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The Effects of Psilocybin in Adults with Major Depressive Disorder and The General Population

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Highlights

- Changes in amygdala activity are observed post-psilocybin administration in MDD cohorts.
- Changes in functional connectivity post-psilocybin treatment is observed in MDD and healthy people.
Psilocybin treatment may decrease depressive symptoms among participants with MDD.

Literature examining neural changes following psilocybin therapy in MDD is limited.

Abstract
The use of psilocybin as treatment for major depressive disorder (MDD) has been examined as a promising alternative to traditional first-line options. We reviewed existing literature to provide a synthesis of the extant neuroimaging observations with psilocybin, and to identify putative therapeutic targets for target engagement studies with psilocybin, and potentially other psychedelics. We assessed neuroimaging observations with psilocybin among participants with MDD and healthy populations. A systematic search was conducted on PubMed, Google Scholar and PsycINFO from database inception to November 17th, 2021. The study quality (i.e., risk of bias) was assessed using the revised Cochrane risk-of-bias tool for randomized trials. A total of ten studies evaluated psilocybin in healthy populations and three studies assessed psilocybin in MDD participants using neuroimaging techniques. Following psilocybin administration, a decrease in amygdala activity and a reduction in depressive symptoms was observed in two studies. Changes in functional connectivity and activation of prefrontal limbic structures, specifically the ventral medial prefrontal cortex and amygdala, was seen in healthy populations. There was high heterogeneity in methodology (e.g., dosing schedule and imaging methods) amongst included studies. Longitudinal studies are needed to further elucidate psilocybin treatment for MDD, its long-term effects and the possibility of sustained therapeutic effects.
Key words: psilocybin; functional magnetic resonance imaging; fMRI; major depressive disorder; depression; treatment resistant depression; mood disorders

1. Introduction

Major depressive disorder (MDD) is a chronic and debilitating mood disorder that impacts approximately 300 million individuals worldwide (Kessler et al., 2005). By 2030, MDD is projected to affect 23% of the global population, making it the leading cause of global disease burden (Hay et al., 2017; Mathers & Loncar, 2006). Despite its high prevalence, relatively early age at onset, as well as a chronic and severe course of illness, most individuals receiving evidence-based treatment for MDD do not achieve syndromal and functional recovery (Rush et al., 2008). Approximately 30-50% of patients fail to respond to conventional treatments, and the economic burden of mental disorders and their treatment is expected to exceed $1.8 trillion USD globally over the next three decades (Davis et al., 2020; Doran & Kinchin, 2019). The foregoing description of MDD at the population level provides the impetus for identifying genuinely novel, rapid onset treatments for adults with MDD.

Extant literature has evaluated the safety and efficacy of psychedelic medicines in the treatment of disparate mental disorders including, but not limited to, mood and anxiety disorders (Dos Santos et al., 2018; Family et al., 2020; Moreno et al., 2006). The use of psychedelics, such as psilocybin and lysergic acid diethylamide (LSD) for spiritual, religious, and healing purposes has been documented for more than 2000 years (Gordon Wasson et al., 2008). However, the therapeutic use of psychedelics are not currently recommended (or approved by regulators) due to insufficient safety, tolerability, and effectiveness data. The therapeutic potential of psychedelics in the treatment of mental disorders, such as MDD, anxiety, and post-traumatic stress disorder (PTSD) was initially explored in the 1950s (Hofmann et al., 1958). Throughout the next 15 years, it was estimated that tens of thousands of individuals across North America,
Europe, and the United Kingdom (UK) were treated by clinicians with psychedelic agents (Caldwell, 1968). However, in the 1960s, increased rates of recreational use, along with health and safety concerns, resulted in the prohibition of psychedelic use in the United States (and globally). Psilocybin, LSD and MDMA were listed as “schedule 1” controlled substances, which significantly limited clinical research that sought to determine legitimate application of these agents (Gardner et al., 2019; Stevens, 1987).

In the 1990s, research on the therapeutic potential of psychedelics resumed in the U.S. and Europe, marking the ‘second wave’ of psychedelic research. Since then, a number of clinical trials have demonstrated the therapeutic potential and safety of the classic psychedelics in the treatment of addiction, mood, and anxiety disorders (Bogenschutz et al., 2015; R. L. Carhart-Harris et al., 2018; Robin L. Carhart-Harris et al., 2016; Robin L. Carhart-Harris & Goodwin, 2017; Gill et al., 2020; Grob et al., 2011; Moreno et al., 2006; Ross et al., 2016). Available evidence suggests that psilocybin, a naturally occurring alkaloid, may be efficacious at rapidly reducing depressive symptoms in adults with MDD. For example, Carhart-Harris et al. (2016) assessed the efficacy of two doses of oral psilocybin (10mg placebo and 25mg therapeutic dose) with psychological support, one week apart, in patients with treatment-resistant depression (TRD) and found significant decreases in depressive symptoms, which remained significant six months following treatment (R. L. Carhart-Harris et al., 2018; Robin L. Carhart-Harris et al., 2016; Davis et al., 2020).

A number of additional clinical trials have explored the therapeutic efficacy of psilocybin-assisted psychotherapy for the treatment of MDD (R. L. Carhart-Harris et al., 2018; Robin L. Carhart-Harris & Goodwin, 2017; Davis et al., 2020; Gill et al., 2020; Griffiths et al., 2016). Literature suggests that the antidepressant effects of psilocybin, along with its active metabolite
psilocin, are a result of their modulation of serotonergic and glutaminergic neurons. In particular, 5HT2 receptor agonist effects lead to antidepressant effects through desensitization and downregulation of receptor density (Ling et al., 2022; Van Oekelen et al., 2003; Wing et al., 1990). Notably, 5-HT2A receptors are expressed in the visual cortex, and thus, mediate the visually hallucinogenic effects of psilocybin. Downstream effects of 5-HT2A receptor agonism leads to activation of secondary messengers and ultimately, alterations in gene expression. Previous studies have suggested that overexpression of 5-HT2A receptors in MDD patients positively correlates with both severity and duration of depression (Kometer et al., 2013). Thus, 5-HT2ARs desensitization and downregulation might explain the antidepressant and anxiolytic properties of the psilocybin. However, it remains unclear the relative role of 5HT2A agonism and the subsequent integration therapy. Moreover, antidepressant effects may also be exerted through increases in extracellular glutaminergic concentrations in the prefrontal cortex due to 5HT2A receptor agonism (Béïque et al., 2007; Vollenweider & Kometer, 2010). The foregoing effects are thought to result in the modulation of the α-amino-3-hydroxy- 5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl- D-aspartate (NMDA) receptors, which play a role in the upregulation of neurotrophin expression, such as the brain-derived neurotrophic factor (Zanos et al., 2018). The associated cascade of molecular events is hypothesized to lead to symptom relief in persons affected by MDD.

Multiple neuroimaging studies have explored the effects of psilocybin in the central nervous system of healthy participants. For example, positron emission tomography (PET) studies with healthy participants indicate increased neuronal activity in the prefrontal cortex and limbic regions following moderate doses of psilocybin (Vollenweider & Kometer, 2010). However, there remains a paucity of studies evaluating the functional changes of psilocybin and the neural
correlates associated with the improvements in depressive symptomatology compared to the general population. Herein, we assess the literature for neuroimaging studies evaluating neural changes in individuals with MDD following psilocybin-based psychotherapy compared to the general population. The overarching co-primary aims of this review are to provide a synthesis of the extant literature with respect to neuroimaging observations with psilocybin, and to identify putative therapeutic targets for target engagement studies with psilocybin, and potentially other psychedelics.

2. Methods

2.1 Literature Search and Study Selection

Three independent reviewers (HG, PP and PP) searched the literature for studies that used imaging techniques to evaluate the effects of psilocybin-based psychotherapy in participants with MDD. We conducted a search on PubMed, Google Scholar and PsycINFO for English-language articles published between database inception to November 17th, 2021 using the following medical search heading (MeSH) terms and search strings: (Psilocybin) AND ((depression OR (major depressive OR treatment-resistant depression) AND (imaging OR neuroimaging OR MRI OR magnetic resonance imaging OR fMRI OR functional magnetic resonance imaging OR positron emission tomography OR diffusion tensor imaging). Moreover, in an effort to elucidate the possible therapeutic effects of psilocybin treatment, we compared the neuroimaging findings from MDD populations to healthy volunteers. Accordingly, a separate search was used to identify the neural effects of psilocybin in healthy volunteers using the following medical search heading (MeSH) terms and search strings: (Psilocybin) AND (imaging OR neuroimaging OR MRI OR magnetic resonance imaging OR fMRI OR functional magnetic resonance imaging OR positron emission tomography OR diffusion tensor imaging). An additional search was
performed in the reference list of identified articles. Our systematic review reported results using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist was used to improve the reliability of included studies and comprehensively report the study methods and results (Moher et al., 2010).

2.2 Eligibility Criteria

The titles and abstracts of all identified publications were screened for eligibility. Our primary aim was to evaluate neuroimaging findings from studies evaluating the effects of psilocybin-based psychotherapy in participants with MDD. The treatment group required a clinician-confirmed diagnosis of MDD and/or MDD diagnosis according to validated scales [e.g., The Diagnostic and Statistical Manual of Mental Disorders (DSM)]. Neuroimaging studies included any of the following procedures: diffusion tensor imaging, functional magnetic resonance imaging, or PET. As a comparison, we evaluated neuroimaging findings following psilocybin administration in healthy volunteers. Herein, we excluded the following: 1) unpublished data sets, case studies, conference reports, non-refereed abstracts, or observational studies, 2) multiple reports from the same data set, 3) absence of clinical assessment of depression, 4) no functional imaging technique used within the clinical sample population and 5) Animal studies. Studies that did not report, evaluate, or sufficiently describe the foregoing information were excluded from analysis.

2.3 Study Selection

Authors HG, PP, PP and BG reviewed all articles that met inclusion criteria to assess for the following primary outcome: the effects of psilocybin-based psychotherapy in treating participants with MDD. Data were extracted using a standard data extraction form for: sample size, gender distribution, intervention features (e.g., method of assessment, details of controls),
mean age, imaging technique, study design, psilocybin dose, outcome of interest, and reported findings. Where there was more than one intervention assessment of depression, the primary measure was used.

2.4 Assessment of Bias

Study quality (i.e., risk of bias) was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2: A revised Cochrane risk-of-bias tool for randomized trials, n.d.). Bias was assessed in accordance with the six domains evaluating risk of bias: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in the selection of the reported result, and bias arising from conflicts of interest (RoB 2: A revised Cochrane risk-of-bias tool for randomized trials, n.d.). Complete results from the Cochrane risk-of-bias guidelines are presented in Table 1.

3. Results

3.1 Search results

After removal of duplicates, our database search returned 587 unique articles evaluating the effects of psilocybin-based psychotherapy in participants with MDD. An additional 6 articles were found through a manual search of the references. Subsequently, 593 titles and abstracts were manually screened for eligibility. Following a full text review of 10 articles, seven were removed for the following reasons: three articles were removed because they did not include imaging, two were removed for no MDD participant group, and a further two were removed for reporting results from an already included dataset. Our database search for neuroimaging studies evaluating the effects of psilocybin in healthy participants yielded a total of 1287 unique records. After a manual reference search, 1314 publications were assessed for eligibility. A total of 64 studies were evaluated for full-text review. Following full-text review, 10 articles met the
outlined inclusion criteria. The search results are presented according to PRISMA guidelines in Figure 1.

3.2 Study Design and Characteristics

Three studies evaluated the effects of psilocybin-based psychotherapy in participants with MDD (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018). One study used the Quick Inventory of Depressive Symptomatology (QIDS) for the assessment of depressive symptoms and two studies used the shortened 16-item QIDS (QIDS-SR16) (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018). Across all studies, participants in the MDD cohort received a low dose (10 mg), followed by a high dose (25 mg) of psilocybin, one week apart. Participants were provided with a four-hour session of preparatory psychological support before administration of the first, low dose (10 mg) of psilocybin. Psychological support was also provided immediately before, during, and after both the low and high doses. Additionally, participants engaged in a psychological integration session the day after receiving the high dose. Participants underwent baseline fMRI scanning prior to any psychological or pharmacological interventions, and post-treatment fMRI scanning one day following the high dose treatment, before the psychological intervention therapy (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018). Study characteristics are summarized in Table 2.

Ten studies evaluated the effects of psilocybin-based psychotherapy in healthy participants (Barrett, Doss, et al., 2020; Barrett, Krimmel, et al., 2020; R. L. Carhart-Harris et al., 2012; Robin L. Carhart-Harris et al., 2012; O. Grimm et al., 2018; Kraehenmann et al., 2015; Lebedev et al., 2015; Lord et al., 2018; Preller et al., 2020; Smigielski et al., 2019). Seven studies used a
counterbalanced, placebo-controlled design, in which participants were administered a placebo and a psilocybin dose at two separate visits (R. L. Carhart-Harris et al., 2012; Robin L. Carhart-Harris et al., 2012; O. Grimm et al., 2018; Kraehenmann et al., 2015; Lebedev et al., 2015; Lord et al., 2018; Preller et al., 2020). Four studies administered one dose of 2mg psilocybin and one placebo dose, at least seven days apart (R. L. Carhart-Harris et al., 2012; Robin L. Carhart-Harris et al., 2012; Lebedev et al., 2015; Lord et al., 2018). Meanwhile, three counterbalanced, placebo-controlled studies implemented a placebo and psilocybin session separated by at least 14 days (O. Grimm et al., 2018; Kraehenmann et al., 2015; Preller et al., 2020). Two of these studies used a 0.16 mg/kg dose of psilocybin, with fMRI scans conducted 70 to 90 minutes following psilocybin or placebo administration (O. Grimm et al., 2018; Kraehenmann et al., 2015). One study used a 0.2 mg/kg dose of psilocybin, with resting state fMRI scans taken 20, 40, and 70 minutes following psilocybin or placebo administration (Preller et al., 2020).

Two studies used a single-blind, placebo controlled design, where participants were administered a placebo dose at 8 a.m., followed by a dose of psilocybin at 12 p.m. Psychological support was provided to participants in each study before, during, and after administration of the placebo and psilocybin, and two separate fMRI scans were taken 90 minutes following the administration of both the placebo and psilocybin (Barrett, Doss, et al., 2020; Barrett, Krimmel, et al., 2020). One study used a 0.143 mg/kg dose of psilocybin (Barrett, Krimmel, et al., 2020), while the other study used a 0.357 mg/kg dose of psilocybin (Barrett, Doss, et al., 2020).

In a double-blind, placebo-controlled study, participants were administered 0.315 mg/kg of psilocybin on day four of a five-day mindfulness retreat. Pre-treatment fMRI scans were taken one day before the retreat, while post-treatment fMRI scans were taken one day following the retreat. Participants were required to meditate during the scans, where they progressed from a
resting state, to focused attention, and finally open awareness in blocks of seven minutes (Smigielski et al., 2019).

In two studies, participants underwent two, 12-minute, eyes-closed, resting state fMRI scans. The placebo or psilocybin was administered six minutes into each scan, resulting in four unique, six-minute long scans: pre-treatment, post-treatment, pre-placebo, and post-placebo (Lebedev et al., 2015; Lord et al., 2018). One study employed a 18-minute fMRI scan, with the psilocybin or placebo being administered six minutes following the start of the scan (Robin L. Carhart-Harris et al., 2012). Notably, one study employed a task-free fMRI scan for 12 minutes, with the psilocybin or placebo administered at the six-minute mark. Moreover, 7.5 minutes into the scan, participants performed an autobiographical memory task, during which participants recalled emotionally salient and positive life events, producing a behavioural scan. The duration of the behavioural scan was 18.5 minutes (R. L. Carhart-Harris et al., 2012).

Two studies evaluating participants with MDD, and three studies evaluating healthy participants assessed neural activity during emotional processing tasks using fMRI scans (Barrett, Doss, et al., 2020; O. Grimm et al., 2018; Kraehenmann et al., 2015; Mertens et al., 2020; Roseman et al., 2018). Studies assessing participants with MDD used a classic face/emotion perception task, where participants were presented with fearful, happy, or neutral faces from the Karolinska Directed Emotional Faces (KDEF) set during the BOLD fMRI scan (Mertens et al., 2020; Roseman et al., 2018).

In contrast, in three fMRI trials with healthy participants, one study used the Affective Picture System (IAPS), where participants were presented with negative/threatening and neutral images during an amygdala reactivity task in the fMRI scanner (Kraehenmann et al., 2015). Meanwhile,
another non-MDD study evaluated emotional processing one day before, one week after, and one month after psilocybin administration using three different tasks during the fMRI scan: the emotion discrimination task, emotion recognition task, and emotional conflict Stroop task (Barrett, Doss, et al., 2020). Finally, a separate study assessed emotional processing following psilocybin administration in healthy volunteers using an event-related face discrimination task in the fMRI scanner using the STOIC-Face database (O. Grimm et al., 2018).

3.3 Changes in amygdala activation

Two studies assessed changes in neural activation in the amygdala of participants with MDD following treatment with psilocybin (Robin L. Carhart-Harris et al., 2017; Roseman et al., 2018). One study used cerebral blood flow (CBF) to analyze amygdala activation and found reduced left amygdala activation one-day post-treatment (Robin L. Carhart-Harris et al., 2017). Another study used bilateral-amygdala-mask voxel-wise fMRI analysis with the Karolinska Directed Emotional Faces (KDEF) set during the BOLD fMRI scan and reported that treatment with psilocybin resulted in increased right amygdala activity for fearful, happy and neutral faces. Increased activation in the right amygdala was also observed when comparing the fearful and neutral conditions (fearful > neutral). The activated clusters in each condition were located in similar locations of the right amygdala. However, after correcting for 10 tests, only the increased activation in response to fearful stimuli remained significant ($p = .001$) (Roseman et al., 2018). Taken together, both studies reported contrasting findings regarding activation in the amygdala post-treatment in participants with MDD.

Two studies assessed amygdala reactivity to negative and threatening emotional stimuli following psilocybin administration in healthy participants using emotion processing tasks...
(Barrett, Doss, et al., 2020; Kraehenmann et al., 2015). During an amygdala reactivity task using the International Affective Picture System (IAPS), Kraehenmann et al. (2015) found that right amygdala activity was significantly attenuated during the processing of negative ($p=0.001$) and neutral stimuli ($p<0.001$) (Kraehenmann et al., 2015). Subsequent analysis of the same dataset by Kraehenmann et al. (2016) revealed that compared to placebo, psilocybin decreased the modulating effects of negative visual stimuli on top-down connectivity from the amygdala to the primary visual cortex ($p=0.01$) (Kraehenmann et al., 2016). Altogether, these results indicate amygdala reactivity to negative stimuli is reduced following psilocybin administration.

Psilocybin reduced amygdala activation to negative stimuli is in line with findings from Barrett et al. (2020), which evaluated the long-term effects of psilocybin on the amygdala during an emotion recognition task one-week following psilocybin administration (Barrett, Doss, et al., 2020). Post-hoc analysis revealed a significant reduction in activation in the left ($p<0.00005$) and right ($p=0.00005$) amygdala in response to angry, fearful, happy, sad, and neutral facial stimuli. However, both left ($p<0.00005$) and right ($p<0.005$) amygdala activations returned to baseline one month following administration. Notably, no significant changes in amygdala activation were observed during the emotion discrimination task or the Stroop task (Barrett, Doss, et al., 2020). Consequently, results from studies with healthy participants are also inconsistent with findings from Roseman et al. (2016), which suggest an increase in amygdala activation during the processing of negative stimuli in participants with MDD following treatment with psilocybin (Roseman et al., 2018).

3.4 Changes in functional connectivity
Two studies with MDD participants assessed post-treatment changes in functional connectivity (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020). Carhart-Harris et al. (2017) assessed resting state connectivity and Mertens et al. (2020) assessed changes in functional connectivity during the KDEF task, compared to resting state (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020). Functional connectivity refers to the statistical relationship between the measures of activation in two distinct brain regions. Resting state functional connectivity is measured when the participant is at rest, in the absence of any tasks. This is in contrast with task-based functional connectivity, which is measured while the participant performs a task, such as the KDEF task.

The study by Carhart-Harris et al. (2017) found no significant change in amygdala resting state functional connectivity when comparing post-treatment scans to pre-treatment scans (Robin L. Carhart-Harris et al., 2017). In contrast, Mertens et al. (2020) found increased functional connectivity during the processing of happy and neutral faces between the amygdala and the visual areas (i.e., the right lateral occipital cortex, the intracalcarine and supracalcarine cortex, cuneus, and precuneus), compared to resting state (both p<0.001). The significant cluster was centred around the right intracalcarine and supracalcarine cortices (Mertens et al., 2020).

Both studies also evaluated post-treatment changes in functional connectivity at the level of the ventromedial prefrontal cortex (vmPFC) (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020). Carhart-Harris et al. (2017) observed an increase in vmPFC resting state functional connectivity with the bilateral inferior-lateral parietal cortex (iPC). Notably, they observed a decrease in resting state functional connectivity between the parahippocampus and the lateral and medial prefrontal cortex (mPFC) (Robin L. Carhart-Harris et al., 2017).
In contrast, Mertens et al. (2020) observed a post-treatment decrease in functional connectivity between the vmPFC and the right amygdala during the processing of fearful ($p = .032$) and neutral ($p = .041$) faces. Independent whole-brain analyses also revealed increased functional connectivity between the vmPFC and amygdala with the occipital-parietal cortices during the face processing component of the KDEF (Mertens et al., 2020). Moreover, Carhart-Harris et al. (2017) observed a post-treatment increase in resting state functional connectivity between the subgenual anterior cingulate cortex (sgACC) and the posterior cingulate cortex/precuneus (PCC) (Robin L. Carhart-Harris et al., 2017). Meanwhile, Mertens et al. (2020) reported no changes in functional connectivity between the sgACC and the PCC (Mertens et al., 2020).

Nine studies evaluating healthy participants reported data regarding changes in functional connectivity following administration of psilocybin (Barrett, Doss, et al., 2020; Barrett, Krimmel, et al., 2020; Robin L. Carhart-Harris et al., 2012; O. Grimm et al., 2018; Kraehenmann et al., 2015; Lebedev et al., 2015; Lord et al., 2018; Preller et al., 2020; Smigielski et al., 2019). Three studies evaluated functional connectivity during emotion processing tasks (Barrett, Doss, et al., 2020; O. Grimm et al., 2018; Kraehenmann et al., 2015). Data from Kraehenmann et al. (2015) was analyzed by Kraehenmann et al. (2016) using dynamic causal modeling and Bayesian model selection to assess the effect of psilocybin on connectivity in the visual limbic prefrontal network during the processing of threatening stimuli. Data from the placebo and psilocybin groups suggests that the bidirectional connections between the primary visual cortex and amygdala, and between the amygdala and the lateral PFC are modulated by threat affect. Furthermore, a significant decline in top-down connectivity from the amygdala to the primary visual cortex in response to threatening stimuli was observed ($p = 0.01$) (Kraehenmann et al., 2015, 2016).
Notably, during the processing of emotional faces following psilocybin administration, Grimm et al. (2018) reported a decrease in connectivity between the left striatum and the right amygdala in the angry condition, compared to the neutral condition. Moreover, during the processing of happy faces, compared to neutral faces, reduced connectivity between the right amygdala and the frontal pole was observed. No significant effects of psilocybin were observed in the fearful condition, compared to the neutral condition (O. Grimm et al., 2018). Meanwhile, Barret et al. (2020) observed increased resting state functional connectivity across a number of neural regions with no discernable network pattern. In particular, increased resting state functional connectivity strength was observed in 38 functional connections, while reduced connectivity was observed for 10 connections one-week post-psilocybin treatment. One month following psilocybin administration, a pattern of increased connectivity remained for 29 functional connections, seven of which were also increased at the one-week mark. Meanwhile, reduced connectivity was observed for 18 neural connections at the one-month follow-up (Barrett, Doss, et al., 2020).

Six studies evaluated changes in functional connectivity post-psilocybin in healthy controls at rest (Barrett, Krimmel, et al., 2020; Robin L. Carhart-Harris et al., 2012; Lebedev et al., 2015; Lord et al., 2018; Preller et al., 2020; Smigielski et al., 2019). Two studies assessed changes in brain-wide connectivity post-psilocybin in healthy participants (Lord et al., 2018; Preller et al., 2020). Lord et al. (2018) reported an overall increase in global connectivity, along with post-treatment reductions in connectivity in the fronto-parietal network. Meanwhile, Preller et al. (2020) observed a decrease in brain-wide connectivity in associative regions, and an increase in brain-wide connectivity in sensory regions. In particular, significant hypoconnectivity was observed in several subcortical and bilateral cortical areas, including the mPFC and lateral PFC, cingulum insula, and the temporoparietal junction (p<0.05). Furthermore, significant
hyperconnectivity was observed in sensory regions, namely the bilateral occipital cortex, the right superior temporal gyrus, the precuneus and the left postcentral gyrus (p<0.01). The degree of psilocybin-induced hypo- and hyper-connectivity was associated with baseline connectivity (p<0.05), and the effects of psilocybin were also associated with the spatial expression of the 5-HT\textsubscript{2A} and 5-HT\textsubscript{1A} genes in a time-dependent manner (Preller et al., 2020).

A separate study assessed the neural correlates of psilocybin-induced ego-dissolution, and found that psilocybin was associated with reduced functional connectivity between the medial temporal lobe and high-level cortical regions, decreased interhemispheric communication, and disintegration of the salience network (Lebedev et al., 2015). A study by Smigielski et al. (2019) found neural decoupling between the mPFC and PCC (p=0.003), and the mPFC and the left and right angular gyrus (both p=0.030) during open awareness meditation (Smigielski et al., 2019).

An earlier study by Carhart-Harris et al. (2012) demonstrated reduced CBF and BOLD signalling in the mPFC, PCC, ACC, and the thalamus, where decreased mPFC and ACC activity was positively correlated with the subjective effects of psilocybin in healthy participants (Robin L. Carhart-Harris et al., 2012).

Finally, a study by Barret et al. (2020) found acutely decreased activity in both the left and right claustrum, particularly a reduction in the amplitude of low-frequency fluctuations, and variance of BOLD signals. This decrease in activity was associated with subjective drug effects, where participants experiencing greater subjective effects of psilocybin demonstrated greater decreases in amplitude of low-frequency fluctuations, and variance of BOLD signals. Moreover, reductions in the amplitude of low-frequency fluctuations, and variance of BOLD signals was also associated with reduced functional connectivity between the left claustrum and fronto-parietal
3.5 Changes in depressive symptoms

Two studies assessed the correlation between changes in depressive symptoms and neural activation in the amygdala in participants with MDD (Robin L. Carhart-Harris et al., 2017; Roseman et al., 2018). Carhart-Harris et al. (2017) found that reduced depressive symptoms, measured by the QIDS-SR16, one day post-psilocybin treatment were correlated with reduced CBF, and subsequently reduced activation, in the amygdala ($p = 0.01$) (Robin L. Carhart-Harris et al., 2017). The study by Roseman et al. (2018) found that increased activation in the right amygdala during the KDEF task was significantly correlated with in-scanner ratings of depression, BDI and QIDS scores, where greater activation was associated with lower ratings of depressive symptom severity (Roseman et al., 2018).

Two studies looked at the association between functional connectivity and depressive symptoms in participants with MDD. Both studies found correlations between depressive symptoms and changes in functional connectivity between regions of the PFC, and other brain regions (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020). For example, Carhart-Harris et al. (2017) found increased resting state function connectivity between the vmPFC and ilPFC ($p = 0.03$), as well as decreased connectivity between the parahippocampus and the lateral PFC and mPFC ($p = 0.04$) was predictive of treatment response five weeks post-treatment (Robin L. Carhart-Harris et al., 2017).

Mertens et al. (2020) found that functional connectivity between the vmPFC and the occipital-parietal cluster during the KDEF task was significantly correlated with BDI scores one week
post-treatment \((p=0.048)\). Notably, they also found that decreased connectivity between the vmPFC and the amygdala during the processing of neutral and fearful faces was associated with rumination levels one-week post treatment, where lower connectivity was associated with lower levels of rumination \((p=0.018)\). Rumination levels were measured using the 22-item, self-report Ruminative Response Scale (Mertens et al., 2020).

4. Discussion

Our review explored the neural effects of treatment with psilocybin in participants with MDD and healthy controls. We found a varying degree of changes in neural activation and connectivity in distinct neural regions following treatment with psilocybin across the three studies with an MDD cohort (Robin L. Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018). For example, one of the reviewed studies assessed neural activation and functional connectivity in participants with MDD at rest, and found reduced activation in the left amygdala, increased connectivity between the vmPFC and ilPC, and between the sgACC and PCC, as well as reduced connectivity between the parahippocampus and the lateral and mPFC (Robin L. Carhart-Harris et al., 2017). Meanwhile, two studies observed post-treatment changes in neural activation or functional connectivity during the KDEF task (Mertens et al., 2020; Roseman et al., 2018). Roseman et al. (2018) found increased activation in the right amygdala in response to fearful faces, while the other found increased functional connectivity between the amygdala and visual regions during the processing of happy and neutral faces (Mertens et al., 2020; Roseman et al., 2018).

Finding of amygdala in healthy participants were consistent with results from Carhart-Harris et al. (2017), where participants demonstrated reduced activation in the amygdala across two studies featuring participants without MDD (Barrett, Doss, et al., 2020; Kraehenmann et al., 2018).
When evaluating functional connectivity, the study by Kraehenmann et al. (2015) found reduced connectivity in the bidirectional connections between the amygdala and the primary visual cortex, and the amygdala and lateral PFC. This relationship was modulated by threat affect (Kraehenmann et al., 2015). Moreover, a separate study found reduced connectivity between the left striatum and right amygdala during the processing of angry faces, and reduced connectivity between the right amygdala and the medial frontal pole during the processing of happy faces (O. Grimm et al., 2018).

4.1 Neural Correlates of the Antidepressant effect of Psilocybin

Changes in amygdala activation have been previously implicated in mood disorders. For example, amygdala activation is shown to increase during depressive episodes (Ma, 2015; Yang et al., 2010). Extant findings suggest that serotonin reuptake inhibitors (SSRIs) and related antidepressant medications have a generalized down-regulating effect on amygdala activity. This down-regulating effect of traditional antidepressants may have potential therapeutic effects.

Clinical trials with psilocybin in healthy volunteers have shown a similar effect in the amygdala region. For example, Kraehenmann et al. (2015) performed fMRI analysis following psilocybin administration to 25 healthy volunteers and determined amygdala activity was significantly reduced and was correlated with positive mood in the volunteers. A number of other studies have also shown amygdala activity to be reduced following psilocybin administration (Barret et al., 2020; Carhart-Harris et al., 2017).

Alterations in prefrontal-limbic functional connectivity have often been highlighted in MDD populations. The reviewed studies showed significant changes in the functional connectivity and activation of prefrontal-limbic structures, particularly for the vmPFC and amygdala. Previous findings have reported increased activation of vmPFC and amygdala in MDD patients. This may
be a result of a pro-inflammatory state in the MDD population, which has been shown to worsen the prognosis and severity of the course of illness (Catena-Dell’Osso et al., 2013). An analysis by Mertens et al. (2020) of the psychophysiological interaction (PPI) model demonstrated that functional connectivity between the vmPFC and the right amygdala was reduced after treatment with psilocybin while viewing fearful and neutral faces. One explanation for this observation is that vmPFC has a downregulating effect on amygdala activity following psilocybin treatment and this effect may lead to better clinical outcomes in TRD patients.

The foregoing reduction in functional connectivity was not significantly associated with the reduction in depressive symptom severity at one week post-treatment, however, it was correlated with levels of rumination. Lower functional connectivity between the vmPFC and right amygdala was significantly correlated with less rumination. Rumination is typically associated with the continuation and progress of depressive symptoms (Cooney et al., 2010). Extant literature suggests amygdala activity may be modulated through interaction with the vmPFC. For example, Motzkin et al. (2016) observed that lesions in vmPFC, through a disinhibitory effect, may lead to heightened amygdala activation in response to negative stimuli and this activity may be correlated with increased anxiety and depressive symptoms. The findings from Mertens et al. (2020) provides a potential neural correlate for improved mood that has previously been replicated by clinical trials with healthy volunteers. In contrast, the findings from Roseman et al., (2018) show increased amygdala response following psilocybin administration. These findings are of particular interest because previous imaging trials in healthy volunteers and the findings of Mertens et al. (2020) have shown decreased amygdala activation. Replication of these study findings will be imperative to further elucidate the effect psilocybin-based psychotherapy has on amygdala activation in MDD populations.
4.2 The Effects of Psilocybin and Traditional Antidepressant Treatment Options

The default mode network (DMN) is closely related to the development of negative emotions in depressed patients through increased rumination. Enhanced within-network connectivity of the DMN was reported by Carhart-Harris et al. (2017), however, previous literature has observed reductions in within-DMN connectivity following psychedelic administration, including psilocybin (Robin L. Carhart-Harris et al., 2012), LSD (Robin L. Carhart-Harris et al., 2016), and ayahuasca (Palhano-Fontes et al., 2015). Notably, a similar increase in connectivity was seen following administration of the SSRI, escitalopram (Preuss et al., 2020). Structures involved in the DMN (i.e., PFC, parietal cortex, cingulate cortex, temporal gyrus) are believed to have increased activity in patients with MDD, particularly during tasks of emotional processing tasks. Grimm et al. (2009) presented healthy controls and MDD participants with pictures meant for emotional stimulation and participants were asked to either categorize them as negative or positive, or asked to simply view them. The fMRI analyses revealed low, negative BOLD responses in patients with MDD for both tasks, which correlated with increased depressive symptoms (S. Grimm et al., 2009).

Moreover, in a separate clinical trial with escitalopram, pre-treatment fMRI revealed hyperactivity in regions of the PFC and bilateral amygdala in patients with MDD; this increased activity has been consistently reported in MDD (Vai et al., 2016). Nonresponders showed a significant reduction in connectivity between the hyperactive regions post-treatment, whereas response to escitalopram was associated with increased connectivity similar to healthy controls. These changes align with the findings of Mertens et al. (2020), where emotional processing and functional connectivity were both measured in MDD participants following psilocybin administration. The fMRI analyses revealed a significant decrease in right amygdala-vmPFC
connectivity in patients with MDD upon viewing fearful and neutral faces (Chen et al., 2008). This reduction suggests similar effects are observed by psilocybin and SSRIs in MDD participants. Future studies should continue to investigate the underlying mechanism of action by targeting these key regions of interest (e.g., the DMN) in order to elucidate the possible mechanisms and neural correlates of the anti-depressant effects of psilocybin-based psychotherapy.

4.3 Limitations and Priority Avenues for Future Research

The included studies present important findings for the investigation of underlying mechanisms of action and neural correlates of the antidepressant effects following psilocybin-based psychotherapy in MDD and healthy populations. However, the findings from our review were significantly limited by the small number of studies that met inclusion criteria for the MDD group (k=3) and ultimately, the sample size of participants available for the neuroimaging analyses (n=55). The low study and sample size introduces a high level of heterogeneity and limits the conclusions that can be drawn from this dataset. A high priority for future studies will be to replicate the current findings with a larger, clinically representative sample size. One potential reason for the low sample size of included studies could be the high cost of fMRI. Current findings subserve the need to further investigate the potential antidepressant effects of psilocybin. As such, in an effort to improve cost-effectiveness, other imaging techniques may be considered. For example, functional near infrared spectroscopy (fNIRS) offers flexibility and cost-effectiveness in comparison to traditional fMRI (Scarapicchia et al., 2017). One study using fNIRS and a task-based paradigm (i.e., verbal frequency test (VFT)) was able to differentiate between MDD patients and healthy controls (Husain et al., 2020). Thus, future psilocybin studies may consider improved cost-effectiveness to increase the sample size of present studies.
Replication and further investigation of findings represents an important next step following the contrasting results observed in the Mertens et al. (2020) and Roseman et al. (2018) clinical trials.

Second, all MDD studies were open-label clinical trials without a placebo-control group. Replication of current findings will be necessary with sufficient characterization of potential subgroups. Mertens et al. (2020) discusses the difficulties with organizing an appropriate placebo-control, particularly at high doses, due to the subjective effects of psychedelic drugs. However, further investigation will require placebo-control in order to sufficiently evaluate the differential changes in brain responses following psilocybin-based psychotherapy.

Third, the comparison of findings from MDD populations and healthy participants proved challenging due to a number of factors, including, but not limited to the sample size, study design, dose administration, imaging procedure and study outcomes. For example, two studies with healthy controls administered psilocybin during the fMRI scan (Lebedev et al., 2015; Lord et al., 2018). The inconsistencies in dosing schedules may influence the observed effects following psilocybin administration. For example, Barrett et al., 2020 observed changes in amygdala activity one week following psilocybin-dose administration, however, the activity returned to baseline after a one month follow-up (Barrett, Doss, et al., 2020). Therefore, longitudinal studies are needed to further elucidate the long-term effects of psilocybin treatment and whether sustained therapeutic effects are indeed possible.

5. Conclusion

Our qualitative review evaluated the neural effects of treatment with psilocybin in participants with MDD and healthy controls. Studies evaluating psilocybin effects in MDD participants found changes in neural activation at the level of the amygdala. One study found reduced left
amygdala activation, while two studies observed increased activation of the right amygdala. Meanwhile, fMRI findings in healthy populations observed a general reduction in amygdala activation. Amygdala activation is shown to increase during depressive episodes and a reduction in the foregoing activation may be associated with psilocybin’s antidepressant effects. However, current lines of psilocybin literature utilizing imaging techniques in mood disorder populations are limited. Moreover, there exists high heterogeneity in methodology (e.g., dosing schedules, imaging procedures, cohort characteristics) that limit the generalizability of current findings. Additional longitudinal studies that account for, and address these confounding factors are needed to effectively evaluate the antidepressant therapeutic potential of psilocybin and corresponding neural changes following treatment.
Conflict of Interest

Dr. Roger McIntyre has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

Dr. Joshua D Rosenblat has received research grant support from the Canadian Institute of Health Research (CIHR), Labatt Family Innovation Fund, Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from Janssen, Allergan, Lundbeck, Sunovion and COMPASS. He is the Chief Medical and Scientific Officer of Braxia Scientific and the medical director of Braxia Health (Canadian Rapid Treatment Centre of Excellence).

Dr. Rodrigo B. Mansur has received research funding from the Canadian Institutes of Health Research, Physician Services Incorporated foundation, the Baszucki Brain Research Fund, and an Academic Scholar Award from the University of Toronto, Department of Psychiatry.
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) study selection flow diagram
<table>
<thead>
<tr>
<th>Source</th>
<th>Domain 1: Risk of bias from the randomization process</th>
<th>Domain 2: Risk of bias due to deviations from the intended interventions</th>
<th>Domain 3: Risk of bias due to missing outcome data</th>
<th>Domain 4: Risk of bias in measurement of the outcome</th>
<th>Domain 5: Risk of bias in the selection of the reported result</th>
<th>Domain 6: Other bias</th>
<th>Overall assessment of bias</th>
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<tr>
<td>Carhart-Harris et al., 2017</td>
<td>Low</td>
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<td>Unclear</td>
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<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Roseman et al., 2018</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Low</td>
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<tr>
<td>Mertens et al., 2020</td>
<td>High</td>
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<td>Unclear</td>
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<td>Lebedev et al., 2015</td>
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<td>Low</td>
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### Table 2: Table illustrating the characteristics of imaging studies evaluating the effects of psilocybin in participants with major depressive disorder

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Gender (No. %)</th>
<th>Mean Age (SD)</th>
<th>Imaging Procedure</th>
<th>Mental Illness</th>
<th>Psychiatric Assessment</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carhart-Harris et al., 2017</td>
<td>16</td>
<td>F: 25% M: 75%</td>
<td>42.8</td>
<td>fMRI</td>
<td>TRD</td>
<td>QIDS-SR16</td>
<td>Open-label feasibility study; no control</td>
</tr>
<tr>
<td>Roseman et al., 2018</td>
<td>20</td>
<td>F: 30% M: 70%</td>
<td>44.7</td>
<td>fMRI</td>
<td>TRD</td>
<td>QIDS-SR16, BDI, STAI</td>
<td>Open-label study</td>
</tr>
<tr>
<td>Mertens et al., 2020</td>
<td>19</td>
<td>F: 32% M: 68%</td>
<td>44.7</td>
<td>fMRI</td>
<td>TRD</td>
<td>QIDS-SR16, BDI, STAI</td>
<td>Open-label study</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- M=male, F=female, SD=standard deviation, TRD=treatment resistant depression, STAI=State-Trait Anxiety Inventory, QIDS-SR16=quick inventory of depressive symptomatology (self-report) (16-item), BDI=Beck depression inventory, fMRI=functional magnetic resonance imaging
Table 3: Table illustrating the characteristics of imaging studies evaluating the effects of psilocybin in healthy volunteers

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size</th>
<th>Gender (No. %)</th>
<th>Mean Age (SD)</th>
<th>Imaging Procedure</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carhart-Harris et al., 2012</td>
<td>15</td>
<td>F: 33% M: 67%</td>
<td>34.1</td>
<td>fMRI</td>
<td>Placebo-controlled cross-over study</td>
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<tr>
<td>Carhart-Harris et al., 2012</td>
<td>10</td>
<td>F: 20% M: 80%</td>
<td>31</td>
<td>fMRI</td>
<td>Placebo-controlled cross-over study</td>
</tr>
<tr>
<td>Barrett et al., 2020</td>
<td>12</td>
<td>F: 58%, M: 42%</td>
<td>32.1</td>
<td>fMRI</td>
<td>Open-label pilot study</td>
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<td>Barrett et al., 2020</td>
<td>15</td>
<td>F: 33%, M: 67%</td>
<td>51.3</td>
<td>fMRI</td>
<td>Placebo-controlled within-subject study</td>
</tr>
<tr>
<td>Grimm et al., 2018</td>
<td>18</td>
<td>F: 36%, M: 64%</td>
<td>23.94</td>
<td>fMRI</td>
<td>Double-blind cross-over study</td>
</tr>
<tr>
<td>Kraehenmann et al., 2015</td>
<td>25</td>
<td>F: 13%, M: 87%</td>
<td>32</td>
<td>fMRI</td>
<td>Double-blind, randomized cross-over study</td>
</tr>
<tr>
<td>Lebedev et al., 2015</td>
<td>15</td>
<td>F: 0%, M: 100%</td>
<td>31</td>
<td>fMRI</td>
<td>Within-subject counterbalanced placebo-controlled study</td>
</tr>
<tr>
<td>Lord et al., 2018</td>
<td>9</td>
<td>F: 48%, M: 52%</td>
<td>26.3</td>
<td>fMRI</td>
<td>Double-blind randomized counterbalanced cross-over study</td>
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<tr>
<td>Preller et al., 2020</td>
<td>23</td>
<td>F: 39%, M: 61%</td>
<td>51.66</td>
<td>fMRI</td>
<td>Double-blind randomized counterbalanced cross-over study</td>
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<tr>
<td>Smigielski et al., 2019</td>
<td>38</td>
<td></td>
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<td></td>
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</table>

Abbreviations: M=male, F=female, SD=standard deviation, fMRI=functional magnetic resonance imaging
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Kometer, M., Schmidt, A., Jäncke, L., & Vollenweider, F. X. (2013). Activation of serotonin 2A


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All other authors have no conflicts of interest to disclose.