


Neuroimaging Correlates of Treatment Response with Psychedelics in Major Depressive Disorder: A Systematic Review

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Abstract

Preliminary evidence supports the use of psychedelics for major depressive disorder (MDD). However, less attention has been given to the neural mechanisms behind their effects. We conducted a systematic review examining the neuroimaging correlates of antidepressant response following psychedelic interventions for MDD. Through MEDLINE, Embase, and APA PsycINFO, 187 records were identified and 42 articles were screened. Six published studies and one conference abstract were included. Five ongoing trials were included from subjective outcomesTrials.gov. Our search covered several psychedelics, though included studies were specific to psilocybin, ayahuasca, and lysergic acid diethylamide. Three psilocybin studies noted amygdala activity and functional connectivity (FC) alterations that correlated with treatment response. Two psilocybin studies reported that FC changes in the medial and ventromedial prefrontal cortices correlated with treatment response. Two trials from a single study reported global decreases in brain network modularity which correlated with antidepressant response. One ayahuasca study reported increased activity in the limbic regions following treatment. Preliminary evidence suggests that the default mode and limbic networks may be a target for future research on the neural mechanisms of psychedelics. More data is required to corroborate these initial findings as the evidence summarized in this review is based on four datasets.

Keywords

depression, treatment-resistant depression, neural correlates, psychedelics, psilocybin, LSD, ayahuasca, systematic review

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Introduction

Depressive disorders are among the leading causes of disability worldwide.¹ From 1990 to 2017, the number of global cases of depression reportedly increased by 49.86%.² With the global incidence of depression on the rise, the social, economic, and health-related burdens of this psychiatric disorder

are increasingly evident at both the individual and societal levels.

Monoaminergic antidepressants have been used extensively as a first-line treatment for depressive disorders.³ However, it is estimated that only 42–53% of depressed patients respond to antidepressant medications.⁴ Psychotherapies, such as cognitive

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behavioural therapy and interpersonal psychotherapy, have also been used as a first-line treatment for depression, though as many as 40% of patients with Major Depressive Disorder (MDD) do not benefit from these therapies.^{5,6} Due to the high rates of non-response to first-line interventions, there is a growing need for novel, more effective treatment options.

In recent years, psychedelic compounds have gained interest in the field of psychiatry as viable pharmacological treatments for psychiatric disorders.⁷ Such compounds include psilocybin, ayahuasca, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), and N, N-Dimethyltryptamine (DMT). Their antidepressant effects appear to be notably more rapid and long-lasting compared to traditional antidepressant medications.⁸ Additionally, psychedelics appear to effectively alleviate depressive symptoms while also providing depressed patients with unique and adaptive psychological benefits, including increased cognitive flexibility,⁹ mindfulness,⁹ psychological flexibility,¹⁰ acceptance,¹¹ connectedness,¹¹ and catharsis.¹² One clinical trial¹³ implied that these unique effects may be exclusive to psychedelics, in that they are not commonly found with classical antidepressant medications. Moreover, psychedelic interventions have shown preliminary clinical efficacy in treating depressive disorders, including MDD and treatment-resistant depression (TRD).¹⁴ For instance, psilocybin with psychological support has been shown to reduce anhedonia¹⁵ and pessimism bias¹⁶ in patients with TRD. Psilocybin has also been shown to rapidly alleviate symptoms of anxiety and depression in MDD patients^{17–19} and patients with life-threatening diseases,²⁰ as well as effectively treat secondary depression in cancer patients.¹⁹ Moreover, single-dose ayahuasca administrations have shown a rapid reduction in depressive symptoms in patients with recurrent depression.²¹

Recent evidence has pointed to disrupted functional connectivity (FC) within and between higher-order intrinsic connectivity networks (ICNs) in depression.²² Neuroimaging research has suggested that MDD is characterized by functionally deviant coupling within the central executive network (CEN), default mode network (DMN), and salience network (SN).^{22–24} The CEN and SN have been connected to attentional processes, cognitive control, task-switching, and decision-making,^{25–27} all of which are often impaired in depression.^{28–30} The DMN has been associated with internalized thought and self-reflection.³¹ Individuals with depression have been found to excessively engage in these cognitive processes.^{32,33} Hyperactivity of the DMN is linked to depressive symptomatology, including rumination³⁴ and disturbed self-referential processing.³⁵ In patients with TRD, studies have shown reduced FC between the CEN and DMN and between the anterior and posterior DMN.³⁶ Depressed patients have also exhibited decreased flexibility in the SN compared to healthy controls.³⁷

Depressed patients have also been found to have aberrant FC within the brain's limbic regions, including the amygdala, hippocampus, medial prefrontal cortex (mPFC), and anterior cingulate cortex (ACC).³⁸ Enhanced FC between the

amygdala and prefrontal regions has been associated with rumination and worry in depressed patients.³⁹ Given that the limbic regions are central to emotional regulation, it is unsurprising that disturbances in emotional processing are a prominent feature of depressive symptomatology.^{40,41}

In MDD and TRD patients, select ICNs and brain regions are implicated in mediating antidepressant response. For MDD, a meta-analysis⁴² found that following antidepressant drug treatment, the amygdala, hippocampus, parahippocampal region, ventral ACC, orbitofrontal cortex, and insula showed decreased activation, while the dorsolateral, dorsomedial, and ventrolateral prefrontal cortices (PFC) showed increased activation. In TRD, cerebellar–cerebral FC in the PFC and DMN were significantly decreased. At the same time, increased FC was shown in the parahippocampal gyrus and visual recognition network (lingual gyrus, middle occipital gyrus, and fusiform) following antidepressant treatment.⁴³ Identifying neuroimaging correlates of antidepressant treatment response has allowed researchers to better understand the mechanisms behind the action of monoamine-based psychopharmacology – specifically, how antidepressant medications impact select brain regions and ICNs, leading to clinical improvement of MDD symptoms.

Previous research has highlighted efforts taken toward understanding the therapeutic effects of psychedelics by studying brain activity and FC.⁴⁴ However, the neural mechanisms behind the antidepressant effects and unique psychological benefits of psychedelics remain less understood compared to conventional antidepressant medications. This gap may be due to the lack of neuroimaging outcomes in MDD clinical trials exploring the efficacy and feasibility of psychedelic treatments, given the novelty of the field. Existing evidence concerning the neural underpinnings behind the effects of psychedelic treatments primarily emerges from studies conducted among healthy participants. Psychedelics appear to target the frontomedial, medial temporal, and occipital cortices, as well as exert an inhibitory effect on the DMN.⁴⁵ One model proposes that psychedelics dysregulate neuronal activity among various brain regions by agonistically acting on 5-HT_{2A} serotonin receptors, which gives rise to transient breakdowns of ICNs.⁴⁶ The 5HT_{2A} receptor is a main proteomic binding site of serotonergic psychedelics⁴⁷ (i.e., ayahuasca, DMT, LSD, psilocybin, etc.) and is abundantly expressed throughout the CEN, DMN, and SN.⁴⁸ Psychedelics may, therefore, bring about their therapeutic effects by targeting particular ICNs in which 5HT_{2A} receptors are heavily populated. In line with this serotonin receptor model, a recent meta-analysis⁴⁹ on psychedelic interventions in healthy individuals found altered FC and activation patterns in regions with high densities of 5HT_{2A} receptors – notably, the peristriate area 19 of the occipital cortex, dorsal anterior and posterior cingulate cortices (PCC), mPFC, dorsolateral PFC (DLPFC), supramarginal gyrus, temporal cortex, and right amygdala.⁴⁸ Several of these brain regions comprise the DMN.

Given the lack of research investigating the neural mechanisms of psychedelic treatment response in MDD, there is a growing need to examine neuroimaging studies in this domain. Specifically, neuroimaging research may demonstrate how the therapeutic effects of psychedelics are achieved via functional alterations within ICNs and implicated brain regions. Furthermore, the identification of these neural correlates may give rise to valuable prognostic tools that can be used to predict successful responses to psychedelic interventions among patients with depression. This knowledge could lead to an appropriate selection of MDD patients to undergo psychedelic treatments as opposed to conventional antidepressant treatments, which are often accompanied by adverse effects,^{50,51} delayed onset of action,⁵² and lack of therapeutic response.⁵³

A previous systematic review⁴⁵ provided a comprehensive outline of clinical studies that studied neuroimaging correlates of psychedelic interventions in healthy individuals. However, to our knowledge, there is no systematic review that examines such correlates in patients with depression. We review both published and ongoing clinical trials to provide a more detailed and practical overview of the current research landscape, avoid positive results bias, and highlight the advancements and future directions in this field.

Methods

We conducted a comprehensive search of both published studies and registered clinical trials encompassing various neuroimaging modalities and psychedelic interventions in MDD patients. This article was prepared in accordance with the PRISMA guidelines for systematic reviews.⁵⁴ Refer to Supplementary 1 to view a detailed description of the Methods for registered clinical trials.

Search Strategy

Published studies. A neuroimaging-focused search of three databases (MEDLINE, Embase, and APA PsycINFO) was conducted through the OVID and PubMed search engines. The following search terms were included: *psilocybin, ayahuasca, LSD, DMT, MDMA, mescaline, depress**, *neuroimag**. To view the complete search strategy, refer to Supplementary 2. We searched grey literature using the European database OpenGrey (<http://www.opengrey.eu/>), which included an advanced search of the term *psychedelic** in conjunction with the terms pertaining to various neuroimaging modalities (ie, positron emission tomography [PET], single-photon emission computed tomography [SPECT], functional magnetic resonance imaging [fMRI], magnetic resonance imaging [MRI], electroencephalography [EEG], magnetoencephalography [MEG]). The end date of the searches was April 18, 2022. Two authors (A.D. and S.K.) were responsible for independently conducting the primary screening and assessment of retrieved articles for inclusion.

Inclusion Criteria

The present systematic review included published studies, registered/ongoing clinical trials, and conference abstracts involving psychedelic interventions in patients with depression. Studies had to contain neuroimaging measures as primary or secondary outcomes. The enrolled participants had to have a valid depression diagnosis according to a recognized depression scale or the MDD diagnostic criteria as per the *Diagnostic and Statistical Manual of Mental Disorders* (i.e., DSM-IV or DSM-5) or the *International Classification of Diseases* (i.e., ICD-9 or ICD-10). Studies that enrolled patients with comorbid psychiatric disorders were excluded, with the exception of comorbid anxiety disorders due to the high rate of their co-occurrence with MDD. Moreover, non-primary articles (i.e., reviews, systematic reviews, meta-analyses, etc), non-interventional studies (ie, observational studies), and non-human trials were excluded from the review. Non-English articles were also excluded. Studies were only included if subjects were 18 years or older. Finally, no date limit was applied.

Screening Process

The PRISMA flow diagram outlines the screening process for both published and registered clinical studies (Figure 1). The screening was conducted independently by the two first authors (A.D and S.K). Results were compared to detect any potential discrepancies, which were resolved by a tertiary arbitrator (I.D).

Variable Extraction

Published studies. The following variables of interest were extracted: the mean age, participant sex, as well as the intention-to-treat (ITT) and per-protocol (PP) sample sizes. The psychiatric diagnosis of the participants was recorded, as well as the inclusion criteria required to meet a valid depression diagnosis at screening (i.e., Hamilton Rating Scale for Depression [HAM-D], Montgomery-Åsberg Depression Rating Scale [MADRS], Beck Depression Inventory [BDI], etc) or the MDD diagnostic criteria as per the *Diagnostic and Statistical Manual of Mental Disorders* (ie, DSM-IV or DSM-5), including any reported minimal scale thresholds set up by researchers for inclusion. Furthermore, several study characteristics were extracted: study duration, drug administration route, dosage, number of treatments, comparison type (ie, placebo-controlled or open-label), allocation (ie, randomized or nonrandomized), masking procedure (ie, single-masked or double-blind), and interventional model (ie, single group assignment, parallel assignment, or crossover assignment).

Furthermore, information about the treatment protocol of the psychedelic intervention was extracted (i.e., the class of psychedelic, dosage, and duration of the treatment period).

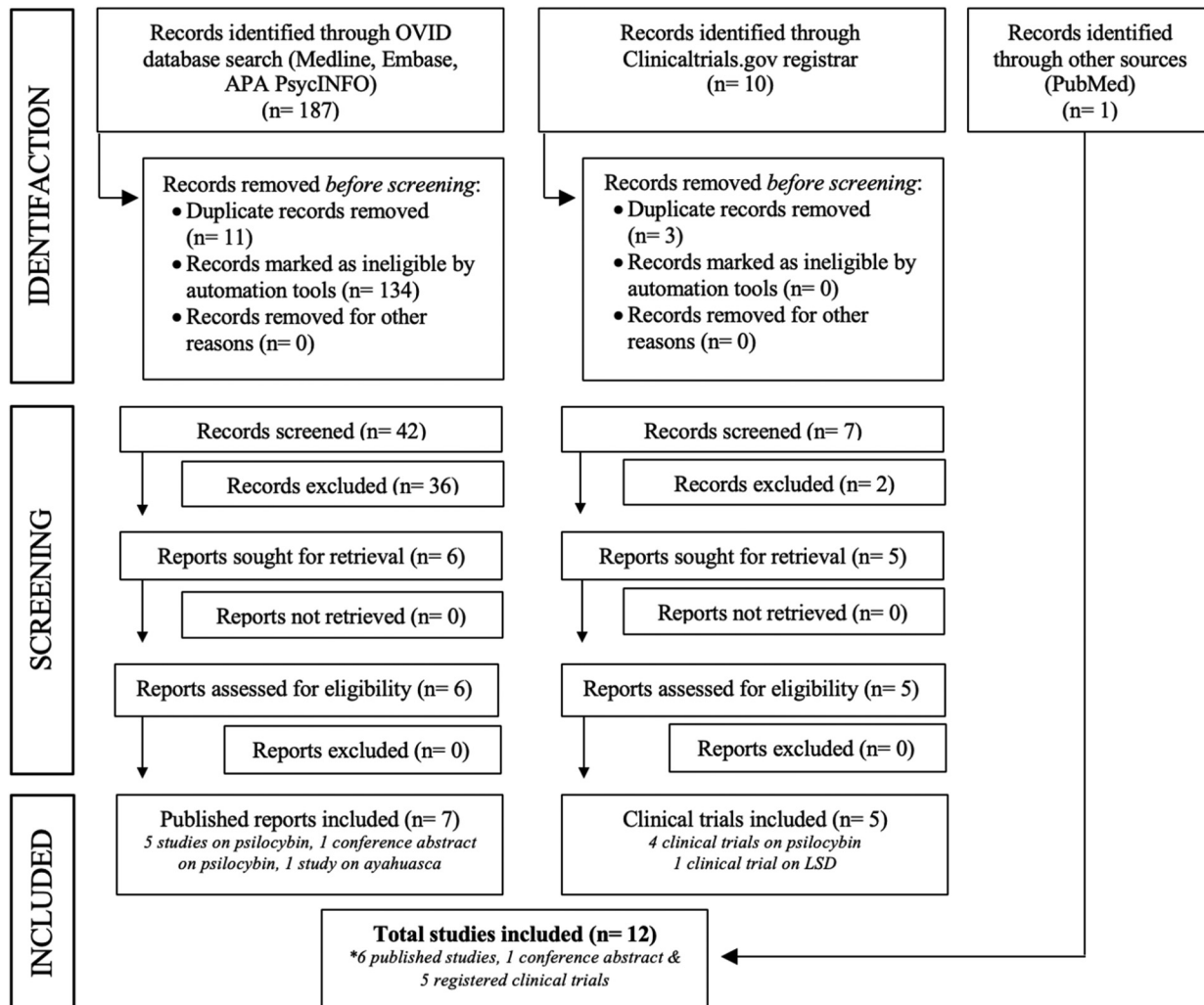


Figure 1. PRISMA flow diagram of published studies and registered trials screened and evaluated for eligibility.

The neuroimaging modalities used in the studies (i.e., EEG, fMRI, MEG, MRI, MRS, PET, and SPECT) and analyzed metrics (i.e., the amplitude of low-frequency fluctuation [ALFF], blood-oxygen-level-dependent [BOLD] response, cerebral blood flow [CBF], FC, neurometabolic concentrations) were reported. Moreover, the neural correlates of assessor-rated clinical outcomes, subjective clinical outcomes (i.e., self-report measures), and adverse effects within each study were also extracted. Notably, the p -values and correlation coefficient (Pearson's r) values were recorded when presented to highlight the statistical significance of the given findings, as well as the direction and strength reported in the correlation analyses.

Quality of Assessment

All published studies included in this systematic review were assessed for quality of evidence using the Grading of Recommendations, Assessment, Development, and

Evaluations (GRADE) checklist.⁵⁵ The corresponding table summarizing the included studies in terms of the GRADE criteria can be found in Supplementary 3. All but one trial included in this review was open-label, creating a high potential for performance bias. In addition, all included studies reported data consistent with their outcomes of interest, suggesting a low risk of selective reporting bias.

Results

Search Results

A total of 187 relevant articles were retrieved through the OVID databases and assessed for eligibility. Overall, 42 articles remained after applying automation tools to limit the search results to only English language articles, clinical trials, and studies containing adult participants. Of the 42 articles, 16 were excluded due to focusing on psychedelic

interventions in healthy individuals, 14 due to being unrelated to psychedelic interventions or depression, 5 due to being non-primary articles (i.e., book chapters, reviews), and 1 due to having no accessible results. After assessing the full text of the 6 remaining articles for eligibility, 5 published studies^{56–60} and 1 conference abstract^{61,62} were included. An additional article by Daws et al⁶³ (2022) was retrieved from other sources (i.e., PubMed). The conference abstract included in this review by Wall et al^{61,62} (2021) has also been recently made available as a pre-print.⁶² Detailed results of the published studies are provided in Table 1. It is important to note that 4 out of 7 published studies^{56–58,61,62} included in this review reported their neuroimaging and clinical findings from the same cohort of subjects. Therefore, the main characteristics of the studies listed in Table 1 were similar to each other. However, we have displayed these characteristics to resemble how they were reported in the included studies, to highlight pertinent neuroimaging aspects in this review. No relevant clinical studies were obtained from the OpenGrey database. Additionally, detailed results of ongoing clinical trials are provided in Supplementary 1.

Psychedelic Type

Five published studies^{56–58,60,63} and one conference abstract^{61,62} used psilocybin as their primary intervention. Of these studies, Daws et al⁶³ (2022) conducted both an open-label trial and a randomized controlled trial (RCT); these two trials will be referred to separately throughout the review. One published study⁵⁹ examined ayahuasca (Figure 2).

Research Design

Four studies^{56–59} followed an open-label, non-randomized, single-group interventional model. One clinical trial from Daws et al⁶³ (2020) also used an open-label, non-randomized, single-arm design, whereas the second clinical trial from Daws et al⁶³ (2020) was a double-blind RCT. Doss and colleagues⁶⁰ (2021) used an open-label interventional design that was randomized and not placebo-controlled. Roseman et al⁵⁸ (2018) was categorized as a feasibility trial but did not include a placebo group. Lastly, the conference abstract^{61,62} followed an interventional, open-label and single-group assignment design.

Sample Size and Clinical Diagnosis

All six published studies^{56–60,63} had ITT and PP sample sizes of less than 30 participants. Wall et al^{61,62} (2021) did not report their ITT sample size but had a PP sample size of fewer than 30 participants. Carhart-Harris et al⁵⁷ (2017) had PP sample sizes of 16 participants for their arterial spin labeling (ASL) analysis and 15 for their resting-state FC

(RSFC) analysis. Doss et al⁶⁰ (2021) had PP sample sizes of 20 for resting-state analysis and ACC scans, 19 for left hippocampus scans, and 18 for right hippocampus scans. Daws et al⁶³ (2022) had PP sample sizes of 16 for their open-label trial and 22 for the RCT. Three studies^{56–58} and one conference abstract^{61,62} included patients diagnosed with TRD in the trials, while two studies^{59,60} included patients with MDD. Additionally, Daws et al⁶³ (2022) recruited TRD patients for their open-trial study but MDD patients for their RCT (Figure 3).

Treatment Parameters

Four studies^{56–58,63} and one conference abstract^{61,62} investigating psilocybin used the same dosage and number of treatments. These studies each had a first session consisting of a 10 mg per os (p.o.) test dose followed a week later by a 25 mg p.o. therapeutic dose. Doss et al⁶⁰ (2021) used a moderately high dose of 20 mg/70 kg followed by a second high dose of 30 mg/70 kg administered 1.6 weeks apart. The RCT in Daws et al⁶³ (2022) used 25 mg psilocybin sessions on two separate dosing days with 3 weeks of daily placebo capsules following each dosing day. Mertens et al⁵⁶ (2020), Roseman et al⁵⁸ (2018), Doss et al⁶⁰ (2021) and Daws et al⁶³ (2022) specified that psilocybin was administered via a capsule. Carhart-Harris et al⁵⁷ (2017) and Wall et al^{61,62} (2021) did not specify the route of administration. Each subject in Sanches et al⁵⁹ (2016) drank a single dose of 120 to 200 mL of ayahuasca (See Table 2).

Clinical, Safety, and Tolerability Outcomes

All six published studies^{56–60,63} analyzed changes in depression scores using either the 21-item HAM-D, BDI, GRID-HAMD or MADRS. Only one study⁵⁹ reported vomiting as an adverse effect of ayahuasca, present in 47% of their patients. The RCT by Daws et al⁶³ (2022) did not observe adverse effects following psilocybin treatment. The remaining studies did not report or mention collecting the data on adverse effects (See Table 2).

Neuroimaging Modality & Psychedelic Type

Six studies^{56–58,60} and one conference abstract^{61,62} collected neuroimaging measurements at baseline and post-treatment. Roseman et al⁵⁸ (2018) and Mertens et al⁵⁶ (2020) collected functional neuroimaging data the morning after psilocybin administration, while Carhart-Harris et al⁵⁷ (2017) and the open-label trial by Daws et al⁶³ (2022) collected functional neuroimaging data 1 day after treatment. Roseman et al⁵⁸ (2018) and Mertens et al⁵⁶ (2020) collected fMRI data during an emotional face paradigm pre- and post-psilocybin. Carhart-Harris et al⁵⁷ (2017) collected fMRI data at resting-state pre- and post-psilocybin. These researchers also used perfusion-weighted imaging (PWI) to measure changes in

CBF at baseline and 1 day after a psilocybin treatment. Doss et al⁶⁰ (2021) collected fMRI and magnetic resonance spectroscopy (MRS) data pre-and post-psilocybin. The RCT by Daws et al⁶³ (2022) collected data at baseline and at 1 day and 3 weeks post-treatment. During the psilocybin therapy session, patients were sitting in a comfortable environment and listening to music. Additionally, follow-up sessions took place after the psilocybin therapy session to discuss participants' experiences. Wall et al^{61,62} (2021) collected fMRI data 1 week prior to the first psilocybin session and 1 day after the second psilocybin session. fMRI scans were acquired at rest and also while the participants were listening to music. Sanches et al⁵⁹ (2016) collected SPECT data before ayahuasca intake and 8 h following treatment (See Table 3).

Neuroimaging Outcomes

fMRI BOLD response/activity. Roseman et al⁵⁸ (2018) was the only published study that used an emotional faces task with BOLD fMRI to measure changes in neural activity following psilocybin administration. Following the second dose, increased activity was found in the right amygdala, temporal lobe and visual areas. The conference abstract by Wall et al^{61,62} (2021) used ALFF to measure changes in brain activity following psilocybin. Following psilocybin intake, greater ALFF was observed in the bilateral superior temporal cortex during music listening and in a small cluster of the right ventral occipital lobe during the resting state. Additionally, increased responsiveness was located in the superior and bilateral superior temporal lobes and supramarginal gyrus during the music listening scans.

fMRI functional connectivity. Mertens et al⁵⁶ (2020) used a task-based emotional faces paradigm while Carhart-Harris et al⁵⁷ (2017) and Daws et al⁶³ (2022) measured FC at resting state. Mertens et al⁵⁶ (2020) found decreases in ventromedial PFC (vmPFC) to right amygdala FC during face processing post-treatment. They also found increases in FC between the amygdala and vmPFC to occipital-parietal cortices during face processing. In addition, increases in FC were found between the amygdala and visual areas, as well as between the vmPFC and right angular gyrus, right lateral occipital cortex, and other visual areas in the right hemisphere following psilocybin treatment. Carhart-Harris et al⁵⁷ (2017) reported decreases in FC between the DMN and right frontoparietal network as well as increased DMN within-network FC post-treatment. Carhart-Harris et al⁵⁷ (2017) also found increases in FC within the anterior and posterior cingulate cortices and decreases in FC between the medial/lateral PFC and parahippocampus following treatment. Finally, they reported increases in FC between the vmPFC and bilateral inferior-lateral parietal cortex (ilPC) post-treatment. Doss et al⁶⁰ (2021) found no significant changes in ACC-PCC static FC. The researchers did find increased dynamic functional connectivity (dFC) between

the ACC and PCC 1 week after psilocybin therapy. However, this was no longer present at 4 weeks post-psilocybin administration. Daws et al's⁶³ (2022) open-label trial found increased between-network FC between the DMN and CEN and the DMN and SN as well as reductions in within-DMN FC one day after psilocybin treatment.

fMRI brain modularity. Daws et al⁶³ (2022) used brain network modularity as a metric following psilocybin treatment. In both their open-label trial and RCT, they found brain network modularity was significantly reduced at 1 day and 3 weeks post-psilocybin therapy.

PWI cerebral blood flow. Carhart-Harris et al⁵⁷ (2017) used whole-brain analysis to measure CBF and found decreases in the resting-state CBF within the amygdala and temporal lobe following a second psilocybin dose.

SPECT. Sanches et al⁵⁹ (2016) used SPECT imaging to measure brain functioning following ayahuasca administration. Researchers reported increases in activation within the left nucleus accumbens (NAcc), right insula, and left subgenual area.

MRS. Doss et al⁶⁰ (2021) used MRS to investigate biochemical changes following psilocybin administration. The researchers found that glutamate and N-acetylaspartate (NAA) were decreased in the ACC 1-week post-psilocybin (See Table 4).

Neuroimaging Correlates of Treatment Response

In three psilocybin studies,^{56–58} changes in amygdala activity and FC were correlated with treatment response. Mertens et al⁵⁶ (2020) found that reduced right amygdala to vmPFC FC was significantly associated with reduced depressive rumination scores at 1-week post-treatment. This study⁵⁶ also reported increased FC between the amygdala and visual areas under psilocybin, though these changes were not significantly associated with depressive outcomes. Carhart-Harris et al⁵⁷ (2017) reported that decreased CBF in the amygdala was predictive of lower depressive scores. Moreover, Roseman et al⁵⁸ (2018) found that increased right amygdala activity in response to fearful versus neutral faces was strongly predictive of favorable clinical outcomes.

Changes in the ventromedial and medial PFC FC were significantly correlated with depressive outcomes in two studies. Mertens et al⁵⁶ (2020) found that 1 week following psilocybin treatment, decreased right amygdala to vmPFC FC was associated with depressive rumination scores. Additionally, they found vmPFC-occipital lobe-parietal lobe FC was negatively affected which was correlated with BDI scores.⁵⁶ Carhart-Harris et al⁵⁷ (2017) found that increased vmPFC to bilateral ilPC FC and

Table 1. Summary of Published Psychedelic Interventional Studies.

	Sanchez et al⁶² (2016)	Carhart-Harris et al⁵⁷ (2017)
Country	Spain	United Kingdom
Intention-to-treat (ITT) sample size	17	19 participants in ASL and RSFC analyses
Per-protocol (PP) sample size	17	16 patients (ASL analyses), 15 patients (RSFC analyses)
Female (%)	14 (82.35%)	ASL Analyses: 4 (25%) RSFC Analyses: 4 (26.67%)
Mean & SD sample age	M = 42.71 years of age, SD = 12.11	ASL Analyses: M = 42.8 years of age, SD = 10.1 RSFC Analyses: M = 42.8 years of age, SD = 10.5
Study design	Intentional, open-label, single-group assignment study.	Intentional, open-label, single-group assignment study
Study duration	<ul style="list-style-type: none"> No formal preparation sessions prior to drug intake. The session was performed individually and took 4 h to complete. After the drug effects had subsided no psychological interventions were completed, and participants remained under 24-h observation. Neuroimaging occurred before and eight hours after treatment 	Participants underwent two psilocybin sessions a week apart
Baseline versus Post-treatment scans	<ul style="list-style-type: none"> Complete. After the drug effects had subsided no psychological interventions were completed, and participants remained under 24-h observation. Neuroimaging occurred before and eight hours after treatment 	<ul style="list-style-type: none"> CBF, BOLD, and RSFC were measured prior to any intervention and one day after the highest dose Long-term clinical outcomes were measured 5 weeks post-treatment
Psychedelic Dosage	Ayahuasca A single dose of 120 to 200 mL of ayahuasca (2.2 ml/kg).	Psilocybin The first session used 10 mg p.o., followed by 25 mg p.o. one week after.
Psychedelic-Assisted therapy	N/A	N/A
Psychiatric diagnosis	Recurrent MDD	TRD
Inclusion criteria	A subjective outcomes Interview to confirm the diagnosis using the DSM-IV-SCID-IV.	A diagnosis of TRD according to the 16-item Quick Inventory of Depressive Symptoms (QIDS-SR16) scale.
Neuroimaging technique	SPECT	fMRI & PWI
Neuroimaging metric	^{99mTc} -ECD SPECT	Resting-State BOLD, RSFC & CBF
Neuroimaging findings	<ul style="list-style-type: none"> ↑ activity in the left NAcc, right insula, and left subgenual areas ($P < 0.01$, corrected), as indicated by ↑ CBF in these areas 	<ul style="list-style-type: none"> ↓ CBF in the left Heschl's gyrus, left precentral gyrus, left planum temporale, left superior temporal gyrus, left amygdala, right supramarginal gyrus and right parietal operculum ↑ RSFC between the sgACC and PCC ↑ vmPFC RSFC with the bilateral iPPC ↑ RSFC in the DMN ($p = 0.018$), DAN ($p = 0.042$), and POP ($p = 0.016$) Between-network ↓ in RSFC was observed between the DMN and rFP ($p = 0.0031$), as well as between-network ↑ in RSFC between the sensorimotor network and rFP ($p = 0.045$) Reduced PH RSFC with clusters located in the medial and lateral PFC Reduced CBF within the amygdala
Neural correlates of clinical outcomes	Not reported	<ul style="list-style-type: none"> Patients who reported "mystical" or "peak" experiences under psilocybin had the most significant ↓ in PH RSFC in limbic regions (ie, bilateral amygdala) and cortical regions within the DMN (ie, PCC). Reduced PH RSFC with clusters located in the medial and lateral PFC, with the magnitude of this reduction being predictive of better treatment response at 5 weeks ($p = 0.04$) Post-treatment ↑ in vmPFC RSFC with the bilateral iPPC were predictive of successful treatment response at 5 weeks ($p = 0.03$) Reductions in amygdala CBF were positively correlated with reduced depressive symptoms ($r = 0.59$; $p = 0.01$)
subjective outcomes/ subjective outcomes	<ul style="list-style-type: none"> ↓ in HAM-D and MADRS scores from 80 to 180 min ($P < 0.01$) and from D1 to D21 ($P = 0.000$) post-treatment On D21 post-treatment, the average HAM-D score was 7.56 ± 4.7, indicating mild depression Significant ↓ in the BPRS Anxious-Depression subscale observed 	<ul style="list-style-type: none"> At week 1 post-treatment, 19 patients showed some reduction in depressive symptoms, with 12 meeting criteria for response (change = -10.2 ± 5.3, $t = -6.4$, $p < 0.001$) At 5 weeks post-treatment, six of the 15 (BOLD) and 16 (CBF)

(continued)

Table 1. Continued.

	Sanches et al⁶² (2016)	Carhart-Harris et al⁵⁷ (2017)
Adverse effects	at 40 to 180 min post-treatment ($P < 0.01$) and from D1 to D21 post-treatment ($P = 0.000$). Vomiting reported in 47% of volunteers	patients showed treatment response ($\leq 50\%$ reductions in QIDS-SRI 16 score) Not reported
Summary of Published Studies (Continued)		
Country	United Kingdom	United Kingdom
Intention-to-treat (ITT) sample size	20	20
Per-protocol (PP) sample size	19	19
Female (%)	6 (31.57%)	6 (31.57%)
Mean & SD sample age	M = 44.7 years of age, SD = 10.9	M = 44.7 years of age, SD = 10.9
Study design	<ul style="list-style-type: none"> Interventional, single group assignment, open-label, feasibility trial. 	Interventional, open-label, single-group assignment study
Study duration	<ul style="list-style-type: none"> Patients underwent two psilocybin-assisted therapy sessions one week apart. Patients were invited a week before to meet with their therapist and discuss concerns as well as to simulate aspects of the dosing period. Neuroimaging occurred the morning after the high dose was administered 	Participants underwent two psilocybin-assisted therapy sessions a week apart
Baseline versus Post-treatment scans		<ul style="list-style-type: none"> Baseline fMRI scanning took place prior to any intervention fMRI scans were taken the morning following the high-dose session
Psychedelic Dosage	Psilocybin The first session used 10 mg p.o. as a test dose (low dose), followed by a second 25 mg p.o. as a therapeutic dose (high dose), administered one week apart.	Psilocybin The first session administered a 10 mg p.o. test dose, followed by a second 25 mg p.o. therapeutic dose, one week apart.
Psychedelic-Assisted therapy	Yes <ul style="list-style-type: none"> Therapists were instructed to build rapport with patients to help relieve any anxiety about the high-dose session. Two therapists approached patients in a non-directive and supportive manner 	Yes (3 components): <ul style="list-style-type: none"> A preparation session before the first dose (duration: 4 h) Acute and peri-acute support (ie, before, during and immediately after dosing) An integration session with allocated psychiatrists one day after the high dose
Psychiatric diagnosis	TRD	TRD
Inclusion criteria	A diagnosis of moderate to severe major depression, as defined by a score of 16+ on the 21-item HAM-D scale.	A diagnosis of moderate to severe major depression, as defined by a score of 16+ on the 21-item HAM-D scale.
Neuroimaging technique	fMRI	fMRI
Neuroimaging metric	Task-based BOLD (Emotional Faces Image Task)	Task-based BOLD (Emotional Face Paradigm)
Neuroimaging findings	<ul style="list-style-type: none"> ↑ BOLD responses in the right amygdala during exposure to fearful faces ($p = .001$), happy faces ($p = .022$), with a trend level effect in response to neutral faces ($p = .066$) No significant BOLD responses were reported in the left amygdala ↑ BOLD activation in visual areas during the emotional face task ($p < .05$) Enhanced activation in the right amygdala and right middle temporal gyrus for the fearful > neutral contrast ($p < .05$) 	<ul style="list-style-type: none"> ↑ FC between the amygdala and visual areas (intracalcarine and supracalcarine cortex, cuneus, precuneus and right lateral occipital cortex) during face processing tasks versus rest ($p < 0.05$) Enhanced FC between the amygdala and visual regions during happy ($p < 0.001$) and neutral ($p < 0.001$) faces, but not fearful faces ↑ vmPFC to left occipital and parietal lobes (ie, the supracalcarine cortex, intracalcarine cortex, precuneus and lingual gyrus) FC during face processing compared to rest ↓ vmPFC to right amygdala FC during fearful and neutral faces (but not happy faces) ↑ vmPFC FC with the right angular gyrus, right lateral occipital cortex, right occipital pole, and right occipital-fusiform gyrus during fearful faces ($p = 0.044$), with the cuneal cortex during happy faces ($p = 0.040$) and with the left cerebellum during neutral faces ($p < 0.001$)

(continued)

Table 1. Continued.

	Roseman et al ⁵⁹ (2018)	Mertens et al ⁵⁸ (2020)
Neural correlates of clinical outcomes	<ul style="list-style-type: none"> ↑ amygdala activation in response to fearful > neutral faces were strongly predictive of successful treatment outcomes ($p < .05$) One-week post-treatment, change (10.2 ± 5.3), response (63.2%) and remission (57.9%) in BDI scores were associated with psilocybin-induced ↑ in amygdala responses to fearful > neutral faces ($p < .05$), with ↑ amygdala activity relating to better clinical outcomes Changes in QIDS scores at 1-day (68.4%), 1-week (63.2%) and 3-weeks (63.2%) post-psilocybin linked to ↑ amygdala response to fearful > neutral faces ($p < .05$), with ↑ amygdala activity correlating with better clinical outcomes Responders showed ↑ amygdala response during fearful > neutral paradigm; non-responders and non-remitters showed ↓ amygdala response At day 1 post-treatment, 15 of 19 TRD patients (79%) showed a clinical reduction in depressive symptoms (reduction from baseline $\geq 50\%$) 	<ul style="list-style-type: none"> One-week post-treatment, reduced vmPFC to right amygdala FC significantly correlated with lower depressive rumination scores ($r = 0.34$, $p = 0.018$) vmPFC-occipital-parietal FC was correlated with STAI scores ($r = 0.54$, $p = 0.017$) and BDI scores ($r = -0.46$, $p = 0.048$) at one-week post-psilocybin
subjective outcomes/ subjective outcomes		<ul style="list-style-type: none"> A significant reduction in BDI scores was noted at week 1, with 63.2% of patients showing treatment response (50% drop in BDI score) and with 57.9% meeting requirements for remission ($BDI \leq 9$).
Adverse effects	Not reported	Not reported
Summary of Published Studies (Continued)	Wall et al^{55,56} (2021)	Doss et al⁶⁰ (2021)
Country	United Kingdom	United States
Intention-to-treat (ITT) sample size	Not reported	24
Per-protocol (PP) sample size	19	N = 20, 20, 18, and 19 for resting state, ACC, left hippocampus, and right hippocampus scans, respectively
Female (%)	Not reported	16 (66.67%)
Mean & SD sample age	Not reported	M = 39.83, SD = 12.23
Study design	<ul style="list-style-type: none"> Interventional, open-label, single-group assignment Participants were administered psilocybin on two separate occasions while accompanied by research personnel fMRI scans during resting state and music listening were obtained following psilocybin intake Participant responses to the 5D-ASC questionnaire were collected each session 	<ul style="list-style-type: none"> Interventional, open-label, non-placebo controlled, randomized controlled trial 13 participants were randomly assigned to an immediate treatment group and 11 were randomly assigned to a delayed treatment group Participants were administered psilocybin while sitting in a comfortable environment and listening to music Follow-up meetings took place after psilocybin therapy to discuss participants' experiences
Study duration	~ 2 weeks	Participants underwent two psilocybin-assisted therapy sessions ~ 1.6 weeks apart
Baseline versus Post-treatment scans	fMRI data were obtained one week before the first session and the day after the second session.	<ul style="list-style-type: none"> Baseline clinical, cognitive, and neuroimaging measurements were conducted prior to psilocybin therapy Baseline scans collected approximately 4 weeks before the first psilocybin session Post-treatment scans collected 1 week after the second psilocybin session (obtained on the same days as cognitive testing)
Psychedelic Dosage	Psilocybin The first session involved a 10 mg dose, followed by a second dose of 25 mg, one week apart.	Psilocybin First session involved a moderately high dose (20 mg/70 kg), followed by a second high dose (30 mg/70 kg), administered ~ 1.6 weeks apart. Psilocybin was consumed orally in opaque gelatin capsules.

(continued)

Table 1. Continued.

	Wall et al ^{55,56} (2021)	Doss et al ⁶⁰ (2021)
Psychedelic-Assisted therapy	Yes	Yes
Psychiatric diagnosis Inclusion criteria	TRD TRD diagnosis	MDD MDD diagnosis (≥ 17 on the GRID-Hamilton Depression Rating Scale or GRID-HAMD)
Neuroimaging technique Neuroimaging metric Neuroimaging findings	fMRI Resting-state fMRI, music listening fMRI, ALFF analysis <ul style="list-style-type: none"> Following psilocybin intake, greater ALFF was observed in the bilateral superior temporal cortex during music listening Post-psilocybin, greater ALFF was in a small cluster of the right ventral occipital lobe during resting state Significant effect of psilocybin treatment on responsiveness in the superior temporal lobe ($p = 0.04$) reported during the music scan, indicating an increase in this region's responsiveness to music Psilocybin had no effect on occipital cortex activity Post-treatment increases in response were found in the bilateral superior temporal lobes and supramarginal gyrus during music listening scans Post-treatment decreases in response were observed in the medial frontal lobes during resting-state scans 	fMRI & Magnetic resonance spectroscopy (MRS) Resting-state BOLD, RSEC, neurometabolite concentrations (MRS) <ul style="list-style-type: none"> Glutamate ($p = 0.020$, $d = 0.57$) and NAA ($p = 0.007$, $d = 0.68$) were decreased in the ACC 1 week post-psilocybin No significant change in ACC-PCC static FC ($p > 0.250$) Increased dFC between the ACC and PCC found 1 week after psilocybin therapy ($p = 0.010$, $d = 0.64$), but this association became no longer significant at 4 weeks post-psilocybin therapy ($r(16) = 0.44$, $p = 0.079$)
Neural correlates of clinical outcomes	<ul style="list-style-type: none"> Post-treatment response increases in the bilateral superior temporal lobes and supramarginal gyrus during music listening were significantly correlated with three of the sub-scales of the 5D-ASC questionnaire ($r = 0.507$-0.552, $p = 0.014$-0.027). 	<ul style="list-style-type: none"> All correlations between changes in glutamate or NAA and changes in GRID-HAMD scores or PCET perseverative errors were non-significant Moderate positive association found between increases in dFC and decreases in PCET perseverative errors 1 week post-psilocybin ($r(16) = 0.48$, $p = 0.043$) All changes in ACC-PCC functional connectivity and changes in GRID-HAMD scores were non-significant
subjective outcomes/ subjective outcomes	Not reported	<ul style="list-style-type: none"> Psilocybin therapy significantly decreased GRID-HAMD scores in almost all participants from baseline to 1 week and at 4 weeks post-treatment ($p < 0.001$; $n^2p = 0.75$) Reduced errors on in Penn Conditional Exclusion Test (PCET) observed from baseline to 1 week and 4 weeks post-psilocybin therapy ($p < 0.001$; $n^2p = 0.35$)
Adverse effects	Not reported	Not reported
Daws et al⁶¹ (2022)		
Country	Open-label trial United Kingdom, United States	Double-blind RCT United Kingdom, United States
Intention-to-treat (ITT) sample size	19	Psilocybin arm: 30 Escitalopram arm: 29
Per-protocol (PP) sample size	16 (3 patients excluded due to excessive fMRI head motion)	Psilocybin arm: 22 (2 lost due to COVID-19 lockdown, 1 discontinued intervention, 5 excluded due to excessive fMRI head motion)

(continued)

Table 1. Continued.

	Open-label trial	Double-blind RCT
Female (%)	4 (25%)	Escitalopram arm: 21 (1 lost due to COVID-19 lockdown, 4 discontinued interventions, 3 excluded due to excessive fMRI head motion) Psilocybin arm: 8 (36.36%) Escitalopram arm: 6 (28.57%)
Mean & SD sample age	M = 42.75, SD = 10.15	Psilocybin arm: M = 44.5, SD = 11.0 Escitalopram arm: M = 40.9, SD = 10.1
Study design	Interventional, single-arm, open-label clinical trial	<ul style="list-style-type: none"> Interventional, double-blind RCT MDD patients randomly allocated to escitalopram arm or psilocybin arm
Study duration	~ 1 week	~ 6 weeks
Baseline versus Post-treatment scans	<ul style="list-style-type: none"> Baseline clinical assessment and resting-state fMRI conducted prior to dose 1 A second clinical assessment and fMRI scan were recorded 1 day after dose 2 	<ul style="list-style-type: none"> Baseline clinical assessment and resting-state fMRI conducted prior to dose 1 Both groups attended a post-treatment clinical assessment and fMRI visit 3 weeks and 1 day after dose 2
Psychedelic	Psilocybin	Psilocybin
Dosage	The first session involved a 10 mg oral dose, followed by a second psilocybin therapy oral dose of 25 mg, 1 week apart.	Psilocybin arm: 2 x 25 mg psilocybin therapy on two separate dosing days (DDs) with 3 weeks of daily placebo capsules following each DD. Escitalopram arm: 2 x 1 mg psilocybin therapy DDs with 3 weeks of 10 mg daily escitalopram following DD1 and 20 mg of escitalopram following DD2.
Psychedelic-Assisted therapy	Yes	Yes
Psychiatric diagnosis	TRD	MDD
Inclusion criteria	<ul style="list-style-type: none"> Diagnosis of unipolar MDD (16+ on the 21-item HAM-D scale). Patients must have TRD as defined by no improvement in depressive symptoms despite multiple courses of antidepressant medication 	Diagnosis of unipolar MDD (16+ on the 21-item HAM-D scale).
Neuroimaging technique	fMRI	fMRI
Neuroimaging metric	fMRI resting-state, RSFC, brain network modularity	fMRI resting-state, RSFC, brain network modularity, dynamic flexibility
Neuroimaging findings	<ul style="list-style-type: none"> Brain network modularity was significantly reduced 1 day after psilocybin therapy (mean difference, -0.29; $t_{15} = 2.87$, 95% CI 0.07 to 0.50, $P = 0.012$, $d = 0.72$), suggesting a global increase in FC Reductions in within-DMN FC (mean difference -0.54; $t_{15} = -2.99$, 95% CI -0.92 to -0.15, $P = 0.009$, $d = 0.75$; Fig. 4d), increased between-network FC between the DMN and EN (mean difference, 0.53; $t_{15} = 3.01$, 95% CI 0.15 to 0.90, $P = 0.01$, $d = 0.75$) and between the DMN and SN (mean difference, 0.55; $t_{15} = 2.89$, 95% CI 0.14 to 0.95, $P = 0.01$, $d = 0.72$; FDR-corrected) were observed 1 day after psilocybin therapy 	<ul style="list-style-type: none"> Brain network modularity was significantly diminished at 3 weeks post-psilocybin therapy (mean difference, -0.39; $t_{21} = -2.20$, 95% CI -0.75 to -0.02, $P = 0.039$, $d = 0.47$) Escitalopram arm showed no changes in network modularity relative to baseline (mean difference, 0.01; $t_{20} = 0.07$, 95% CI -0.35 to 0.33, $P = 0.95$, $d = 0.02$)
Neural correlates of clinical outcomes	<ul style="list-style-type: none"> Decreased brain modularity was significantly correlated with 	<ul style="list-style-type: none"> Reductions in brain network modularity were significantly associated

(continued)

Table 1. Continued.

	Open-label trial	Double-blind RCT
	<p>improvements in BDI scores at 6 months ($r_{14} = 0.64$, 95% CI 0.29 to 0.84, $P = 0.023$), 3 months ($r_{14} = 0.46$, 95% CI 0.03 to 0.74, $P = 0.114$, uncorrected) and 1 week ($r_{14} = 0.29$, 95% CI -0.16 to 0.64, $P = 0.284$, uncorrected) post-treatment</p> <ul style="list-style-type: none"> Pre-treatment versus post-treatment (1 day) changes in modularity were significantly associated with changes in BDI score at 6 months relative to baseline ($r_{14} = 0.54$, 95% CI 0.14 to 0.78, $P = 0.033$) 	<p>with clinical improvements in depression symptom severity at 3 weeks post-psilocybin treatment ($r_{20} = 0.42$, $P = 0.025$, one-tailed) in the psilocybin arm, increased EN dynamic flexibility strongly correlated with greater improvement in depressive symptoms at week 6 ($r_{20} = -0.76$, 95% CI -0.90 to -0.50, $P = 0.001$)</p> <ul style="list-style-type: none"> In the psilocybin arm, strong correlations between increased EN dynamic flexibility and greater symptom improvement were also found when combining certain EN regions with the salience and dorsal attention networks. The escitalopram arm showed no significant correlations between changes in modularity and changes in BDI scores ($r_{19} = 0.08$, $P = 0.361$, one-tailed) No significant correlations between changes in BDI scores and changes in dynamic flexibility were observed in the escitalopram arm
Clinical/ subjective outcomes	<ul style="list-style-type: none"> Significant BDI reductions were observed at 1 week compared to baseline (mean difference, -21.0 points; $t_{15} = 7.11$, 95% confidence interval (CI) -27.30 to -14.71, $P < 0.001$, Cohen's $d = 1.78$) and remained significant at 6 months (mean difference, -14.19 points; $t_{15} = 4.26$, 95% CI -21.29 to -7.09, $P < 0.001$, $d = 1.07$) 	<ul style="list-style-type: none"> Depressive symptoms (as assessed by BDI scores) were significantly reduced after psilocybin compared to escitalopram Baseline BDI scores were significantly different than at 2 weeks (mean difference, -8.73; $t_{41} = -3.66$, 95% CI -13.55 to -3.91, $P = 0.002$, Cohen's $d = 0.98$), 4 weeks (mean difference, -7.79; $t_{41} = -2.69$, 95% CI -13.62 to -1.95, $P = 0.013$, $d = 0.77$) and at 6 weeks (mean difference, -8.78; $t_{41} = -2.61$, 95% CI -15.58 to -1.97, $P = 0.013$, Cohen's $d = 0.75$) in the psilocybin arm.
Adverse effects	Not reported	4 patients discontinued escitalopram due to adverse effects: no reports of adverse effects for psilocybin

Abbreviations: ALFF = Amplitude of Low-Frequency Fluctuations, ASL = arterial spin labelling, BDI = Beck Depression Inventory, BOLD = bold oxygen level dependent, BPRS = Brief Psychiatric Rating Scale, CBF = cerebral blood flow, DAN = dorsal attention network, DMN = default mode network, DSM-IV-SCID-IV = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, EN = executive network, FC = functional connectivity, fMRI = functional magnetic resonance imaging, HAM-D = Hamilton Depression Rating Scale, iIPC = inferior-lateral parietal cortex, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = Major Depressive Disorder, NAA = N-acetylaspartate, PCC = posterior cingulate cortex/precuneus, PH = parahippocampus, POP = posterior opercular network, PWI = perfusion-weighted imaging, QIDS-SR16 = Quick Inventory of Depressive Symptomatology (16-item) (self-report), RCT = randomized controlled trial, rFP = right frontoparietal network, RSFC = resting state functional connectivity, sgACC = subgenual anterior cingulate cortex, SN = salience network, SPECT = single-photon emission computerized tomography, STAI = State-Trait Anxiety Inventory, TRD = treatment-resistant depression, vmPFC = ventromedial prefrontal cortex, 5D-ASC = 5 Dimensions of Altered States of Consciousness.

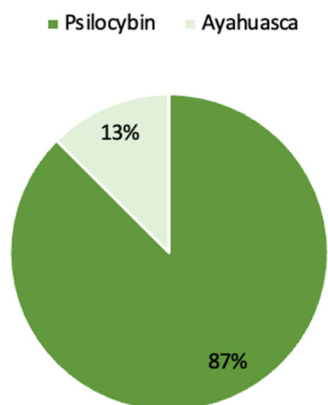


Figure 2. Type of psychedelic intervention examined in the published studies and conference abstract.

decreased parahippocampal to PFC FC were predictive of psilocybin treatment response at 5 weeks post-treatment. In the latter study, reduced FC between the parahippocampus and the medial and lateral portions of the PFC also significantly predicted treatment response at 5 weeks post-psilocybin.⁵⁷

Decreased brain modularity was significantly correlated with improvements in BDI scores at 1 week, 3 months and 6 months post-psilocybin in the open-label trial by Daws et al⁶³ (2022). The RCT by Daws et al⁶³ (2022) also found that decreases in brain network modularity were significantly associated with clinical improvements in depressive symptoms at 3 weeks post-psilocybin. In the same RCT,⁶³ increased CEN dynamic flexibility also strongly correlated with greater improvement in depressive symptoms at 6 weeks post-treatment.

Ongoing Clinical Trials: Overview of Results

Detailed information on ongoing clinical trials can be found in Supplementary 1. Four of the five ongoing clinical trials^{64–67} are using psilocybin as their primary intervention, and one trial⁶⁸ is investigating LSD. When examining changes in brain activity, all clinical trials will assess changes in depressive symptomatology using various standardized questionnaires following psilocybin and LSD administration (See Table S1 in the supplementary for more detailed findings). fMRI is the most common neuroimaging modality being used to measure psilocybin effects in clinical trials, with three trials^{65,66,68} including it as their outcome measure. One clinical trial⁶⁴ is using PET to measure the effects of psilocybin on brain activity, while another study⁶⁷ is using EEG. Another fMRI-based clinical trial⁶⁸ is also using both DTI and PWI (ie, ASL) to measure brain perfusion in LSD administration.

Discussion

Summary of the Findings from Published Studies

The present systematic review investigated six interventional studies and one conference abstract on neuroimaging correlates of psychedelic response in MDD patients. Due to the high variability in neuroimaging metrics, sample sizes, and study designs, a meta-analysis was considered unsuitable for examining the current state of the literature.⁶⁹

Preliminary evidence suggests that FC and brain activity changes in the DMN—particularly, the amygdala and mPFC/vmPFC— may be associated with psilocybin treatment response in MDD patients. Select psilocybin studies reported alterations in the activity and FC of the temporal gyri, ACC and PCC/precuneus, and visual areas following psilocybin intake. However, alterations in these regions were not associated with treatment response. The single study on ayahuasca reported increased activation in the limbic regions, including the left NAcc, right insula, and left subgenual areas, though these changes did not correlate with treatment response.

Neuroimaging Correlates of Psychedelic Treatment Response in MDD Patients

Psilocybin. Previous research has illustrated that select ICNs and brain regions are implicated in the neural mechanisms behind antidepressant response. In particular, the CEN, DMN and SN, which integrate critical brain areas including the dorsal ACC (dACC), anterior insula, DLPFC, and amygdala, all have demonstrated specific alterations in MDD patients who underwent treatment with typical antidepressants.⁷⁰ In the open-label trial by Daws et al⁶³ (2022), psilocybin led to reductions in within-DMN FC and increases in DMN to SN and DMN to CEN FC. Though these FC changes did not correlate with clinical outcomes in said trial,⁶³ changes in within-DMN and between-DMN FC may explain the observed improvements in depressive symptoms following psilocybin treatment given that changes to this network have previously been associated with antidepressant response.^{71,72} Furthermore, it is plausible that FC reductions to this network may alleviate depressive symptoms, considering that greater DMN dominance and heightened FC have been associated with depressive symptomatology, particularly rumination, among MDD patients.^{34,73}

The RCT by Daws et al⁶³ (2022) observed that psilocybin-induced increases in CEN dynamic flexibility strongly correlated with greater improvement in depressive symptoms, even when combining several CEN regions with the SN and dorsal attention network. Diminished dynamic flexibility has been closely linked to depressive symptoms.⁷⁴ Thus, psilocybin may lead to clinical

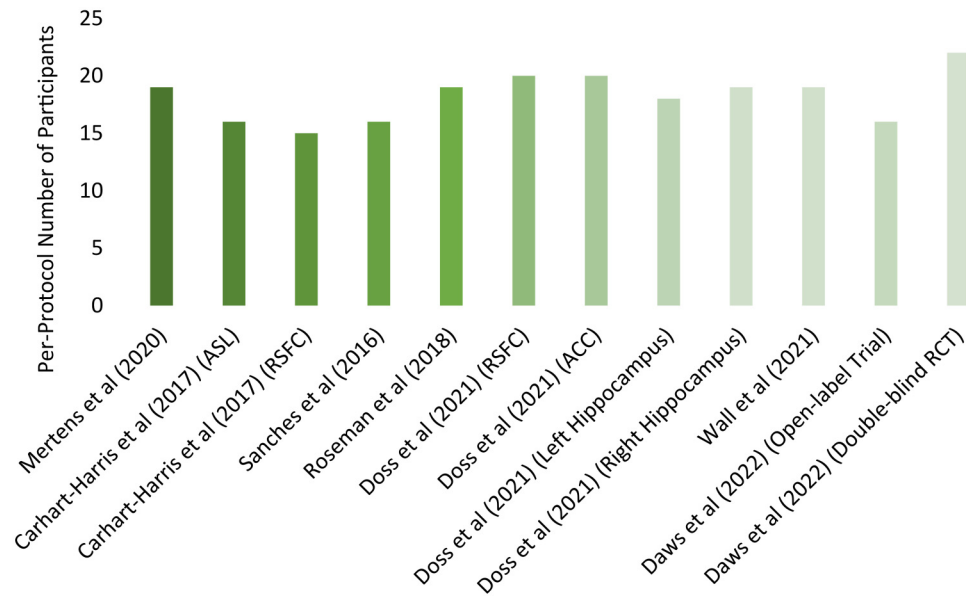


Figure 3. Published studies by the per-protocol sample size for each study. Note: Carhart–Harris et al (2017) has two different sample sizes for their ASL and RSFC sample sizes. Doss et al (2021) has four different sample sizes for their RSFC, ACC, left hippocampus and right hippocampus analyses. Daws et al (2022) has two different sample sizes for their psilocybin open-label trial and double-blind RCT.

Table 2. Treatment Dose and Duration of Treatment Period for Published Studies.

Study Citation	Dose	Number of Treatments	Duration of Treatment Period	Administration Route
Carhart-Harris et al⁵⁷ (2017)	Test Dose: 10 mg of psilocybin treatment Dose: 25 mg of psilocybin treatment	2	Test dose and treatment dose were given 1 week apart	N/A
Roseman et al⁵⁹ (2018)	Test Dose: 10 mg of psilocybin treatment Dose: 25 mg of psilocybin treatment	2	Test dose and treatment dose were given 1 week apart	Oral
Mertens et al⁵⁸ (2020)	Test Dose: 10 mg of psilocybin treatment Dose: 25 mg of psilocybin treatment	2	Test dose and treatment dose were given 1 week apart	Oral
Sanches et al⁶² (2016)	120 to 200 mL of ayahuasca (2.2 ml/kg)	1	4 h	Oral
Wall et al^{55,56} (2021)	Test Dose: 10 mg of psilocybin treatment Dose: 25 mg of psilocybin treatment	2	Test dose and treatment dose were given 1 week apart	N/A
Doss et al⁶⁰ (2021)	First dose: 20 mg/70 kg Second high dose: 30 mg/70 kg	2	First dose and second dose administered 1.6 weeks apart	Oral
Daws et al⁶¹ (2022) Open-label trial	First Dose: 10 mg of psilocybin treatment Second Dose: 25 mg of psilocybin treatment	2	First dose and second dose were given 1 week apart	Oral
Daws et al⁶¹ (2022) RCT	Two 25 mg psilocybin treatment session on two separate dosing days	2	Three weeks of daily of placebo capsules following each dosing day (6 weeks)	Oral

Abbreviations: LSD = lysergic acid diethylamide, RCT = Randomized Control Trial.

improvements in depressive symptoms by altering functional dynamics of specific neural networks.

A key finding was that psilocybin-induced changes in the amygdala activity and FC correlated with treatment response

in select studies.^{56–58} Recent studies have highlighted the amygdala's role in antidepressant treatment response in MDD patients. For example, changes in intrinsic connectivity between the amygdala and subgenual cingulate cortex

Table 3. Neuroimaging Technique by Psychedelic Intervention in Published Studies.

Neuroimaging Technique				
Psychedelic	fMRI	SPECT	PWI	MRS
Psilocybin	6		1	1
Ayahwasca		1		

Abbreviations: fMRI = functional magnetic resonance imaging, MRS = Magnetic resonance spectroscopy, PWI = perfusion-weighted imaging, SPECT = single-photon emission computerized tomography.

have been associated with antidepressant treatment response to ketamine in patients with TRD.⁷⁵ Moreover, changes in amygdala BOLD response to sad facial stimuli have been predictive of antidepressant treatment response to scopolamine in MDD patients.⁷⁶ Changes in the amygdala activity and FC may, therefore, broadly characterize antidepressant response and extend to psilocybin treatment. However, it remains unknown whether the reported activity and FC changes result from the specific effect of the psychedelic. Future studies should focus on differentiating the amygdala functional properties specific to psilocybin from those characterizing responses to other antidepressant interventions that target neurotransmission.

It is of note that clinical trials enrolling healthy volunteers have also reported changes in the amygdala activity and mood following psilocybin treatment. Barrett et al⁷⁷ (2020) reported that a single dose of psilocybin in healthy volunteers reduced negative affect and the amygdala responsiveness to facial stimuli 1-week post-treatment. In another study⁷⁸ involving a single-dose administration of psilocybin to healthy subjects, psilocybin-induced decreases in the right amygdala responsiveness to negative stimuli were correlated with enhanced positive mood following intake. Therefore, psilocybin-induced changes in the amygdala activity may in fact explain improvements in depressive symptoms in MDD patients, given that associations between the amygdala activity and mood are well established in healthy individuals.

Another preliminary finding emerging from two reviewed studies^{56,57} was that FC changes in the mPFC/vmPFC correlated with improvements in depressive symptoms. Recent studies have highlighted the role of the vmPFC and mPFC, which are integral components of the DMN, in mediating antidepressant response among MDD patients. For instance, vmPFC to cerebellar vermis FC has been implicated in selective serotonin reuptake inhibitor (SSRI) treatment response in MDD patients, with responders showing decreased FC between these regions compared to non-responders.⁷⁹ Moreover, mPFC intrinsic connectivity prior to antidepressant treatment has been predictive of remission outcomes in MDD patients.⁸⁰ Despite existing evidence supporting the amygdala and mPFC/vmPFC as neural correlates of treatment response following conventional antidepressants,

more data are necessary to determine how robust and replicable these neural correlates are and whether they are equally pertinent in the context of psilocybin.

As summarized in the review by Dos Santos et al⁴⁵ (2016), Carhart-Harris et al⁸¹ (2012) reported that the magnitude of decreased mPFC activity was related to the subjective effects of psilocybin in healthy volunteers. Additionally, Vollenweider et al⁸² (1997) found that increased activity in the PFC, as revealed by increased CMRglu, was positively associated with psilocybin's dose and subjective effects in healthy subjects. Thus, changes in depressive symptoms associated with altered FC in the mPFC/vmPFC among MDD patients may similarly resemble subjective state changes associated with altered PFC activity among healthy volunteers, so this neural correlate is well worthy of more detailed investigation.

With regard to large-scale neural effects of psilocybin, two trials by Daws et al⁶³ (2022) reported global decreases in brain modularity which significantly correlated with treatment response. Interestingly, enhanced resting-state network modularity has been linked to depression severity.^{83,84} Thus, it is plausible that psilocybin mediates its therapeutic effects by diminishing network modularity among certain neural networks that are commonly overactive in depressed patients.

Other brain regions that showed altered activity and/or FC under psilocybin were the right middle⁵⁸ and left superior temporal gyri,⁵⁷ bilateral temporal cortex,^{61,62} visual areas,^{56,58,61,62} as well as regions of the DMN, including the ACC^{57,60} and PCC/precuneus.^{56,57,60} However, these reported changes did not correlate with improvements in depressive symptoms. Increased PCC/precuneus and middle temporal gyrus activation has been predictive of SSRI treatment response in MDD patients.^{85,86} Taken together, activity changes in these brain regions warrant further investigation into their associations with depressive symptoms and treatment response.

In contrast, reported changes in brain activity may be confounded by experimental tasks that participants were required to complete. For instance, Roseman et al⁵⁸ (2018) found increased activation in the right amygdala and right middle temporal gyrus for the fearful > neutral contrast during an emotional faces image task. In a clinical trial by Pourtois et al⁸⁷ (2005), perception of emotional faces was associated with activation in the medial temporal gyrus and enhanced

Table 4. Main Imaging Findings from Published Studies.

Observed Result	Studies with Observed Result	Task-based, Resting state, Music listening
Psilocybin		
Changes in BOLD response/activity (fMRI)		
Increased right amygdala activity	Roseman et al ⁵⁹ (2018)	Task-based
Increased activity in visual/occipital regions	Roseman et al ⁵⁹ (2018)	Task-based
Increased temporal lobe activity	Roseman et al ⁵⁹ (2018)	Task-based
Greater ALFF in the bilateral superior temporal cortex	Wall et al ^{55,56} (2021)	Music listening
Greater ALFF in the right ventral occipital lobe	Wall et al ^{55,56} (2021)	Resting state
Changes in FC (fMRI)		
Decreased DMN to right frontoparietal network FC	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Increased DMN within-network FC	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Decreased within-DMN FC	Daws et al ⁶¹ (2022) <i>Open-label trial</i>	Resting state
Increased between-network FC between the DMN and EN	Daws et al ⁶¹ (2022) <i>Open-label trial</i>	Resting state
Increased between-network FC between the DMN and SN	Daws et al ⁶¹ (2022) <i>Open-label trial</i>	Resting state
Increased cingulate cortex (ie, PCC, ACC) FC	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Increased vmPFC to bilateral inferior-lateral parietal cortex FC	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Decreased medial and lateral PFC to PH FC	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Increased vmPFC to left occipital and parietal lobe FC	Mertens et al ⁵⁸ (2020)	Task-based
Increased FC between the vmPFC to right angular gyrus, right lateral occipital cortex, and other visual areas in the right hemisphere	Mertens et al ⁵⁸ (2020)	Task-based
Increased FC between the amygdala and vmPFC to occipital-parietal cortices	Mertens et al ⁵⁸ (2020)	Task-based
Decreased vmPFC to right amygdala FC	Mertens et al ⁵⁸ (2020)	Task-based
Increased FC between the amygdala and visual areas (ie, intracalcarine and supracalcarine cortex, cuneus, precuneus and right lateral occipital cortex)	Mertens et al ⁵⁸ (2020)	Task-based
Increased dFC between the ACC and PCC	Doss et al ⁶⁰ (2021)	Resting state
Significant Reduction	Daws et al ⁶¹ (2022) <i>Open-label trial</i>	Resting state
Significant Reduction	Daws et al ⁶¹ (2022) <i>RCT</i>	Resting state
Changes in CBF (PWI)		
Decreased CBF within the amygdala	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Decreased CBF within the temporal lobe	Carhart-Harris et al ⁵⁷ (2017)	Resting state
Magnetic Resonance Spectroscopy (MRS)		
Decreased glutamate and NAA in the ACC	Doss et al ⁶⁰ (2021)	Resting state
Ayahuasca		
^{99m}Tc-ECD SPECT imaging		
Increased activation in the limbic regions (ie, the left NAcc, right insula, and left subgenual area)	Sanches et al ⁶² (2016)	Resting state

Abbreviations: ACC = anterior cingulate cortex, CBF = cerebral blood flow, dFC = dynamics of functional connectivity, DMN = default mode network, EN = executive network, FC = functional connectivity, NAcc = nucleus accumbens, PCC = posterior cingulate cortex, PFC = prefrontal cortex, PH = parahippocampus, PWI = perfusion-weighted imaging, vmPFC = ventromedial prefrontal cortex, RCT = Randomized Control Trial, SN = salience network.

activity in the right amygdala during exposure to fearful faces. Moreover, in a meta-analysis⁸⁸ exploring emotional face processing in healthy subjects, the amygdala and middle temporal gyrus were among the key regions found to be significantly activated while processing emotional stimuli. Therefore, it remains unclear whether the observed alterations in brain activity in Roseman et al⁵⁸ (2018) result from the unique effects of psilocybin or due to the processing of emotional stimuli.

Furthermore, the conference abstract^{61,62} noted greater ALFF in the bilateral superior temporal cortex during music listening. However, a recent meta-analysis⁸⁹ reported activation in the bilateral superior temporal gyrus during music perception in healthy subjects. Consequently, it remains unclear whether the increased ALFF in the bilateral superior temporal cortex in Wall et al^{61,62} (2021) results from psilocybin intake or is due to the neural mechanisms of music perception. Future research should take task-based paradigms into account and introduce control groups to determine the isolated effects of psilocybin on neural activity.

Ayahuasca. A single SPECT study⁵⁹ investigated the effects of ayahuasca in patients with recurrent depression. Ayahuasca was associated with increased activity in the limbic regions, including the left NAcc, right insula, and left subgenual area. Though no specific neural correlates of psychedelic effects were reported, the authors did note that ayahuasca intake led to increases in psychoactivity and reductions in depressive symptoms.

Previous research has highlighted the involvement of the limbic system in the neural mechanisms behind antidepressant response. For instance, increased insula activity in response to emotional stimuli following antidepressant treatment has been correlated with clinical improvements in MDD patients.⁹⁰ Moreover, clinical improvements in depressive symptoms following fluoxetine treatment have been associated with decreased glucose metabolism in the limbic areas, particularly in the subgenual area, hippocampus, insula, and pallidum.⁹¹ Therefore, changes in the limbic system activity may offer valuable insight into the neural correlates of treatment response following ayahuasca.

Furthermore, clinical trials in healthy controls have highlighted ayahuasca's activity in the limbic region. Specifically, the amygdala⁹² and parahippocampus^{92,93} have also shown increased activity under ayahuasca. Another clinical trial⁹⁴ involving healthy participants reported increased ACC to SN connectivity, decreased PCC to DMN connectivity, and increased SN to DMN connectivity following a single session of ayahuasca. In the same trial,⁹⁴ increases in FC between the SN and DMN were significantly associated with negative affect scores. Considering the role of the limbic system in emotion regulation, ayahuasca-induced activity changes within this

region may, therefore, explain clinical improvements in depressive symptoms among MDD patients.

Registered Clinical Trials

Five registered clinical trials provide insight into the changing landscape of psychedelic neuroimaging studies in MDD. While four clinical trials⁶⁴⁻⁶⁷ are investigating the neural effects of psilocybin (80%), one trial⁶⁸ (20%) is exploring the neural effects of LSD-assisted psychotherapy. Given the shortage of research investigating LSD for the treatment of MDD, this trial is especially important as it may increase our understanding on the unique effects of certain psychedelics on brain activity. Neuroimaging research in healthy volunteers has shown that LSD reduces FC of the anterior mPFC and globally alters dynamic FC.⁹⁵ Moreover, LSD-induced decreases in FC between the parahippocampus and retrosplenial cortex have been associated with self-reports of mystical experiences, such as 'ego-dissolution' and 'altered meaning.'⁹⁶

However, neuroimaging research exploring LSD for depression is lacking. For this reason, the single, upcoming LSD trial⁶⁸ can provide valuable insight into the neural mechanisms of LSD in the context of depression. Moreover, this is the only trial to use psychedelic-assisted psychotherapy. Published studies have shown variable methods when using psychedelic-assisted psychotherapy, however, it is important to examine this aspect as well. Comparing interventional methods while investigating neuroimaging correlates and psychedelic efficacy can contribute to the evidence supporting one treatment regimen over another.

Furthermore, all but one⁶⁷ clinical trials investigating psilocybin have estimated sample sizes of 30 or more. This provides researchers with more accurate and reliable data that may be used to refine sample size estimates for future large-scale psychedelics trials for MDD. Overall, unpublished clinical trials offer insight into the neural interactions of psychedelics in MDD patients and how their clinical effects are achieved.

Strengths, Limitations, and Future Directions

A strength of this systematic review is the inclusion of both published and registered clinical trials to provide a more realistic representation of the existing state of research. Moreover, three databases (MEDLINE, Embase, APA PsycINFO), one clinical registry (Clinicaltrials.gov), and one grey literature database (OpenGrey) were searched to gather as much relevant literature as possible.

The main limitation of the current research landscape is the low number of published studies exploring the neuroimaging correlates of psychedelic treatment response in MDD patients, given the relatively recent emerging interest in this area of research. A new systematic review⁹⁷ reported the

use of oral psilocybin as a well-tolerated and efficacious treatment for psychiatric conditions such as depression, anxiety, and substance use disorders. Therefore, though the current scope of psychedelic efficacy trials supports their use, mechanistic neural studies exploring psychedelic activity remain scarce. In a rigorous methodological review of psychedelic clinical trials, Aday et al⁹⁸ (2022) emphasize the importance of including objective and reliable biomarker measures, including predictive biomarkers and surrogate endpoints, in the design of future trials to reduce bias associated with self-report and clinician-administered assessments of clinical outcomes. Including an fMRI component in the design of future psychedelics trials represents one of the avenues for this emerging field of research to delineate plausible neural mechanisms that could predict or explain the action of psychedelics in MDD. Efforts should be made to standardize this fMRI component as more trials enter the psychedelic neuroimaging space – acquisition sequences and data analysis scripts should be shared across labs, new data analysis models should be tested against previously reported models, and hypotheses should be based on previously reported neuroimaging findings, including the neural signatures identified in this systematic review, in attempts to replicate them with independent data.⁴⁴

A secondary key limitation of this review, related to the main limitation, is the small sample sizes used in all the included studies and the identical cohort of subjects employed in Carhart Harris et al⁵⁷ (2017), Roseman et al⁵⁸ (2018), Mertens et al⁵⁶ (2020) and Wall et al^{61,62} (2021). In addition, several studies did not include control groups. Future research should aim to increase study sample sizes and allocate sizeable participants to both control and experimental study groups to increase the validity and strength of the findings and minimize confounding effects. A review by Aday et al⁹⁸ (2022) emphasized the importance of having control groups in psychedelic research. Particularly, there is a need for active control groups in psychedelic research, such as a placebo that mimics some of the effects of psychedelics, to exclude treatment-nonspecific factors as one of the sources of treatment outcome differences. This also applies to neuroimaging studies of psychedelics for MDD - for example, most of the studies included in our review were open-label, resulting in a heightened risk of treatment-nonspecific effects on corresponding clinical outcomes, such as the Hawthorne effect,⁹⁹ whereby MDD patients may have unconsciously changed their behaviour in response to being observed by research personnel.

In the field of neuroimaging, treatment-nonspecific effects associated with the administration of psychedelics remain unknown in relation to how they affect fMRI metrics in participants with MDD. Therefore, in line with the general recommendations to improve the ability to discern the treatment-specific effects of psychedelics,⁹⁸ fMRI studies should aim to identify neural characteristics associated with treatment-nonspecific effects, such as placebo and nocebo

response, as well as with a single versus repeated administration of psychedelics. From the study design perspective, future trials will also benefit from introducing control groups, including active comparator, to identify the impact of treatment-nonspecific effects on clinical and neuroimaging outcomes.

Another limitation of our review concerns the fact that all included studies conducted neuroimaging scans at baseline and shortly after treatment, thereby concealing the long-term impact of psychedelics on neural activity. Future research should aim to corroborate the literature's current findings by conducting clinical trials investigating the neuroimaging correlates of antidepressant response following psychedelic treatments at multiple time points post-treatment and during follow-up to assess the sustainability of treatment effects at the neural level. Moreover, as evidenced by this review, psilocybin and ayahuasca are currently the only psychedelics that have been explored in the context of MDD. Therefore, studies are yet to investigate other psychedelic treatments, such as DMT and LSD, in MDD patients.

Another significant limitation of the included psilocybin studies is the variation in study design concerning the use of either task-based, task-free, or music listening neuroimaging scans, as well as the presence or absence of psychedelic-assisted psychotherapy. While resting-state studies may naturalistically provide insight into the brain functions associated with the experience of being treated with psychedelics, potential for the use of task-based fMRI has also been demonstrated.⁴⁴ It is, therefore, difficult to equally weigh and compare the findings across the studies bearing that methodological variability in scan and treatment protocols may potentially confound neuroimaging results. A review by McCulloch et al⁴⁴ (2022) highlighted this methodological heterogeneity within psychedelic literature, as the field is still in its nascent stages. For instance, eyes-closed and eyes-open resting-state fMRI metrics have both been employed across psychedelic neuroimaging studies.⁴⁴ While it is suggested that scans are acquired with the eyes closed due to visual alterations and associated changes in brain dynamics produced by psychedelics, this underscores the need for more research to determine which procedures work best⁴⁴ by replicating the designs of the included psilocybin studies. This will help determine if these conflicting study methodologies do, in fact, significantly impact neuroimaging outcomes.

Conclusion

Psychedelic interventions appear to have potential clinical benefits for patients with MDD and TRD as fast-acting alternatives to first-line antidepressants. The findings of the present review indicate that the DMN— particularly, the amygdala and mid-prefrontal regions (i.e., mPFC, vmPFC)—may offer a preliminary foundation for hypothesis generation and theory interrogation for future research aiming to

investigate the underlying neural mechanisms of antidepressant response following psilocybin treatment. Although these mechanisms are not clearly understood, the evidence suggests that these brain regions and associated ICNs may be involved in mediating antidepressant response, although this evidence is based only on four datasets with extremely different methods. Psilocybin also appears to target multiple other brain regions within the temporal lobe, DMN (ie, ACC and PCC) and visual areas, though there is no evidence to date to suggest that these correlates can be used to predict antidepressant response following psilocybin treatment. Moreover, ayahuasca may mediate its therapeutic effects by increasing activity in the limbic regions, though this assumption is constrained to the findings of a single clinical trial.⁵⁹ Several ongoing, registered clinical trials plan to further investigate the neuroimaging correlates of psychedelics, such as psilocybin and LSD, in MDD patients specifically. Importantly, incorporating neuroimaging modalities in psychedelic interventions could enhance this developing area of research by providing insight into the neural mechanisms underlying psychedelic treatment efficacy in MDD, although standardization across neuroimaging acquisition parameters and data analysis pipelines is critically needed. Importantly, the neural signatures identified in this review represent early observations. Further research and integration among datasets are required to replicate these observations and draw more definitive conclusions regarding the effect of psychedelics on the brain in patients with MDD.

Declaration of Conflicting Interests

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Data Availability

The data that support the findings of this study are available from the corresponding author, VB, upon reasonable request.


Author Contributions


S.K, A.D and V.B conceptualized the review. S.K and A.D conducted a systematic search of the available literature and performed

the data extraction and analysis. S.K and A.D also produced the first version of the manuscript. All aspects of the manuscript were overseen by I.D and V.B. The remaining authors provided critical revision of the article. All authors read and approved the final version of this manuscript.

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Supplemental Materials

Supplementary 1 is a text document with further data on the ongoing clinical trials included in this review

Supplementary 2 is a text document on the search strategies that were used to retrieve the records for this systematic review (including both OVID search and ClinicalTrials.gov search)

Supplementary 3 is a text document with the results of the quality assessment as per the GRADE checklist for use in systematic reviews

Supplementary 4 is a text document with the PRISMA Checklist to support this systematic review

Supplementary 5 is a text document with the PRISMA Abstract Checklist to support this systematic review

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