Neurobiological Correlates of Psilocybin Response in Depression

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ABSTRACT

Objective: To synthesize the neurobiological basis of brain-resetting effects of psilocybin and identify neuroimaging correlates of psilocybin response in depressed patients.

Data Sources: MEDLINE(R), Embase, APA PsycINFO, Cochrane, and CINAHL were systematically searched on June 3, 2022, with no date restrictions using the following string: (psilocybin) AND (psychedelics) AND (MRI) OR (fMRI)) OR (PET)) OR (SPECT)) OR (imaging)) OR (neuroimaging)).

Study Selection: After duplicates were removed from 946 studies, 391 studies remained, of which 8 qualified for full-text analysis, but only 5 fulfilled the eligibility criteria of randomized, double-blind, or open-label neuroimaging study with psilocybin treatment in depressed patients.

Data Extraction: The Covidence platform was used for deduplication and bias assessment. The *a priori* data points included concomitant psychological intervention, modality of neuroimaging technique, changes in depression scores, brain functional changes, and association between functional and psilocybin response. Assessment bias was assessed with the standard risk of bias tool for randomized controlled trials and the tool for risk of bias in nonrandomized studies of interventions.

Results: Four studies were open-label, and one was a combined open-label and randomized controlled trial using functional magnetic resonance imaging. Psilocybin-assisted psychotherapy was administered in 3 studies, 1 in refractory and 2 in nonrefractory patients. The remaining 2 studies were in refractory patients. The transient increase in psilocybin-induced global connectivity in major neural tracts and specific areas of brain activation was associated with antidepressant response.

Conclusions: Transient functional brain changes with psilocybin therapy resemble the "brain reset" phenomenon and may serve as the putative predictors of psilocybin antidepressant response.

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Despite significant pharmacologic advances, two-thirds of patients with major depressive disorder (MDD) do not respond to their antidepressant treatment. Finding the most effective treatment is often time-consuming due to the relatively early onset of adverse effects and delayed response and leads to medication nonadherence, poor prognosis, high socioeconomic burden, and loss of productive years.[1,2] An increasing number of patients with failed interventions and a longer duration of unremitted depression are among the main reasons for an increased number of patients with treatment-refractory depression.[3] Despite well-recognized improvement in neurovegetative symptoms, the most frequently used class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), have been associated with various adverse effects, including cognitive haze and emotional blunting.[4] Therefore, it becomes imperative to develop novel antidepressants that are rapidly effective across treatment-refractory and treatment-naive populations to achieve premorbid functionality and subjective improvements such as quality of life. The US Food and Drug Administration approval of intranasal esketamine, often labeled as a psychedelic, has reignited interest in exploring the antidepressant effects of other psychedelics, such as psilocybin and 3,4-methylenedioxymethamphetamine. Although esketamine is rapidly effective and has antisuicidal effects, it is expensive and requires 2-hour posttreatment monitoring due to the elevated risk for adverse effects.[5] In addition, patient registration in the risk evaluation and mitigation services is needed before esketamine can be prescribed in a supervised setting.[6]

Moreover, ketamine-induced activation of μ-opioid receptors adds a potential risk for addiction.[7,8] After a long hiatus, the resurrection of psychedelic research has produced promising results in managing several other psychiatric disorders, including obsessive-compulsive disorder, posttraumatic stress disorder, substance use disorder, and existential depression in terminal medical illnesses.[9–11] In a head-to-head comparison, 57% of the patients receiving psilocybin-assisted therapy remitted with a faster onset of efficacy than 28% of those receiving escitalopram, an SSRI, with similar tolerability.[12] More recently, depressed subjects produced a 75% response and 58% remission for at least 12 months after being randomized to receive immediate or delayed psilocybin-assisted psychotherapy.[13] Psilocybin-assisted psychotherapy recently produced a significantly better response and a faster onset of efficacy than escitalopram.[14]

Of note, no adverse effects were reported at the psilocybin doses used in these studies. However, in a recently published large-sample psilocybin trial, the most frequent adverse events reported in the 25-mg group included headache, nausea, dizziness, and fatigue.[15] However, few participants also developed serious adverse events of suicidal ideation and non-suicidal

Clinical Points

- Psilocybin therapy appears promising in patients with treatment-refractory depression.
- Initial neuroimaging findings suggest an association between psilocybin-induced brain changes and antidepressant response.
- Future trials are required before psilocybin can be used safely and effectively in depressed patients.

self-injurious behavior in the 25-mg and 10-mg dose groups. Of note, several participants already had suicidal thoughts and self-injurious behavior at baseline.[15] Regardless, the findings from this study warrant clinical monitoring for suicidality in future trials of psilocybin in depressed patients. In addition, the study did not report any psychosis or altered perceptions in the study subjects.[15] Nevertheless, higher psilocybin doses have been reported to induce psychosis and visual hallucinations, including the "bad trips," which is not unexpected as psilocybin induces significant changes in perception including visual hallucinations, synesthesia, and altered emotions.[16] Bad trips may involve confusion, irritability, anxiety, fear, psychosis, and frightening visions.[17] In a survey, people using psilocybin reported risk of dose-related physical harm, particularly those who used psilocybin without supportive therapy and social support, which underscores the safer and more effective profile of psilocybin-assisted therapy.[18] However, despite reported adverse effects most survey respondents reported psilocybin use as a therapeutic experience.[19] Some studies[20,21] have reported no adverse outcomes with psilocybin.

However, in general, rapid-onset and sustained antidepressant effects of psilocybin have increased interest in conducting neuroimaging studies to understand the neurobiological basis of the unique action profile of psilocybin. Although most neuroimaging studies have been conducted in healthy volunteers, there are growing data to demystify neurobiological mechanisms underlying psilocybin response. This review provides a synopsis of neuroimaging findings with psilocybin in depressed patients, comparing results from healthy volunteers and earlier neuroimaging findings with monoaminergic antidepressants.

METHODS

This review was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[22] Figure 1 provides the study flowchart.

Search Strategy

The online databases MEDLINE(R), Embase Classic + Embase, APA PsycINFO, Ovid Healthstar, Journal@Ovid Full Text, Cochrane, and CINAHL were systematically searched on June 3, 2022, with no date restrictions using the following string: (psilocybin) AND (psychedelics) AND (MRI) OR (fMRI)) OR (PET)) OR (SPECT)) OR (imaging)) OR (neuroimaging)). Only English-language studies were retrieved.

Eligibility Criteria

The review was primarily aimed at synthesizing the pretreatment and posttreatment changes in different functional areas and neural circuits of the brain after patients with MDD were administered a therapeutic dosage of psychedelics, primarily focusing on psilocybin and secondarily to find putative neuroimaging biomarkers that can predict or inform foregoing treatment. Hence, the following criteria were formed for the selection of studies following PRISMA guidelines[23]:

Population. Adult patients aged ≥18 years with a diagnosis of MDD according to the *DSM-IV* or *DSM-5*.

Intervention. A therapeutic dosage of a psychedelic is administered with an intent to treat (ITT) analysis.

Comparison group(s). Antidepressant, placebo, or none.

Outcomes. Comparison of pretreatment and posttreatment change in brain functioning and neural circuits through any neuroimaging modality (ie, functional magnetic resonance imaging [fMRI] or single-photon emission computed tomography [SPECT]) and/or comments on imaging biomarkers of response to psilocybin treatment.

Studies. Any original neuroimaging study, ie, randomized controlled trials (RCTs) or open-label studies.

Data Extraction and Analysis

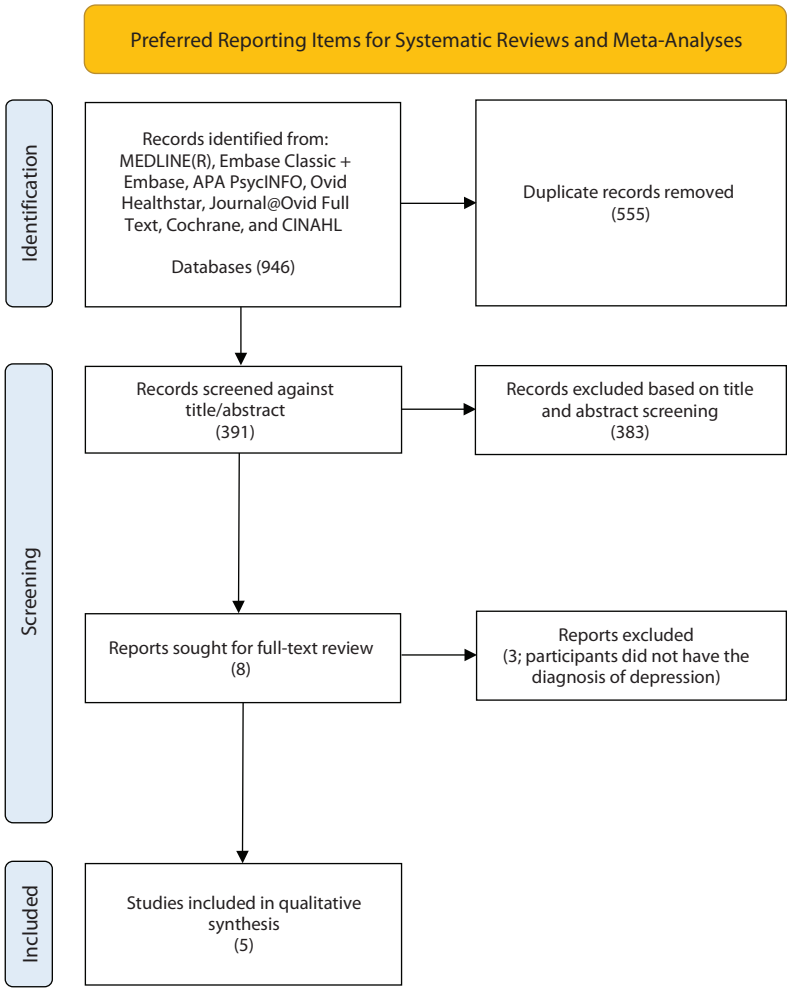
Database search results were imported into the Covidence platform (https://www.covidence.org/) for deduplication, screening, and risk of bias assessment. Two reviewers (M.Y.J. and S.Q.) independently screened the imported titles and abstracts and then assessed the remaining full texts for eligibility. Conflicts in judgment were resolved by discussion.

The data points to be extracted were determined a priori and included the following whenever possible: lead author, study type and duration, dosage and sequence of psilocybin administration, concomitant psychological intervention, modality of neuroimaging technique, baseline and posttreatment depression scores on validated psychological tools, whole and in-network brain functional changes, and correlation or association of brain functional changes with response to psilocybin treatment on any relevant clinical outcome (ie, decrease in depression, anxiety, or rumination symptomatology). A qualitative synthesis of the extracted data was subsequently undertaken.

Risk of Bias Assessment

Assessments of methodological quality were independently conducted by 2 reviewers (S.Q. and Z.Z.) using Cochrane's risk of bias tools.[15] Conflicts in judgments were resolved by discussions that produced the consensus judgments reported herein. Since both blinded RCTs and unblinded open-label trials were included, 2 distinct tools were applied respectively: (1) the standard risk of bias

Figure 1. Study Flowchart



(RoB) tool for RCTs and (2) the tool for risk of bias in non-randomized studies of interventions (ROBINS-I).

RESULTS

Of 946 studies identified in the initial search, 391 articles were left after duplicates were removed. These 391 studies underwent title and abstract screening, of which 8 studies were eligible for full-text analysis. After full-text research, 5 neuroimaging studies on depressed subjects were included in the narrative synthesis.[14,24–27] As shown in Table 1, the first 4 studies were open-label trials without placebo control with a small sample size ranging from 14 to 24.[24–27] However, 1 of the 2 trials in the latest study was an RCT with 43 subjects with MDD.[14] All studies used functional magnetic resonance imaging (fMRI), with one also utilizing magnetic resonance spectroscopy to assess functional and biochemical changes in brain response to psilocybin, respectively.[27] Four studies[14,24–26] were conducted in patients with treatment-refractory depression except for the RCT from the latest study, which was completed in patients with major depression.[14] Two studies[24,26] examined the functional brain changes with psilocybin-assisted supportive psychotherapy. Psilocybin therapy produced a significant antidepressant response in all reviewed studies as assessed with the Quick Inventory for Depressive Symptoms[28] or the Hamilton Depression Rating Scale.[29]

Study characteristics and extracted results are presented in Table 1. Furthermore, the ROBINS-I tool was applied to assess biases in selected open-label trials. Domain-level results of these quality appraisals are summarized in Figure 2. One limitation that needs to be mentioned here is that all studies were conducted in a single center and could have introduced any potential bias not measured by the ROBINS-I tool.

DISCUSSION

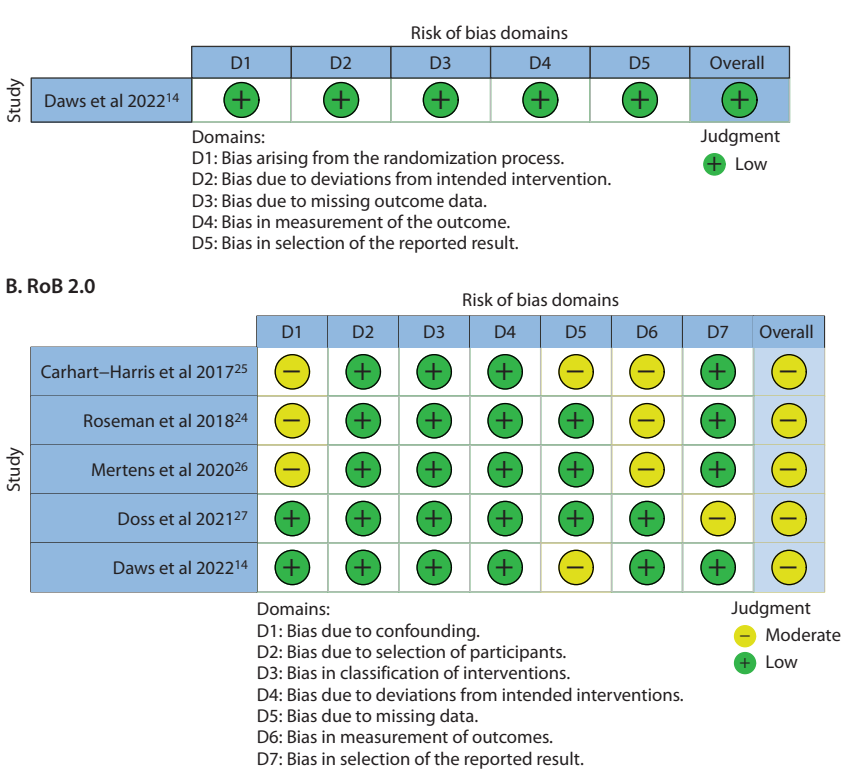
Although several neuroimaging studies with psilocybin are available in healthy volunteers, only a few are available in the depressed population, all of which are open-label and have utilized blood oxygen level–dependent (BOLD) fMRI (Table 1). Nevertheless, these psilocybin studies in depressed patients have reported interesting changes in the abnormal brain functioning reported in depressed patients.[30,31] One of the most important brain networks affected in MDD

Table 1. Summary of Neuroimaging and Clinical Findings From the Reviewed Psilocybin Studies in Patients With Major Depressive Disorder

Reference	Study Design	Sample Size	Male/ Female	Diagnosis	Imaging Method	Psilocybin Dose	Psilocybin-Assisted Therapy	Treatment-Induced Core Imaging Findings	Antidepressant Effects	Antidepressant Response Predictors Within or Between the DMN, CEN, or SN
Carhart-Harris et al 2017[25]	Open-label	Total: N = 19; 16 with ASL and 15 with BOLD fMRI	15/4	TRD	ASL BOLD fMRI	10 mg followed by 25 mg PO after 1 week	None	-Posttreatment decreases in total CBF in LHG, LPG, LPT, LSTG, LA, rSMG, and rPO -Increase in RSFC between sgACC and PCC and between vmPFC and ilPC	-Decreased depression week 1 and 47% response rate week 5	-DMN: AD predicted by increased RSFC between vmPFC-bilateral ilPC week 5 -SN: Decreased CBF in amygdala and decreased RSFC between PH-PFC in 5 weeks
Roseman et al 2018[24]	Open-label clinical trial	N = 20; 19 completed both scans	14/6	TRD	BOLD fMRI	Two doses; 10 mg followed by 25 mg PO after 1 week	Psychological support before, during, and after the sessions	Increased activation in right amygdala for fearful and happy faces	-Response of 68.4% in 1 day, 63.2% in week 1, 57.9% in week 2, and 47.3% in week 3	SN: Right amygdala activation to fearful vs neutral faces predicted response but only at week 1
Mertens et al 2020[26]	Open-label clinical trial	Total: N = 20 (analysis done for 19)	14/6	TRD	BOLD fMRI	Two doses; 10 mg followed by 25 mg PO after 1 week	None	-Increased FC between the amygdala and occipital cortex/precuneus -Decreased FC between the vmPFC and right amygdala in response to fearful and neutral	-Response in 63.2% and remission in 57.9%	DMN: Change in FC between vmPFC and OPC correlated with decrease in depressive symptoms at week 1 -SN: Correlation between AD response and amygdala FC did not survive correction
Doss et al 2021[27]	Open-label clinical trial	N = 24	8/16	MDD	fMRI, MRS	Two doses PO 1.6 weeks apart; 20 mg/70 kg and 30 mg/70 kg	Supportive psychotherapy with psilocybin administration	-Increase in cognitive flexibility in week 4 -Increase in dFC between ACC and PCC inversely correlated with cognitive flexibility -Reduced glutamate and NAA in the ACC in week 1	-All patients with significant improvement in 17-item GRID version of HDRS score at 1 week and 5 weeks	CEN: No correlation between increased cognitive flexibility and response at week 4 -DMN: Only baseline sFC model predicted AD response at week 4
Daws et al 2022[14]	Open-label plus RCT	Open-label: N = 16 RCT: total N = 43; controls: n = 21; psilocybin group: n = 22	Open-label: 12/4 RCT: 29/14	TRD in open-label; MDD in RCT	fMRI	-Open label: 10 and 25 mg 1 week apart -RCT: psilocybin group: 2 x 25 mg or 2 x 1 mg 3 weeks apart; control group: escitalopram 10–20 mg/d x 6 weeks	Psilocybin-assisted therapy	-Both trials with increased modularity across DMN, CEN, and SN post psilocybin therapy	-AD in both trials was rapid and correlated with decreased network modularity -Rapid and better AD response with both psilocybin doses than escitalopram -No differences in adverse effects	DMN, CEN, and SN: Decreased network modularity implying a global increase in network integration correlated with AD response at week 6

Abbreviations: AD = antidepressant, ASL = arterial spin labeling, BOLD = blood oxygen level dependent, CEN = central executive network, dFC = dynamic functional connectivity, DMN = default mode network, FC = functional connectivity, fMRI = functional magnetic resonance imaging, GRID-HDRS = GRID Hamilton Depression Rating Scale, ilPC = inferior-lateral parietal cortex, LA = left amygdala, lHG = left Heschl's gyrus, LPG = left precentral gyrus, LPT = left planum temporale, LSTG = left superior temporal gyrus, MRS = magnetic resonance spectroscopy, NAA = N-acetylaspartate, OPC = occipital-parietal cortex, PCC = posterior cingulate cortex, PH-PFC = parahippocampal-prefrontal cortex, QIDS-SR16 = Quick Inventory of Depressive Symptomatology (16-item), rPO = right parietal operculum, RSFC = resting state functional connectivity, rSMG = right supramarginal gyrus, sFC = static functional connectivity, sgACC = subgenual anterior cingulate cortex, SN = salience network, vmPFC = ventromedial prefrontal cortex.

Figure 2. Domain-Level Results of the Quality Appraisals



Abbreviations: RoB = risk of bias, ROBINS-I = risk of bias in nonrandomized studies of interventions.

is the default mode network (DMN)[31] associated with self-referential processing.[32] Several studies have reported increased activity in DMN,[31] which explains excessive self-focus in depressed patients.[33] Increased activity in DMN also dysregulates other higher-order brain networks, such as the central executive network (CEN) associated with cognitive inflexibility[34] and the salience network (SN) associated with negative perceptions about self and the future.[34,35] As depicted in Table 1, most neuroimaging findings from the reviewed studies involve changes in activation or functional connectivity within or between one or more of the specific brain regions in the DMN (ventromedial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior lateral parietal cortex), CEN (dorsolateral prefrontal cortex and the lateral posterior parietal cortex), and SN (anterior cingulate cortex, amygdala, and parahippocampal gyrus).

The first study[25] reported a greater decrease in resting-state functional connectivity (RSFC) in the parahippocampal–prefrontal cortex and a greater increase in the ventromedial prefrontal cortex–inferior lateral parietal cortex after a single 25-mg oral dose of psilocybin in responders than in the nonresponders. Both changes in psilocybin-induced connectivity predicted antidepressant response at 5 weeks. Increased connectivity in the ventromedial prefrontal cortex–inferior lateral parietal cortex reflected increased visuospatial ability to perceive self in the context of environment, while decrease in parahippocampal–prefrontal cortex connectivity represented prefrontal disinhibition allowing the spiritual experience. Although increased RSFC in the anterior cingulate cortex–posterior cingulate cortex/precuneus did not correlate with treatment response, increased connectivity between the anterior and posterior nodes of DMN may reflect a balance between emotionally laden self-perception versus other perspectives, respectively, and may help improve rumination and autobiographical memory in depressed patients. Other fMRI studies in depressed patients also found a significant relationship between a greater RSFC within the ventromedial prefrontal cortex and rumination scores in MDD, suggesting an inability to disengage DMN from self-perspective.[36,37] It is worth mentioning that similar changes in DMN connectivity results have been reported in depressed subjects who responded to electroconvulsive therapy (ECT).[38]

Psilocybin-induced connectivity changes are transient and time dependent, and mood stabilization has been reported after a post-acute reduction in the DMN integrity with psilocybin[25] and other psychedelics, such as LSD (lysergic acid diethylamide)[39] and ayahuasca.[40] The acute changes in connectivity are labeled as a "brain reset" mechanism as seen with ECT, in which initial disintegration facilitates a later reintegration and resumption of normal functioning. Of note, a concurrent reduction in BOLD activity has also been reported with a decrease in RSFC in posterior cingulate cortex/precuneus and medial prefrontal cortex with ayahuasca.[40] In addition, the psilocybin-induced decoupling between anterior medial and posterior medial DMN was replicated in another study[41] during a 5-day mindfulness

retreat associated with altered self-perception and subjective ego dissolution.

The second study[24] in depressed subjects, using an fMRI task for face recognition, reported a significant correlation between activation in the right amygdala to fearful and happy faces after a single dose of psilocybin lasting for 3 weeks. These findings contrast with the dampening of amygdala activity in response to negative emotional stimuli with conventional antidepressants, particularly SSRIs.[14,25] These neuroimaging differences between psilocybin and SSRIs suggest entirely different mechanisms of emotional processing,[14] where SSRIs reduce emotional responsiveness, resulting in emotional numbness,[4] while psilocybin desensitizes patients to deal with painful emotions.[24,42]

However, psilocybin-induced amygdala activation is transient, and mood stabilization occurs after a reduction in amygdala activation. These findings resemble the acute connectivity changes reported with psilocybin[25] and ECT.[38,43] Psilocybin-induced brain reset in cerebral blood flow has also been reported in healthy volunteers.[44,45] The acute disintegration followed by reintegration of neural circuits with psilocybin provides a brief but powerful window of opportunity for cognitive reframing, particularly with concurrent psychological support.[24,26] Posttreatment increases in cerebral blood flow in the anterior cingulate cortex, medial prefrontal cortex, lateral prefrontal cortex, and medial temporal cortex have been associated with the hallucinatory ego disintegration in healthy subjects.[46] Similar brain changes have been reported during ECT-induced seizures.[38,43]

The next study utilizing an fMRI face recognition task also reported acute changes in functional connectivity between important nodes of the DMN and amygdala in response to fearful and neutral faces after a week of psilocybin-assisted therapy.[26] The most noticeable findings were a transient posttreatment reduction in right amygdala connectivity with ventromedial prefrontal cortex with increased amygdala connectivity with the visual cortex, including precuneus.[26] Although the antidepressant response was not correlated with a reduction in ventromedial prefrontal cortex–right amygdala functional connectivity, rumination scores were significantly decreased at 1 week and 3 months after psilocybin treatment. These findings are consistent with results from earlier studies and support time-dependent changes behind brain reset with psilocybin therapy.

The next reviewed study[27] reported an increase in psilocybin-induced cognitive and neural flexibility. The neural flexibility was expressed as the dynamic functional connectivity (dFC) between the anterior cingulate cortex and posterior cingulate cortex, a finding replicated from a previous study.[25] However, none of the neuroimaging models predicted antidepressant response except the model trained on baseline static functional connectivity at 4 weeks. In addition, the reversal of the positive correlation between neural and cognitive flexibility after a week of psilocybin treatment suggests that sustained improvement in dFC may be counterproductive for cognitive flexibility. In other words, psilocybin therapy provides a transient window of opportunity for cognitive improvement, which closes after a sustained increase in dFC between the anterior cingulate cortex and posterior cingulate cortex. This is analogous to psilocybin-induced brain reset as reflected by disintegration and reintegration of neural circuits to deal with painful negative emotions. This study[27] also reported a decrease in glutamate and *N*-acetylaspartate in the anterior cingulate cortex, which is counterintuitive as it reflects a decrease in neuronal metabolism or a deficit in white matter integrity. However, these changes may also reflect a transient brain reset. The latest psilocybin study[14] in depressed subjects combined an open-label and a double-blind RCT of orally administered psilocybin in treatment-refractory and non–treatment-refractory patients, respectively. The second trial compared 2 doses of 25 mg of psilocybin therapy 3 weeks apart with daily 10–20 mg of escitalopram for 6 weeks. Both trials reported a rapid and durable response, which correlated with a lower strength of division (or modularity) between the DMN, CEN, and SN, suggesting a global integration in network activity. These network changes are most probably mediated by the psilocybin-induced activation of serotonin 2A (5-HT_{2A}) receptors,[47] most prominently expressed in the DMN, CEN, and SN.[48] In contrast, antidepressant response with escitalopram was significantly lower than the psilocybin response and did not correlate with changes in any brain networks.[14] The lack of selective activation of 5-HT_{2A} receptors with SSRIs is perhaps the main reason escitalopram failed to show psilocybin-like changes in the brain networks.[49] The findings from the first RCT carry more weight than the results from the open-label studies and support psilocybin's global integration of important brain networks dysregulated during depression. The preliminary findings from this review should be interpreted with caution, as they are primarily based on open-label studies with small sample sizes. Only the large sample RCT can confirm the neuroimaging findings from the reviewed studies.

CONCLUSION

The neuroimaging findings from the reviewed studies have produced promising predictors of psilocybin response, which are uniquely different from neurobiological changes observed with conventional antidepressants. Psilocybin and other psychedelics are the only antidepressants after ECT with a positive correlation between a transient brain reset mechanism and antidepressant response, which can potentially revolutionize depression treatment. Future research should be conducted in large RCTs to replicate and confirm the results from the reviewed studies, particularly concerning the global integration of dysregulated brain networks underlying psilocybin's response. In addition, the novel neurobiological effects of psilocybin justify transdiagnostic investigations, even including terminally ill patients and those with pervasive disorders such as autism and personality disorders. In addition, none of

the studies reported any adverse effects with psilocybin therapy. The only adverse effects documented in the RCT were in the escitalopram group, wherein 4 of the 29 patients discontinued due to adverse reactions, but none of the 30 patients randomized to the psilocybin group discontinued the study [14]. Most likely, there were no reportable adverse effects at the doses employed in the reviewed studies, which were much lower than those reported to result in a bad trip. In addition, no more than 2 psilocybin doses (10 mg and/or 25 mg) were used in all the reviewed studies, which could be another reason for the lack of adverse effects. However, a recent large sample trial[15] reported headache, dizziness, and fatigue in the study subjects, with a few having serious adverse events including suicidal ideation and nonsuicidal self-injurious behavior. In addition, since depressed patients may have different genetic or neurobiological vulnerabilities, caution is warranted in using even the lower dose of psilocybin, particularly without psychotherapy and social support, until future research determines the safe and effective use of psilocybin in depressed patients.

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