior cingulate cortex, *Am* amygdala, *BDI* beck depression inventory, *BIS* barratt impulsiveness scale, *BOLD* blood oxygen-level dependent, *BPRS* brief psychiatric rating scale, *CADSS* clinician-administered dissociative states scale, *CBF* cerebral blood flow, *CDRS-R* children's depression rating scale-revised, *CEN* central executive network, *DAN* dorsal attention network, *DASS* depression anxiety stress scales, *dFC* dynamic functional connectivity, *DLPFC* dorsolateral prefrontal cortex, *DMN* default-mode network, *DMPFC* dorsomedial prefrontal cortex, *FA fractional anisotropy FC* functional connectivity, *FDG-PET* fluorodeoxyglucose-positron emission tomography, *FMPFC* frontomedial prefrontal cortex, *fMRI* functional magnetic resonance imaging, *FPN* frontoparietal network, *GABA* gamma-amino-butyric acid, *GBC* global brain connectivity, *GBCr* global brain connectivity regression, *gFCD* global functional connectivity density, *Glx* glutamate-glutamine, *GMV* gray matter volume, *HAM-D* hamilton depression scale, *HC* healthy controls, *HeGyr* heschl's gyrus, *HRMS* high resolution mass spectroscopy, *IFGyr* inferior frontal gyrus, *ILF* inferior longitudinal fasciculus, *ilPC* inferior lateral parietal cortex, *INS* insula, *IV* intravenous, *MADRS* montgomery asberg depression rating scale, *MDD* major depressive disorder, *NAc* nucleus accumbens, *MRI* magnetic resonance imaging; *MRS* magnetic resonance spectroscopy, *OC* occipital cortex, *OFC* orbitofrontal cortex, *Op* operculum, *PCC* posterior cingulate cortex, *PCGyr* precentral gyrus, *PFC* prefrontal cortex, *pgACC* pregenual anterior cingulate cortex, *PTSD* post-traumatic stress disorder, *QIDS-SR* quick inventory of depressive symptomatology-self report, *rCMRGlu* regional cerebral metabolic rate for glucose metabolism, *RFPN* right frontoparietal network, *RRS* rumination response scale, *RSFC* resting state functional connectivity, *SD* standard deviation, *Sfgyr* superior frontal gyrus, *Sg* subgenual area, *SHAPS* snaith hamilton pleasure scale, *SLF* superior longitudinal fasciculus, *SMA* supplementary motor area, *SN* salience network, *SPECT* single-photon emission computerized tomography, *SNRI* serotonin noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *SUV* standardized uptake value, *TEPS* temporal experience of pleasure scale, *TGyr* temporal gyrus, *TRD* treatment resistant depression, *UF* uncinate fasciculus, *VMPFC* ventromedial prefrontal cortex, *VST* ventral striatum, *5-HT1B* 5-hydroxytryptamine receptor 1B, *13C MRS* magnetic resonance spectroscopy.

*The DMN is composed of the VMPFC, the PCC, bilateral inferior PC, and the middle temporal lobe.

n = 4 studies, and the Snaith-Hamilton Pleasure Scale (SHAPS) in n = 6 studies.

Clinical outcomes

In the only study evaluating the use of **ayahuasca** in 17 MDD subjects, depressive symptoms, assessed using the HAM-D, the MADRS, and the Brief Psychiatric Rating Scale (BPRS), significantly decreased from 80 min to day 21 [48].

In the four studies concerning **psilocybin** [64–67], a significant reduction in depressive symptoms (BDI, HAM-D, QIDS-SR) compared to baseline was described 4 and 5 weeks after treatment. Besides, all four studies reported mystical experiences associated with psilocybin administration [64–67]. However, a single study [64] indicates a significant correlation between these experiences and neuroimaging changes in individuals with treatment-resistant depression.

Ketamine administration reduced BDI [43, 45, 52, 68, 69], HAM-D and MADRS [47, 50, 52, 59, 62, 68–74] scores compared to placebo. Furthermore, several studies highlighted the anti-anhedonic action of ketamine, with a significant reduction of SHAPS scores after multiple ketamine infusions [53, 54, 62, 75, 76].

Safety and tolerability

In relation to the selected studies, vomiting (47%) and dissociative symptoms were recorded after the administration of **ayahuasca** (from 40 to 80 min) [48]. **Psilocybin** has never been associated with adverse events, whereas in the case of **ketamine**, fluctuating sensations were reported, dissociation, dizziness/nausea, chest tightness, etc [47, 55, 57]. Moreover, one suicide, one active suicidal ideation, and one antidepressant abuse were recorded upon ketamine treatment [46]. Finally, other ketamine-related symptoms such as fatigue, inattention, sedation, light-headedness, restlessness, and palpitations were reported [74]. Other symptoms included transiently impaired vigilance and increased blood pressure (which did not require pharmacologic intervention) [47 , 52, 69]. Those effects were not related to the use of concomitant oral treatments.

Neuroimaging findings

Ayahuasca. In a single open-label study [48], SPECT was used to assess the effects of ayahuasca on brain connectivity in individuals with recurrent depression. The study found, after ayahuasca intake, increased perfusion in the left nucleus accumbens, right insula, and left subgenual area, all regions involved in regulating mood and emotion.

Psilocybin. Studies on psilocybin found significant changes upon drug intake, mainly regarding DMN areas and – among subcortical structures- the amygdala. For instance, a significant relationship between decreased cerebral blood flow in the left amygdala and reduction of *depressive symptoms* was shown at the fMRI, thus confirming a significant role for this structure in the improvement of emotion processing and mood balance, even upon pharmacological modulation. Interestingly, the reduction of the resting-state FC between this structure and DMN-related cortical regions was also linked to *mystical experiences*, possibly due to the role of the amygdala in the induction of mindful states [64, 67, 77]. The centrality of the amygdala in psilocybin-driven neural and clinical changes was also observed with a *face/emotion perception* fMRI task [66]. These neuroimaging findings showed decreased FC between the ventromedial prefrontal cortex (VMPFC) and the right amygdala correlating with lower rumination levels, while increased FC between the amygdala and occipital regions correlated with a reduction of depressive symptoms at one week. Furthermore, increased right amygdala FC specifically during the processing of fearful faces task, significantly correlated with the therapeutic response and remission of BDI scores [66]. Further studies should focus on the predictive role of face/emotion fMRI tasks on treatment response before clinical changes occur.

From a **cortical** point of view, an increased resting-state FC between the VMPFC and the bilateral inferior lateral parietal cortices predicted *treatment response* at one week, while decreased post-treatment FC between para hippocampal and prefrontal cortices predicted 5-weeks responses [64]. This finding is consistent with the role of VMPFC in emotion processing – an activity strictly coupled with the amygdala. Finally, FC between the dorsal anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC) was investigated concerning psilocybin-driven changes in *cognitive flexibility*. However, the two changes appear not correlated [65].

Ketamine/esketamine. Several reports on fMRI changes after ketamine/esketamine intake highlighted the role of the lateral and medial prefrontal cortices, whose alterations have been typically linked to MDD cognitive – but also affective – dysfunctions [29]. Following ketamine administration, increased global brain connectivity regression (GBCr) in dorsal prefrontal cortices (PFC), both lateral and medial (DLPFC, DMPFC), was documented in TRD patients - compared to healthy controls [43, 78]. This finding indirectly indicates a restoring of physiological functioning of prefrontal areas, since decreased PFC GBCr has been regarded as a graph-theory-based signature of conditions related to chronic stress, including PTSD and MDD [79], possibly related to impaired glutamatergic transmission [78].

A position paper suggested the existence of a "Cognitive dyscontrol" biotype of depression, where a hypoconnectivity between the ventral ACC and the DLPFC, along with hyperconnectivity between the dorsal part of the ACC and the DLPFC may promote inhibition deficits linked to complex attention dysfunctions and the incapacity of suppressing DMN-related processes like rumination [80]. After ketamine infusion, a reduced FC between the left dorsal and right ACC and between the right DLPFC and right frontal pole was shown [70], thus suggesting a normalization of the hyperconnectivity between the dorsal ACC and the DLPFC in MDD [80]. The studies by Sahib at al. confirmed the modulation of the brain areas involved in response inhibition, like the DLPFC and the dorsal ACC, documenting their altered FC with several other networks, like the DMN, the FPN, the DAN, and the SN within the right hemisphere, after ketamine administration [60]. Similarly, increased FC between the subgenual ACC and several cortico-subcortical brain regions, like the right anterior PFC in ketamine responders [81], or with caudal anterior cingulate nuclei and anterior insulae, was frequently observed upon ketamine administration [74].

The ventrolateral prefrontal cortex (VLPFC) is also involved in cognitive tasks and emotion control, participating in object-related working memory functions (as opposed to spatial-related ones, which are mostly controlled by the DLPFC) [82]. VLPFC atrophy can be observed in depressed patients, and the activation of the left VLPFC has been linked to abnormal processing of negative affective content [29]. In this context, increased connectivity after ketamine infusions between prefrontal areas (as VLPFC) and subcortical striatal regions (i.e., caudate) has been reported in several fMRI studies [63, 76, 78, 83]. Increases in FC between dorsal caudate-right VLPFC immediately after ketamine infusion, or 10 days after increased dorsal caudate-perigenual ACC connectivity significantly correlated with clinical improvement of anhedonic symptoms (SHAPS score) [76]. Furthermore, other studies [63, 78, 83] indicated global FC increases between right caudate, nucleus accumbens and prefrontal areas, which were significantly related to antidepressant response. Additionally, activity in other subcortical regions associated with fronto-striatal networks and reward-related activity (e.g., ventral striatum; ventral tegmental area) were enhanced in response to reward stimuli after ketamine infusion in MDD subjects [69].

The amygdala participates in several functions, including emotion processing, cognitive control, and elaboration of pain stimuli, through highly flexible interactions with the CEN, SN, and

DMN [29]. Disrupted FC of the amygdala has been observed in several conditions, including generalized anxiety and depressive disorders. Thus, the observation of significant changes in the amygdala's FC upon ketamine administration, mostly involving the CEN, is in line with the literature. In particular, increased FC was observed between the right amygdala FC and the CEN, while decreased FC with the left CEN was documented at the subsequent follow-up. Decreased FC was also observed between the left amygdala and SN regions and predicted anxiety improvements [62].

From a structural point of view, increased volumes of the left amygdala and the left *cornu ammonis* 4 body were documented after six ketamine infusions, as well as a positive correlation between the pre-treatment volumes of the right thalamus and left subiculum head of the hippocampus, and a subsequent improvement of depressive symptoms [84]. The same group described a significant improvement in depressive symptoms and a small increase in right hippocampal volume following ketamine infusions [85]. These findings were confirmed in a study highlighting the critical roles of the amygdala and hippocampal subfields in producing antidepressant effects after repeated ketamine treatment [63].

Changes in cerebral blood flow (CBF) after ketamine infusion have also detected in several fMRI studies. Specifically, increased CBF was documented in the thalamus, while decreased CBF was found in the lateral occipital cortex [71] Interestingly, a 24-h decrease in ventral basal ganglia's CBF values was detected in non-responders, and changes in depression symptom scores negatively correlated with these values [71]. On the contrary, responders showed a correlation between symptom relief and a 6-h-decreased CBF within the medial prefrontal cortex (MPFC) [71]. Increased global CBF has been observed after the first ketamine infusion, with normalization – after the fourth infusion – within the cingulate and primary and higher-order visual association regions. Finally, regional CBF reduction was documented in hippocampi and the right insula after serial infusion [86].

On fewer occasions compared to fMRI, fluorodeoxyglucose PET (^{18F}FDG-PET) has also been employed to investigate the effects of ketamine. The significant effect on the ACC region was also confirmed, since a dose-dependent increased activation of the dorsal ACC and the supplementary motor area (SMA), was found to negatively correlate with depressive symptom severity after ketamine infusion, compared to placebo [51]. Increased cerebral metabolic rates were also documented in the dorsal ACC and the ventral striatum (VST), linked to the anti-anhedonic effect of ketamine in bipolar depression [53, 54]. Similar correlations were also documented for depressive symptoms. Increased metabolic rates in the right VST correlated to the improvement in MADRS scores, and lower metabolism in the left hippocampus was directly associated with depressive symptom severity [56]. Moreover, reduced metabolic rate in the right habenula and the extended medial and orbital prefrontal networks was linked to clinical response to ketamine [50]; whereas, increased regional cerebral metabolic rate in bilateral occipital, right sensorimotor, left parahippocampal, and left inferior parietal cortices post infusion, was linked to the illusory phenomena experienced with ketamine [50]. Higher tracer uptake in the dorsal ACC, along with the prefrontal cortex, SMA, and precentral gyrus, than placebo also predicted treatment response, according to Li and colleagues [55].

Increased infralimbic cerebral metabolic rates positively correlated with baseline suicidal ideation in TRD patients. Accordingly, ketamine administration decreased the infralimbic metabolic rate while increasing it in a large posterior cluster encompassing regions from the left lingual gyrus to the left superior cerebellum and the lateral occipital cortex [49].

In addition to ^{18}FDG, other tracers have been used by some research groups to investigate the various effects of ketamine through PET imaging. Esterline et al. found a significant ketamine-induced decrease in metabotropic glutamatergic receptor (mGluR5) availability through PET with [11 C]ABP688 in MDD and healthy subjects. Based on these findings, they hypothesized a functional link with the immediate glutamatergic surge that occurs after ketamine infusion. Furthermore, they reported a positive correlation between the antidepressant effects of ketamine and the decrease in mGluR5 availability [52].

MRI spectroscopy (MRS) techniques were only used in a few studies, whose results converged upon a dose-dependent effect of ketamine on glutamine-glutamate cycling. Reduction in MPFC glutamine levels after ketamine infusion was documented, possibly in relation to the compound's antidepressant effect [46]. Accordingly, ketamine increased prefrontal glutamate-glutamine cycling compared to placebo, and the ratio of 13 C glutamate/glutamine enrichment, a putative measure of neurotransmission strength, correlated with Clinician-Administered Dissociative States Scale (CADSS) scores [43]. These findings were not observed in the occipital cortices, where baseline levels of glutamate, gamma-aminobutyric acid (GABA), and glutamine were not associated with significant changes in HAM-D scores [47].

DISCUSSION

This is the first systematic review of the literature focusing on neural changes in depressed patients treated with tryptamines or ketamine/esketamine. Most of the data assessed by this review derive from open-label studies, a substantial number of RCT, observational studies, double-blind trials, and cross-over studies were also included. In the following sections, we discuss the results of the review and how tryptamines and ketamine/esketamine can modulate brain networks to counteract depressive symptoms.

Tryptamines

Concerning the antidepressant effect of **ayahuasca** and its neuroimaging correlates, a single, open-label study on the subject does not permit us to reach meaningful conclusions [48]. Multiple studies support the potential antidepressant efficacy of ayahuasca, with recent data also generated from placebo-controlled RCT [87] that indicate safety and low risk of side effects. Therefore, the therapeutic use of ayahuasca in mood disorders is promising but more studies are needed to evaluate the neural correlates of antidepressant responses.

Psilocybin antidepressant mechanism relies upon the modulation of intra- and inter-network connectivity of the DMN. This compound can restore the DMN physiological activity and produce a transient 'hyperconnectivity state' that allows a brain resetting and the departure from rigid and negative network states that produce depressive disorders [88, 89]. In fact, DMN hyperactivity, a trait feature of depressive disorders [90, 91], is, therefore, a primary effect of psilocybin that determines an overall reduction of relapses and inhibition of recurrent depressive episodes. This hypothesis is in line with studies indicating a long-term and sustainable antidepressant action of this compound [92], lasting several months after the first administration. In support, a growing body of evidence indicates that hyperactivity of the DMN is associated with rumination, mind-wandering, and self-referential thoughts in MDD [34, 80]. These features are considered core elements related to the response to psilocybin [93, 94], being suggestive of an effectiveness of psilocybin in MDD patient subtypes, such as those with ruminative depression.

Despite the presence of numerous studies on the acute effects of psychedelics, little is known on the relation between the character of the acute psychedelic experience (i.e., the way the experience goes, not simply the intensity) and the persisting changes in mood, behaviour, and personality [26, 95]. Concerning the 'psychedelic state', psychedelics appear to dysregulate cortical activity, producing an 'entropic' brain state characterized by compromised modular but enhanced global connectivity [88, 89]. These effects have been found to correlate with significant aspects of the 'psychedelic experience', including 'ego-dissolution', and

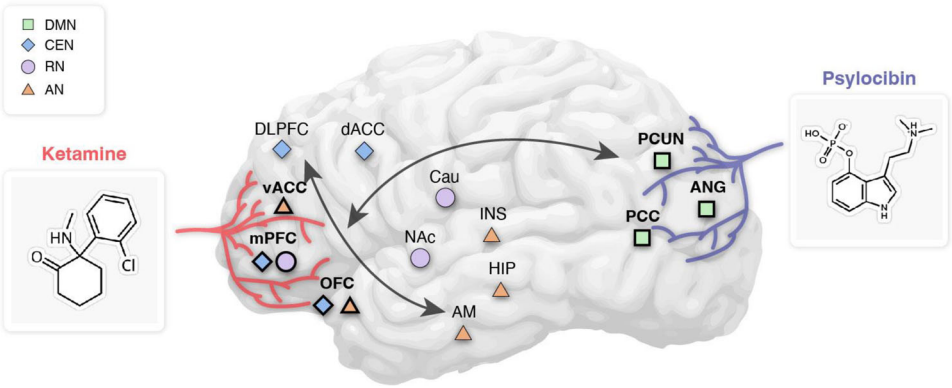

Fig. 2 Effects of antidepressant treatments with ketamine and psylocibin on brain networks. While Ketamine seems to act directly on prefrontal areas and related circuits (e.g., CEN, RN, and AN), psylocibin seems to operate directly on DMN areas, with a specific action on restoring DMN activity. Am, Amigdala; AN, Affective Network; ANG, Gyrus Angular; Cau, Caudate; CEN, Central Executive Network; dACC, dorsal Anterior Cingulate Cortex; DLPFC, Dorsolateral Prefrontal Cortex; DMN, Default-Mode-Network; HIP, Hippocampus; INS, Insula; mPFC, medial Prefrontal Cortex; NAc: Nucleo Accumbens; OFC, Orbito Frontal Cortex; PCC, Posterior Cingulate Cortex; PCUN: precuneus; RN, Reward Network; vACC, Ventral Anterior Cingulate Cortex.

were predictive of post-acute changes in the personality domain of 'openness'. Such experiences, known as "Complete Mystical Experiences" (CME), are hypothesized to be instrumental in producing long-lasting positive effects of psychedelics [96]. The magnitude of psilocybin-induced mystical-type experience positively correlates with improvements in subjective life quality, meaning in life, and mood in patients suffering from anxiety and depression and persisting positive effects 12 months after psilocybin [97].

Finally, psilocybin intake can impact cognitive processes, improving cognitive flexibility and possibly relieving the cognitive disorders that frequently complicate MDD.

Ketamine

With a prominent effect on prefrontal areas (i.e., VMPFC, DLPFC, ACC), confirmed by multi-modal neuroimaging studies, **ketamine** can normalize the MDD-relate cortico-subcortical dysconnectivity by enhancing long-distance connectivity and restoring the central role of the prefrontal cortices in cognitive and emotional processing. The subcortical structures which show a more prominent response to ketamine modulation are the amygdala and the caudate nucleus. The modulation of PFC and caudate correlates with treatment success. Post-treatment FC changes in these regions show more central and balanced features in responders. Prefrontal and striatal structures play a critical role in higher cognitive control, particularly in exploration and goal-directed behaviour. Thus, the enhanced engagement of these frontostriatal regions could underlie the behavioural shift from depression, withdrawal, and rumination to exploratory and externally focused behaviour following recovery [78]. Furthermore, the modulation of glutamatergic cycling, suggested by MRS studies, indicates that ketamine administration can restore glutamatergic signalling involved in key top-down circuits.

Indeed, top-down circuits such as frontostriatal networks appear to be related to specific clinical features, such as anhedonia, a core and difficult-to-treat dimension of depressive disorders [98]. Historically, frontostriatal neural networks associated with hedonic functioning (i.e. RN) have been linked to the activation of dopaminergic pathways [99]. Nevertheless, recent research has suggested that glutamate neurotransmission can exert indirect control over these pathways through a top-down action exerted on striatal areas [100]. In this context, several studies here analysed [53, 54, 62, 63, 69, 76, 78, 83] indicated that multiple ketamine infusions can boost connectivity between striatal areas (e.g., VST, nucleus accumbens and right caudate nucleus) and frontal cortical regions (e.g., VLPFC, ACC, DLPFC), thus leading to a decrease in anhedonic symptoms [53, 54, 62, 69, 76]. Further investigations are needed to elucidate the precise mode of action of ketamine and its derivatives on hedonic system-related circuits, as well as the neurobiological correlates of their rapid anti-suicidal effect, which has been demonstrated in several clinical studies on this matter [101, 102]. This research could be highly beneficial in determining patient populations most likely to respond to ketamine and esketamine.

Network-wise, several studies point out that ketamine modulates the FC between limbic and resting state networks implicated in MDD, as well as between limbic regions and the CEN [62, 63, 72, 74, 75, 103]. These observations indicate that ketamine plays a pivotal role in restoring top-down control of emotion processing, possibly through restoring physiological and flexible cortico-subcortical connections involving the amygdala. This activity is related to the ketamine-induced increase of cognitive control over emotional stimuli, a process that reduces negative affect mood stages [60, 62].

In summary, compared to psychedelics, ketamine has a more distinct impact on networks that involve prefrontal areas (i.e., CEN, RN, AN), thereby *indirectly* affecting the DMN and inter-network connectivity (see Fig. 2). Its specific action on prefrontal-striatal glutamatergic pathways may explain ketamine's efficacy as an anti-anhedonic treatment [53, 54, 62, 69, 76].

In general, the application of novel therapies is justified only if the risks do not outweigh the benefits. Concerns are still being expressed when considering the therapeutic applications of psychedelics. Of note, no addictive potential was recorded in the present review. Nevertheless, significant concerns persist regarding the potential for abuse of these compounds [104, 105]. Future studies should rigorously address this issue, particularly by evaluating subjects with depressive disorders and comorbid substance use disorders.

Furthermore, there is a slight risk for certain patients to experience sporadic adverse psychological effects, including the risk of developing psychotic symptoms. Thus, to minimize risks, clinical trials have excluded participants with a family history of first-degree relatives affected by psychiatric disorders like psychosis and schizophrenia [89]. However, future studies should include patients with psychotics features to better inform if those treatments are safe and effective in this subpopulation [106].

Study limitations

The present review is the first systematic assessment of scientific literature on the use of ketamine, esketamine, and tryptamines for depressive disorders. The first limitation of the current review

concerns the predominance of heterogeneous studies, small sample sizes, and the high rate of descriptive studies. Given this heterogeneity and the scarcity of RCTs or double-blind studies, it was impossible to precisely assess the studies' quality or carry out a meta-analysis. Moreover, the evaluated studies had a limited duration of follow-up. Therefore, estimating the long-term benefits and/or potential long-term side effects produced by the reviewed compounds was impossible. Lastly, this review only included studies published in English.

CONCLUSIONS

The main structural and functional changes involved prefrontal regions (e.g., DLPFC, VLPFC, ACC), as well as subcortical structures (i.e., amygdala and caudate nucleus). Accordingly, the effects of these compounds mostly targeted key hubs of large-scale networks, like the CEN, the AN, the RN, and more directly (tryptamines), or indirectly (ketamine), the DMN. In particular, psylocibin's mechanism of action leads to a 'reset' of DMN activity, whereas ketamine shows instead a more specific action on the networks encompassing prefrontal areas, exerting only an indirect modulation of the DMN. The overall evidence provides a neurophysiological basis for ketamine's efficacy as anti-anhedonic treatment, and its critical role in increasing cognitive control over emotional stimuli, thus reducing negative affect mood stages.

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Giacomo d'Andrea.