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The Effects of Psilocybin on Cognition and Emotional Processing in Healthy Adults and Adults with Depression: A Systematic Literature Review

Laura Inês Nunes Pinto Ramos

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Universidade do Porto
Faculdade de Psicologia e de Ciências da Educação

THE EFFECTS OF PSILOCYBIN ON COGNITION AND EMOTIONAL PROCESSING IN HEALTHY ADULTS AND ADULTS WITH DEPRESSION: A SYSTEMATIC LITERATURE REVIEW

Laura Inês Nunes Pinto Ramos

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In memorial of my Father

"An individual human existence should be like a river — small at first, narrowly contained within its banks, and rushing passionately past rocks and over waterfalls. Gradually the river grows wider, the banks recede, the waters flow more quietly, and in the end, without any visible break, they become merged in the sea, and painlessly lose their individual being."

Bertrand Russel (1872–1970), in *Portraits From Memory and Other Essays*

Resumo

Objetivo. A psilocibina, um agonista serotonérgico que ocorre naturalmente em algumas espécies de cogumelos, tem sido apresentada como uma farmacoterapia inovadora e de ação rápida, procurando ultrapassar as limitações dos antidepressivos convencionais de primeira linha. Investigar os efeitos da psilocibina na cognição e no processamento emocional poderá ajudar a clarificar os mecanismos subjacentes ao seu potencial terapêutico e a orientar estudos com indivíduos com depressão. Assim, a presente revisão visa sintetizar e integrar a literatura acerca dos efeitos da psilocibina nestas duas áreas-chave, tanto na população saudável como com depressão.

Método. Realizou-se uma pesquisa sistemática nas bases de dados PubMed, EBSCOhost, Web of Science e SCOPUS, restringindo-se a publicações de 2000 a 15 de julho de 2022. Após remoção de duplicados, selecionaram-se estudos considerando critérios pré-especificados e extraíram-se dados relevantes. Avaliou-se o risco de viés recorrendo às ferramentas da Colaboração Cochrane para ensaios controlados randomizados (RoB 2.0) e não randomizados (ROBINS-I).

Resultados. Foram incluídos dezoito estudos, sendo dois com adultos com depressão. Nos adultos saudáveis, observaram-se dificuldades nos processos atencionais e inibitórios, e melhorias em domínios da criatividade e cognição social resultantes da toma de psilocibina. Apenas a flexibilidade cognitiva e o reconhecimento emocional foram afetados em indivíduos deprimidos. A comparação dos resultados de ambas as populações revelou-se limitada.

Conclusões. A psilocibina altera de forma aguda vários domínios cognitivos, com enfoque localizado e de forma dependente do tempo. Todavia, dada a enorme heterogeneidade metodológica é necessária mais investigação com amostras clínicas e protocolos estandardizados, sendo também imperativo realizar estudos longitudinais.

Palavras-chave: *psilocibina; cognição; processamento emocional; adultos saudáveis; perturbação depressiva; revisão sistemática*

Abstract

Aim. Psilocybin, a naturally occurring serotonergic agonist in some mushroom species, has shown promise as a novel, fast-acting pharmacotherapy seeking to overcome the limitations of conventional first-line antidepressants. Studying psilocybin effects on cognition and emotional processing may help to clarify the mechanisms underlying the therapeutic potential of psilocybin and may also support studies with people suffering from depression. Thus, this review aims to synthesize and integrate the literature regarding the effects of psilocybin on these two key areas in both healthy and depressed populations.

Method. A systematic search was performed on PubMed, EBSCOhost, Web of Science and SCOPUS databases, restricting to publications from 2000 to 15th July 2022. After duplicates removal, study selection was conducted considering pre-specified criteria. Data extraction was then performed. The quality assessment was evaluated using the Cochrane Collaboration tools for randomized (RoB 2.0) and non-randomized (ROBINS-I) controlled trials.

Results. Eighteen papers were included, with sixteen targeting healthy adults and two adults with depression. Impairments within the attentional and inhibitory processes, and improvements within the creativity and social cognition domains were seen in healthy individuals. Only cognitive flexibility and emotional recognition were found to be affected in depressed subjects. Comparison of outcomes from both populations proved limited.

Conclusions. Psilocybin acutely alters several cognitive domains, with a localized rather than global focus, in a time-dependent manner. However, the remarkable methodological heterogeneity calls for further research, in the context of mental illness and with standardized plans, with longitudinal studies also imperative.

Keywords: *psilocybin; cognition; emotional processing; healthy adults; depression disorder; systematic review*

Introduction

Depression is a widespread and debilitating mental illness associated with an increased risk of suicidality. Approximately 280 million people in the world have a depressive disorder (World Health Organization, 2021). Despite the heterogenous expression of this psychiatric condition, hallmarks of depression comprise dysfunctional coping strategies, anhedonia, pessimism biases and hopelessness, and impaired psychosocial and cognitive functioning (Preller & Vollenweider, 2019; WHO, 2021).

Major depressive disorder (MDD) is the most common form of depression. Failure to respond or achieve remission after two or more adequate trials of medication treatment for MDD is typically referred to as treatment-resistant depression (TRD; Voineskos et al., 2020), causing significant and often chronic functional impairment. Currently, antidepressant drugs, mainly selective reuptake inhibitors (SSRIs), are the prevalent clinical treatment for depression. However, these conventional first-line antidepressants take several weeks to work, have limiting adverse effects, such as sexual dysfunction and emotional *blunting*, and demonstrate an estimated response rate range between 42% and 53% (Cipriani, Furukawa, et al., 2018; Cipriani, Salanti, et al., 2018). In recognition of the limitations described, along with the socio-economic burden (Gill et al., 2022; Voineskos et al., 2020), there is a rising interest in novel and fast-acting pharmacotherapies that use one or few doses.

Commonly termed as serotonergic psychedelics, classic psychedelics constitute a class of psychoactive compounds mainly featured by their agonism or partial agonism of the serotonin 2A receptor (5-HT2Ar; Carhart-Harris, 2019; Johnson et al., 2019; Nichols, 2016). In terms of chemical structure, the constituents of this category of substances fall into the chemical class of *phenylethylamines*, which comprises mescaline, or *tryptamines*, examples include N,N-Dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), and psilocybin (Johnson et al., 2019).

Structurally analogous to serotonin, psilocybin (4-phosphoroyloxy-N,N-dimethyltryptamine) is the principal psychoactive constituent of *Psilocybe* mushrooms and has an ancient history of medicinal use (Carhart-Harris & Goodwin, 2017). Post-oral administration, the effects become apparent after approximately 30 to 60 minutes, peaking at 90 to 180 minutes later and lasting up to six hours in total (Griffiths et al., 2011). Psilocybin acutely evokes profound mystical-type experiences, with alterations in self-consciousness, mood, personality, and in sensory and reality perception (Preller &

Vollenweider, 2016). This mind-altering experience is often perceived as highly personal and spiritual meaningful as it stimulates a sense of selflessness and insightfulness, and feelings of oneness and ineffability, with a sensation of space and time transcendence (Vollenweider & Smallridge, 2022) – edifying what is described as a mystical-type experience. Albeit physiologically safe, the quality of psilocybin experience is deeply shaped by both *set* and *setting*, that is, by psychological and contextual factors, respectively (Carhart-Harris & Nutt, 2017).

Mostly combined with psychotherapy or psychotherapeutic support, psilocybin shows a promise as a treatment for mood disorders (Forstmann & Sagioglou, 2021). Based on researches that point to an effective and sustained reduction in depressive symptoms (Carhart-Harris et al., 2018; Carhart-Harris et al., 2016; Davis et al., 2021; Gukasyan et al., 2022), psilocybin has been granted status by the Food and Drug Administration as a potentially *breakthrough therapy* in 2018-2019 for treating MDD and TRD (Marks, 2021).

The mechanisms of action underlying the antidepressant effects of psilocybin are not fully understood. The study of the global and specific cognitive effects of psilocybin is a potential avenue for expanding this knowledge, yet it is one of the most neglected aspects of psychedelic research in both healthy and depressed populations. In contrast, the various neuroimaging studies performed mostly with healthy volunteers (cf. Gill et al., 2022) have suggested that serotonergic psychedelics modulate brain structures involved in emotional processing, executive functioning, visuo-perception, and other cognitive functions.

Acute increases in blood perfusion/glucose metabolism in prefrontal and limbic areas (dos Santos et al., 2016), decreased threat reactivity in brain regions such as the amygdala (Kraehenmann et al., 2016), decreased functional connectivity (FC) within the default mode network (DMN; Carhart-Harris et al., 2012), and disruption of anticorrelations involving the DMN are some of the brain dynamics induced by psilocybin (Roseman et al., 2014). The DMN is a large-scale network implicated in mind-wandering and self-referential thinking – cognitive processes that are often overactive in depression (Lyons & Carhart-Harris, 2018). The major areas of the DMN include the posterior cingulate cortex (PCC) and precuneus, medial prefrontal cortex (mPFC), and inferior parietal lobule (Li et al., 2014).

One explanatory model proposes that the therapeutic benefit is mediated through 5-HT2A receptor-induced dysregulation of spontaneous neuronal activity in cortical populations, which is linked to a temporary disintegration of intrinsic functional brain networks thereby expanding the functional repertoire of brain states (Carhart-Harris & Friston, 2019). An alternative theory affirms that the normal filtering of sensory inputs via

the thalamus is disrupted by psychedelics leading to altered perceptions (Vollenweider & Geyer, 2001). However, it is conceivable that thalamic effects are driven by psychedelics disrupting cortical activity that projects to the thalamus. Overall, transformations in brain integration and increased neural signal complexity underlie the psychedelic state (Lord et al., 2019), however, the clarification of the 5-HTr role is needed, since psilocybin may modulate neural networks implicated in affective disorders (Carhart-Harris & Goodwin, 2017).

Subjective factors also appear to be at play in relation to the therapeutic efficacy of psilocybin, particularly the presence of a mystical component during the psychedelic experience (Griffiths et al., 2008; Griffiths et al., 2018).

Given the current state of psychopharmacological therapy for depressive disorders and the consequent efforts regarding the clinical study of psilocybin, understanding its cognitive impact is a vital contribution to elucidate the respective antidepressant power and enhance treatment safety. This will allow the drawing of hypotheses that integrate neuropsychological effects and previously discovered neural mechanisms, the identification of significant therapeutic targets to examine in future (clinical) research, and prediction of possible adverse cognitive and emotional processing effects under psilocybin influence.

In summary, the study of the effects of interest in the healthy population will help to clarify the mechanisms underlying the action of psilocybin and will also support studies with people suffering from depression. Hence, this systematic review aims to clarify, synthesize and integrate the literature concerning the cognitive and emotional processing effects of psilocybin in healthy individuals and those with depressive symptoms, extending the findings of Gill et al. (2022), which, in turn, explored the domain of neural changes.

Method

The present systematic review is in conformity with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021).

1. Data Sources and Search Strategy

A systematic literature search was performed between June and July 2022, resorting to PubMed, EBSCO (Academic Search Ultimate, APA PsyInfo, APA PsycArticles, and

Psychology and Behavioral Sciences Collection), Web of Science and SCOPUS databases. The research was restricted to publications from 2000 to 15th July 2022, without any language constraint. The final search string encompassed the following combination of keywords: (“psilocybin*” OR (“psilocybin*” AND (“depression*” OR TRD OR MDD))) AND (“cogniti*" OR “psychologic*” OR “emotion*”). As part of the hand search, eligible supplementary articles were investigated using references cited in systematic reviews covering similar topics, as well as through literature recommendations from relevant studies.

2. Eligibility Criteria

To be considered for inclusion, studies had to adhere to the following criteria: (1) publication in peer-reviewed journals; (2) written language must be English; (3) participants aged 18 years or older; (4) non-randomized or randomized clinical trials; (5) sample composed of healthy individuals and/or individuals with depressive disorder or depressive symptomatology or depression in the context of life-threatening illness. It was not required to include studies involving only participants with clinically elevated symptoms or a diagnosis of a depressive condition; and (6) include an analysis of the cognitive and/or emotional processing effects of psilocybin.

Exclusion justifications implied: (1) qualitative studies, literature reviews, systematic reviews, meta-analyses, and grey literature; (2) unavailability of abstract; (3) animal studies; (4) studies with children and/or adolescents; (5) microdosing studies, as it involves the consumption of a 'sub-threshold' dose of psilocybin, with minimal acute effects (Kuypers et al., 2019); (6) studies not addressing the cognitive and/or emotional processing effects of psilocybin; (7) focus only on psychedelics that are not the central target of the present review or on other substances; and (8) in the case of clinical population studies, focus only on a psychological disorder other than depression or only on non-depressive symptomatology or on depression in the context of non-life threatening illness.

3. Study Selection

The obtained references were imported into Rayyan (Ouzzani et al., 2016) for removal of duplicates and screening of results by title and abstract, considering the inclusion and exclusion criteria. With the assistance of Mendeley, a reference manager, the full text of the remaining studies was evaluated and included if they satisfied the pre-specified criteria. The entire selection process was conducted independently by two reviewers (LR and AM)

and the conclusions of each individual analysis were compared and discussed. Failing to reach unanimity on study inclusion or if it was not clear whether an article should be included or excluded, additional input from a third investigator (AV) was required to resolve the issue.

The two independent researchers had an almost perfect agreement (Cohen's k = .86).

4. Data Extraction

Upon agreement of included articles, data collection was performed using a customized Microsoft Excel worksheet. Information extracted encompassed: (1) study identification details (e.g., authors, year of publication, location); (2) sample characterization (e.g., sample size, mean age, sex distribution, level of education, history of psilocybin use, diagnoses); (3) outcome domain of interest (e.g., inhibitory control) and method of its assessment (e.g., the Stroop task). Considering the primary outcome, any evaluation that prioritized cognitive and emotional processing effects in the healthy and depressed population after psilocybin intake was eligible. If applicable, the different assessment timepoints have been considered; (4) study design; (5) intervention features (e.g., organization, psilocybin dosage and frequency, details of comparators, setting, analyses); and (6) relevant findings, limitations, and future directions. No contact to the study investigators was deemed necessary.

5. Quality Assessment

To analyze each study quality (i.e., risk of bias, RoB), the Cochrane Collaboration instruments were applied by two reviewers (LR and AM) and disagreements were resolved through discussion. For randomized trials, RoB 2.0 tool (Sterne et al., 2019) allowed the assessment of the following domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in the selection of the reported result. For non-randomized trials, ROBINS-I tool (Sterne et al., 2016) was used, enabling examination of seven specific domains: (1) bias due to confounding, (2) bias due to participant selection, (3) bias in classification of interventions, (4) bias due to deviation from intended intervention, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Considering the potential bias for each domain, an overall risk of bias was generated, ranging from high, moderate, or low risk in RoB 2.0, and from

critical, serious, moderate, or low in ROBINS-I, with both tools having the option of *no information* available.

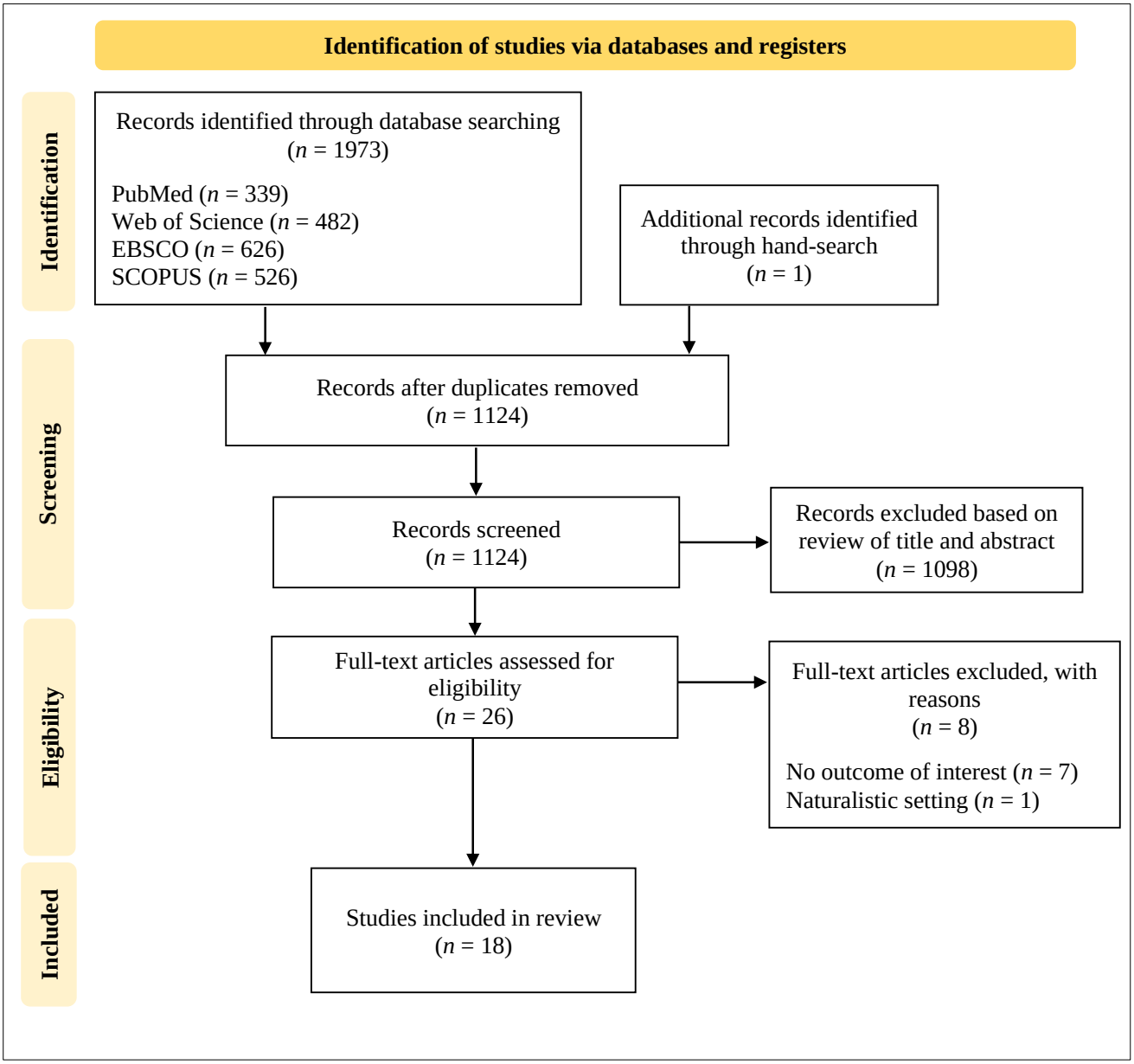
Results

1. Systematic Search

Details of the study selection and inclusion process are depicted in a PRISMA flowchart (see Figure 1; Page et al., 2021). In a first stage, a total of 1973 articles were identified through a systematic search in the four databases previously described. One additional report was obtained through manual search. After duplicates removal (n = 850), a sum of 1124 studies was examined by title and abstract. Of these, 1098 articles were excluded, and the remaining 26 papers underwent a thorough full text evaluation. Subsequently, one study was excluded as it was conducted in a naturalistic setting and other seven investigations did not examine the intended outcomes and were likewise excluded. Thus, 18 citations were included in the systematic review.

Figure 1

PRISMA flow diagram of the selection of studies process



1. Characteristics of Included Studies

Characteristics of the studies are outlined in Tables 1-2 (see Appendixes), referring to healthy and clinical population studies, respectively. Eleven articles included in this review were carried out in Switzerland, three in the UK, two in the USA, one in the Netherlands and one in Germany. Ten of the 18 studies were published between 2011 and 2022, while three studies were posted in 2007, two in 2005, and one in 2004, in 2003 and in 2002.

Sample Characterization

In the set of the 18 studies, 16 targeted healthy adults and two adults with a clinical diagnosis of depression (Doss et al., 2021; Stroud et al., 2018). Overall, the healthy participants comprised a total of 391 individuals (see Table 1). Heterogeneity in sample size is noteworthy. The smallest sample comprised eight individuals (Carter, Burr, et al., 2005) and the largest 89 (Rucker et al., 2022), with the majority having a sample of less than 20 subjects. On the other side, the clinical sample encompassed a total of 57 participants, with the sample size involved being 24 (Doss et al., 2021) or 33 subjects (Stroud et al., 2018; see Table 2).

Regarding diagnoses, one study (Doss et al., 2021) included participants with moderate or severe MDD episodes, as assessed with the Structured Clinical Interview for DSM-5 (SCID-5) and the GRID-Hamilton Depression Rating Scale (GRID-HAMD; a score of ≥17 was required). The other study used the 21-item Hamilton Depression Rating Scale (HAM-D) for the assessment of moderate to severe major depression (corresponding to a score of >17), also requiring that there had been no improvement despite two adequate courses of antidepressant treatment of different drugs lasting at least six weeks within the current depressive episode (Stroud et al., 2018).

Concerning sociodemographic variables, in the healthy studies, the mean age varies approximately between 22 and 37 years old, and over 50% of the total subjects has male sex (n = 230; see Table 1). On the other hand, the mean age ranges approximately between 32 and 45 years old in depression studies, with more than half of the total subjects also male (n = 30; see Table 2). The applicants' level of education is not mentioned in 12 studies (see Table 1-2). In the other six, most subjects have higher education (see Table 1).

The participants' history of psilocybin or overall psychedelic use is of utmost importance. However, three with healthy population (Gouzoulis-Mayfrank et al., 2002; Preller et al., 2016; Umbricht et al., 2003) and both studies with clinical samples did not mention it. Regarding the number of participants with previous psilocybin experience, that is, those who ingested psilocybin at least once during their lifetime, four studies did not specified it (Barrett et al., 2018; Hasler et al., 2004; Mason et al., 2021; Vollenweider et al., 2007). Contrarily, one investigation used a sample with only experienced individuals (Gabay et al., 2018); in another, more than half of the sample had a psilocybin experience (Carter, Burr, et al., 2005); and in the remaining studies, half or less than half of the participants had an experience (Carter et al., 2007; Carter, Pettigrew, et al., 2005; Kometer et al., 2012; Pokorny et al., 2017; Quednow et al., 2012; Rucker et al., 2022; Wittmann et al., 2007).

Research Design and Intervention Features

Eleven studies were randomized controlled trials (RCT) and seven were non-randomized controlled trials (N-RCT), with one of the clinical population studies being RCT (Doss et al., 2021) and the other N-RCT (Stroud et al., 2018).

Regarding the RCT, one was single-blind (Umbricht et al., 2003) and nine were double-blind (see Table 1), with two of them having an independent control group receiving inactive placebo (Mason et al., 2021; Rucker et al., 2022). Seven studies used a within-subjects arrangement with at least one placebo session, mostly inactive (Barrett et al., 2018; Hasler et al., 2004; Kometer et al., 2012; Pokorny et al., 2017; Preller et al., 2016; Quednow et al., 2012; Vollenweider et al., 2007). Within the clinical studies, one was open-label (Doss et al., 2021) and participants were randomly assigned to an immediate treatment and delayed treatment group (see Table 2).

In the N-RCT, and concerning the healthy population, one study was open-label (Gabay et al., 2018) and five studies were double-blind, with only one having an independent control group receiving inactive placebo (Gouzoulis-Mayfrank et al., 2002; see Table 1). Five studies used a within-subjects design (Carter et al., 2007; Carter, Burr, et al., 2005; Carter, Pettigrew, et al., 2005; Gabay et al., 2018; Wittmann et al., 2007). The only clinical N-RCT was also open-label (Stroud et al., 2018; see Table 2) and had a control group receiving no substance at all (see Table 2).

Regarding intervention, psilocybin doses varied largely from study to study, ranging from a minimum of 0.045 (Hasler et al., 2004) to 25 mg/kg (Rucker et al., 2022) in the healthy population. In the clinical sample, doses varied between 10 (Stroud et al., 2018) and 30 mg/70 kg (Doss et al., 2021). In general, the preferable route of ingestion was oral (see Table 1-2), while one study used intravenous route (Gabay et al., 2018) and another made no reference to any (Kometer et al., 2012). Apart from the single session dosing studies within the healthy population (Gouzoulis-Mayfrank et al., 2002; Mason et al., 2021; Rucker et al., 2022), most research applied a dose-escalation approach with weekly or monthly intervals between sessions. The number of dosing sessions of any substance was never more than five (see Table 1-2).

Psychological support was made available to participants in one healthy population study from specially trained assisting therapists (Rucker et al., 2022), being provided throughout the single session and the following day (integration). Both clinical studies provided psychological support, which comprised preparatory sessions (before dosing), (acute) support, and integration [one day and one week after the high-dose session in Stroud

et al. (2018); and after each psilocybin session in Doss et al. (2021)]. Unlike Stroud et al. (2018), in which psychological support was given by two psychiatrists, the facilitators of the sessions in Doss et al. (2021) involved study staff from various professional disciplines and without formal clinical training.

2. Quality Assessment of Studies

A summary of the Cochrane RoB analyses is shown in Figures 2-5, created with the Robvis web application (McGuinness & Higgins, 2021).

Seven RCT (see Figure 2-3) were rated with some concerns regarding the overall RoB (Barrett et al., 2018; Hasler et al., 2004; Mason et al., 2021; Pokorny et al., 2017; Preller et al., 2016; Quednow et al., 2012; Vollenweider et al., 2007). Three were classified with a high RoB on the basis that knowledge of the intervention received was likely to influence the outcome evaluation, two of them being studies with healthy people (Rucker et al., 2022; Umbricht et al., 2003) and one with clinical population (Doss et al., 2021). One study with healthy people was also rated with a high RoB because of lack of information on the extent of missing outcome data (Kometer et al., 2012).

In most trials, the randomization process and allocation concealment were not clearly described. Additionally, five double-blinded studies with a healthy sample were judged to have some concerns in terms of whether outcome assessors, and participants, were blind to treatment assignment due to the psilocybin' distinct physical/psychoactive effects and the absence of administration of an active placebo (Barrett et al., 2018; Hasler et al., 2004; Pokorny et al., 2017; Preller et al., 2016; Vollenweider et al., 2007). Notably, the trial protocols were either not available or insufficiently detailed in both relevant populations. Nevertheless, when there was no evidence of a pre-specified plan, outcome measures and analyses listed in the methods section were compared with those that were reported, indicating unlikely selective outcome reporting.

Figure 2

Risk of bias summary for all randomized trials included

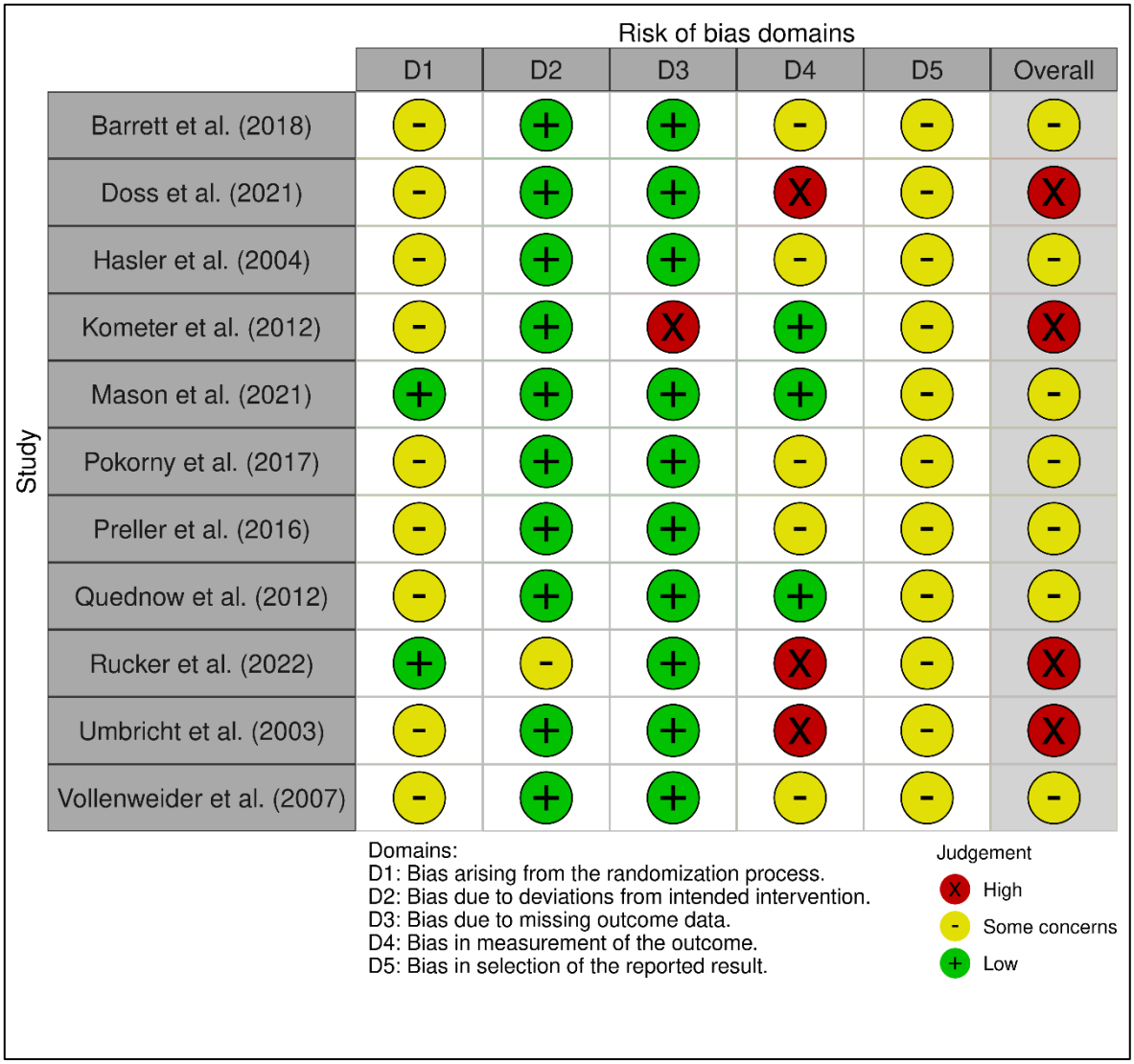
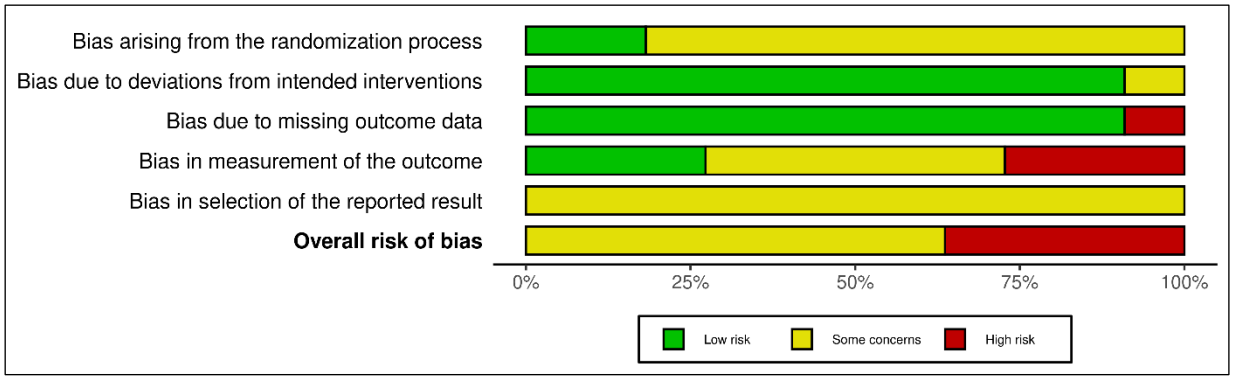


Figure 3

Risk of bias graph for all randomized trials included



Regarding the N-RCT (see Figure 4-5), only one article was classified with a serious RoB due to confounding and bias in subject selection, and its findings are available for less than 95% of the participants (Gabay et al., 2018). The remaining studies were judged to have a moderate RoB, including the remaining clinical paper (Stroud et al., 2018), mainly due to the feasible lack of blinding from outcome assessors (and participants) given the overt effects of psilocybin (Carter et al., 2007; Carter, Burr, et al., 2005; Carter, Pettigrew, et al., 2005; Gouzoulis-Mayfrank et al., 2002; Wittmann et al., 2007). Three papers with healthy individuals provided no information on missing data (Carter et al., 2007; Carter, Burr, et al., 2005; Wittmann et al., 2007).

There was strong agreement between the two judges that conducted the assessment (Cohen's k = .82).

Figure 4

Risk of bias summary for all non-randomized trials included

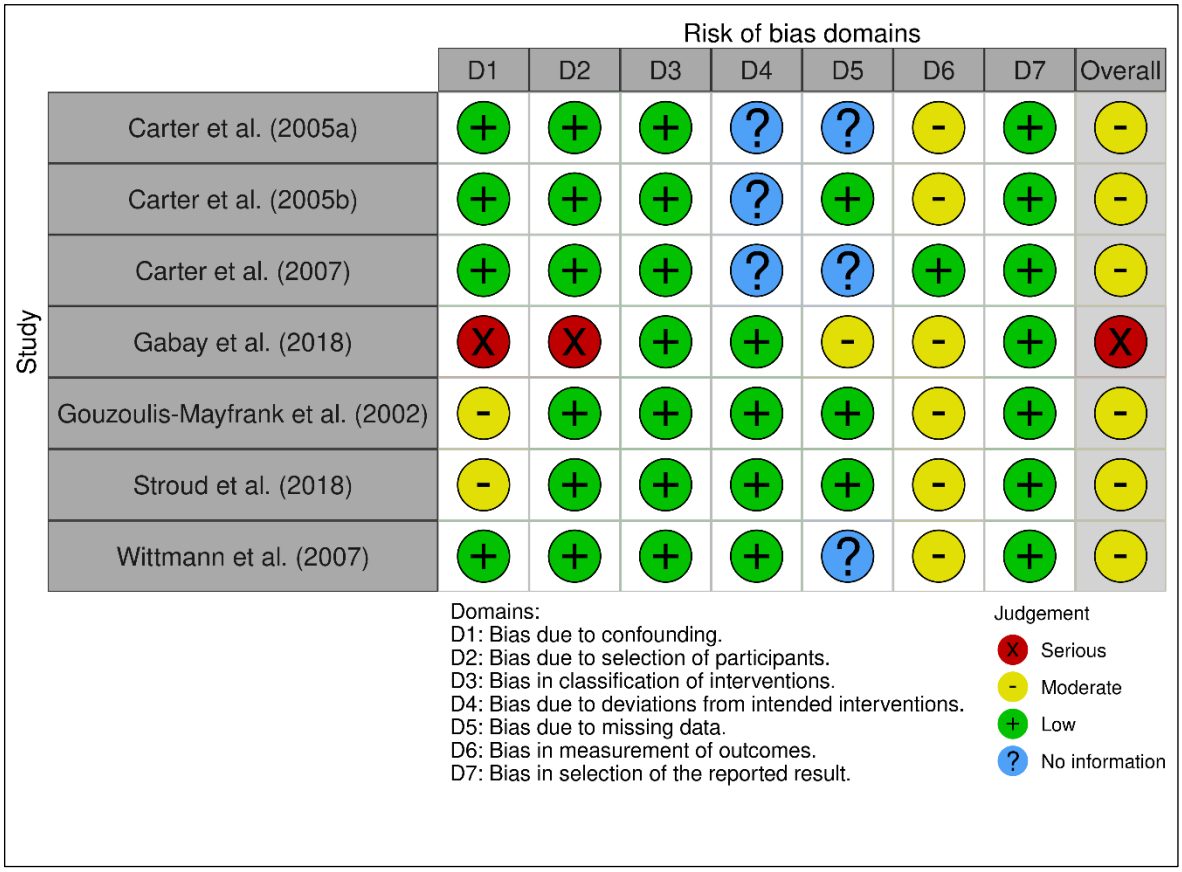
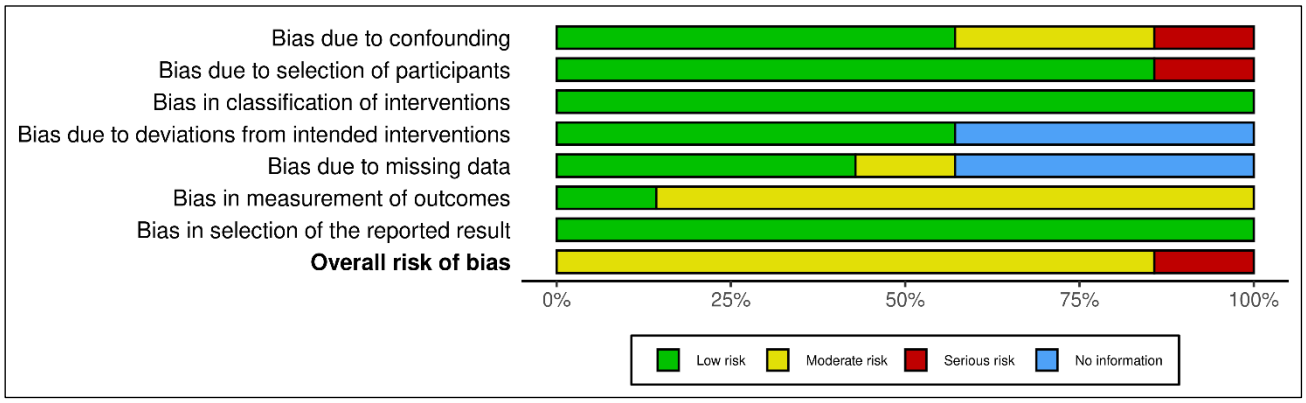


Figure 5

Risk of bias graph for all non-randomized trials included



4. Effects of Psilocybin

Findings regarding the cognitive and emotional processing effects of psilocybin are presented in Tables 1-2 (see Appendixes). All assessed domains of interest are considered, with results from both relevant samples reported individually. The results mentioned are statistically significant ($p < 0.05$) and, if not, this will be reported. Particularly in the study of Rucker et al. (2022), described by the authors as exploratory, results were not adequately powered to detect statistical significance, as such *p*-values are not reported.

4.1. Healthy Population

Global Cognition

As investigated by Barrett et al. (2018), global cognitive impairment, assessed using the Mini-Mental State Examination (MMSE) during peak psilocybin effects (10, 20 and 30 mg/kg, p.o.), was not observed in 20 volunteers (M_{age} = 28.50, *SD* = n/a).

A higher CANTAB global composite indicates better cognitive performance (Rucker et al., 2022). Overall, there was an increasing trend in score for the 10 mg (n = 30, M_{age} = 36.10, *SD* = 9.25) and 25 mg (n = 30, M_{age} = 36.60, *SD* = 10.29) psilocybin groups by day 29 compared with baseline (Rucker et al., 2022). No difference was evidenced for psilocybin groups when compared with controls (n = 29, M_{age} = 35.60, *SD* = 7.69), and also between 25 mg and 10 mg psilocybin by day 29. Psychological support was made available to participants.

Attention

Sustained Attention. In a sample of eight subjects (M_{age} = 29.40, *SD* = n/a), Hasler et al. (2004) aimed to explore the impact of four doses of psilocybin on sustained attention by applying the Frankfurt Attention Inventory (FAIR) 140 minutes after substance administration, evidencing a significant reduction in FAIR scores after the medium (0.215 mg/kg, p.o.) and higher (0.315 mg/kg, p.o.) psilocybin dose. Vollenweider et al. (2007) corroborated the latter findings by revealing a decrease in FAIR scores 105, 180 and 360 minutes after psilocybin in-take (0.115, 0.215, 0.315 mg/kg, p.o.) in 16 participants (M_{age} = 26.40, *SD* = n/a). Both results suggest an impaired sustained attention during the peak and post-peak effect of psilocybin, but heterogeneity in sample size and intervention procedures between studies should be considered (see Table 1).

Carter, Burr, et al. (2005) conducted a trial with eight participants (M_{age} = 27.00, *SD* = 2.70) that showed reduced attentional tracking in a multiple-object tracking task 120 minutes after psilocybin administration (0.215 mg/kg, p.o.). This deficiency in sustained visual attention is seen by the authors as being related to a lack of capability to suppress distractor stimuli.

Rucker et al. (2022) found that there were a tendency demonstrating better performance on sustained attention (Rapid Visual Information Processing A-prime, RVP-A') on average in the groups of 10 mg and 25 mg of psilocybin by day 29 compared with baseline, but no difference was observed between the psilocybin groups nor when they were compared to placebo.

Spatial Attention. Concerning (visuo)spatial attention, through application of the Covert Orienting of Attention task (COVAT), a quasi-RCT revealed overall slowing reaction times after 0.2 mg/kg psilocybin (*n* = 8, M_{age} = 31.40, *SD* = n/a), particularly in invalid trials at short cue target intervals (Gouzoulis-Mayfrank et al., 2002). This outcome perhaps indicates difficulty in disengaging attention from previously attended locations and reorienting it to targets in the contralateral visual field. There was also a failure of response inhibition in valid trials at long cue target intervals for right visual field targets (Gouzoulis-Mayfrank et al., 2002).

Sensorimotor Gating. Vollenweider et al. (2007) measured sensorimotor gating through prepulse inhibition (PPI) of the acoustic startle response 90 and 165 minutes after psilocybin. The authors demonstrated increased PPI at long interstimulus intervals (ISIs, 120 ms) and decreased PPI at short ISIs (30 ms), positively correlated with impaired sustained

attention. Likewise, in a sample of 16 healthy individuals (M_{age} = 26.70, *SD* = n/a), Quednow et al. (2012) measured PPI 60 minutes after psilocybin (0.260 mg/kg, p.o.). Impaired automatic inhibition was exhibited, as explained by decreased PPI at short intervals (30 ms).

Perceptual-Motor Function

In Barrett et al. (2018), psychomotor functioning was measured by the Circular Lights, Balance and Motor Praxis tasks at different timepoints (see Table 1), demonstrating that higher doses of psilocybin (20 and 30 mg/kg, p.o.) slowed psychomotor performance.

The previous authors also investigated the effects of psilocybin on visual perception applying the Penn Line Orientation test (PLOT) 240 minutes after substance administration. Results showed no effect on accuracy in the perception of line orientation, but rather a dose-dependent increase in response time during the commission of errors in the PLOT. In general, likely increased effort for difficult trials during the effects of psilocybin, mainly at the low dose (10 mg/kg, p.o.), due to a greater mean excess clicks for correct trials (Barrett et al., 2018).

Visual perception was also studied by Carter et al. (2007) and Carter, Pettigrew, et al. (2005) through application of the Binocular Rivalry test. Both papers reported a psilocybin-induced slowing of binocular rivalry, meaning a prolongation of the periods of exclusive visual dominance. It was found a decrease in rivalry rate and rhythmicity of perceptual alternations 90 minutes after administration (the peak of psilocybin action) of both low- (0.115 mg/kg, p.o.) and high- dose (0.250 mg/kg, p.o.) conditions (Carter, Pettigrew, et al., 2005), and, similarly, the time between perceptual switches was significantly prolonged by psilocybin (0.215 mg/kg, p.o.) at 60, 90, 135 and 180 minutes (Carter et al., 2007). Also, at 90 and 240 minutes after administration, there was an increased proportion of transitional/mixed percept experience (Carter et al., 2007).

Learning and Memory

By applying an encoding, recall and word recognition task, Barrett et al. (2018) identified a dose-dependent impairment on short-term and episodic memory. Psilocybin (10, 20 and 30 mg/kg, p.o.) decreased the free recall of encoded words. Associative learning was also found to be dose-dependently compromised, as concluded by the substitution recall portion of the Digit Symbol Substitution task (DSST).

In Rucker et al. (2022), there was no difference on episodic memory, measured with Paired Associates Learning-Total Errors Adjusted (PAL-TEA), for the psilocybin groups

(10 and 25 mg/kg, p.o.) 29 days after the dosing session compared with baseline, nor were any differences observed between the groups.

Executive Functioning

Global Executive Functioning. In Rucker et al. (2022), the Spatial Working Memory-Strategy (SWM-S), a measure of executive function and planning from the Cambridge Neuropsychological Test Automated Battery (CANTAB), revealed better performance on average for 25 mg of psilocybin by day 29 compared with baseline. No difference was detected for 10 mg and 25 mg of psilocybin when compared with placebo, nor between both psilocybin groups.

Barrett et al. (2018) indicated a dose-dependent decrease in attempted responses at 120 minutes after psilocybin ingestion on the number of trials attempted in 90 s in the DSST, but no effect on the accuracy of attempted responses – reflecting a successful speed-accuracy trade-off during the acute psychedelic experience (Barrett et al., 2018).

Inhibitory Control. Quednow et al. (2012) used the Stroop test (85 minutes after substance in-take) and psilocybin (0.260 mg/kg, p.o.) was shown to decrease controlled inhibition.

Working Memory. Barrett et al. (2018) found that psilocybin (10, 20 and 30 mg/kg, p.o.) selectively affects working memory (WM) by increasing response time for correct answers on the Letter N-back task, and by exerting a dose-dependent decreasing effect on discriminability and in response bias during the 2-back condition, which requires WM.

Umbricht et al. (2003) evaluated WM after a single dosing session in a sample of 18 participants (M_{age} = 25.10, *SD* = 4.30). By administering an 'AX'- type Continuous Performance task (AX-CPT, *n* = 16) 70 minutes after psilocybin ingestion, an oral dose of 0.28 mg/kg was shown to cause significant performance deficits characterized by a failure to use contextual information, as detected by a significant decline of the hit rate and an increase of false alarms.

Rucker et al. (2022) applied the CANTAB Spatial Working Memory-Between Errors (SWM-BE), which showed the same results as the SWM-S mentioned above.

In Wittmann et al. (2007), spatial WM was assessed in 12 subjects (M_{age} = 26.80, *SD* = 3.60) using the Spatial Span test (SSP) taken from the CANTAB. Significant impairment in spatial WM 100 minutes after the high dose of psilocybin (0.250 mg/kg, p.o.) was found compared with placebo. No effect was observed at the medium dose (0.115

mg/kg, p.o.). Also applying SSP, Carter, Burr, et al. (2005) found no effects of psilocybin (0.215 mg/kg, p.o.) on spatial WM.

Emotional Processing and Social Cognition

Emotional Processing. Barrett et al. (2018) also explored the effects of psilocybin (10, 20 and 30 mg/kg) on emotional conflict processing. Participants completed an adaptation of the emotional conflict Stroop task 240 minutes after administration, exhibiting longer dose-dependent response times and unaffected accuracy – suggesting an efficient speed-accuracy trade-off.

Kometer et al. (2012) applied the Emotional Go/No-go task to 17 subjects (M_{age} = 26.00, SD = 4.36) 130 minutes after substance ingestion, in which reaction time for correct answers was longer for negative and neutral words than for positive ones, and error rates were higher for negative compared with positive stimuli. The latter could translate into an increase in goal-oriented behavior towards positive compared to negative cues after psilocybin (0.215 mg/kg, p.o.). This augmented response bias after psilocybin was modulated by the sequential context of the stimuli: sequential repetition of positive stimuli decreased reaction times, but this sequential facilitatory effect was lacking after negative stimuli.

Kometer et al. (2012) also evaluated emotion discrimination through the Reading the Mind in the Eyes Test (RMET), showing improved recognition for positive but decreased recognition for negative facial expression, as evidenced by increased error rates.

Rucker et al. (2022) revealed no difference between either psilocybin group and placebo on social cognition and emotional processing at day eight or day 85 after the dosing session, assessed by the RMET, Pictorial Empathy Test (PET), Scale of Social Responsibility (SSR), Social Value Orientation (SVO) and the Toronto Empathy Questionnaire (TEQ).

Social Cognition. Preller et al. (2016) analyzed social exclusion under the effects of 0.215 mg/kg oral psilocybin in 21 volunteers (M_{age} = 26.48, SD = 4.76). In the context of the Cyberball task, which simulates an experience of social neglect, there was a reduction in feelings of exclusion after psilocybin, even though there was no difference in the amount of ball throws they received compared to the placebo.

Social decision-making was studied by Gabay et al. (2018). Only 19 subjects from the initial sample (N = 20, M_{age} = 26.60, SD = 7.10) were included in the analysis of results.

Psilocybin (2 mg, IV) reduced the rejection of unfair options in the Ultimatum Game (60 minutes after administration), with the authors arguing there was a heightened concern over interpersonal interactions than material rewards.

In 32 participants (M_{age} = 26.72, *SD* = 5.34), Pokorny et al. (2017) assessed cognitive and emotional empathy using the Multifaceted Empathy Test (MET) 160 minutes after 0.215 mg/kg psilocybin. The classic psychedelic increased emotional empathy, but not cognitive empathy. Moral decision-making was equally measured employing the Moral Dilemma Task (MDT, *n* = 24, M_{age} = 26.63, *SD* = 5.33), proving that morality was unaffected by psilocybin.

Creativity

Creative thinking was investigated by Mason et al. (2021) on a single psilocybin dose (0.17 mg/kg, p.o.). An acutely impairment on divergent thinking (DT) was noticed in the psilocybin group (*n* = 30, M_{age} = 22.73, *SD* = 2.90). Specially, subjects generated less ideas and associations, as shown by significantly lower fluency scores on both the Alternative Uses task (AUT, *n* = 28) and the Picture Concept task (PCT, *n* = 25), and originality scores on the PCT. The authors also evidenced an acute decrement in convergent thinking (CT), as expressed by the PCT. Seven days after psilocybin ingestion, there was an increase in aspects of DT (i.e., greater production of novel ideas on the AUT) compared to controls (*n* = 30, M_{age} = 23.20, *SD* = 3.65). Conversely, at the 7-day follow-up, CT was still significantly impaired when comparing psilocybin with placebo, indicating a reduction in conventional/logical thinking.

Overall, this study reinforces the idea that there is a timeline-dependent differentiation between the outcomes of psilocybin. While there is an impairment during the acute psychedelic phase, there is an augmentation of creativity in the afterglow state.

4.2. Population with Depression

Attention

Selective Attention. The study carried out by Doss et al. (2021) in patients with MDD (*N* = 24, M_{age} = 39.80, *SD* = 12.23) suggested no impact on selective attention evaluated by the Stroop test (*n* = 21) at different timepoints (see Table 2) after psilocybin administration (20 mg and 30 mg/70 kg, p.o.) in the context of supportive psychotherapy.

Executive Functioning

Inhibitory Control. As outlined above, Doss et al. (2021) applied the Stroop test, which, apart from selective attention, also allowed understanding the impact of psilocybin on inhibitory control of patients with MDD. However, in the immediate treatment group (n = 13) no effect on response inhibition was observed.

Abstract Reasoning and Mental Flexibility. Doss et al. (2021) explored the association between psilocybin and abstraction and cognitive flexibility by application of the Short Penn Verbal Reasoning task (n = 22) and the Penn Conditional Exclusion Test (PCET, n = 22), respectively. Mental flexibility increased in the patients, supported by a decrease in perseverative errors on the PCET from baseline to 1-week post-psilocybin therapy, which was maintained for 1-month post-treatment. Abstract reasoning was not impacted.

Emotional Processing

Stroud et al. (2018) compared a group of patients with TRD (n = 17, M_{age} = 44.94, SD = 11.51) to a healthy control group (n = 16, M_{age} = 32.00, SD = 10.40). One-week after the second dosing session (25 mg/kg, p.o.), and combined with psychological support, psilocybin was shown to enhance emotion recognition (assessed by the Dynamically Changing Facial Expression Task, DEER-T) compared to baseline. This improvement was not observed in controls.

Discussion

To date, this is the first systematic review investigating the effects of psilocybin on cognition and emotional processing in both healthy individuals and those with depressive symptomatology. Only 18 papers were found highlighting the paucity of research on how psilocybin affects these two key domains. The aforementioned scarcity is essentially reflected in research with the clinical population of interest. In fact, only two studies focusing on samples with depression were included (Doss et al., 2021; Stroud et al., 2018). Despite these latter constraints and the high heterogeneity across trials, the results draw attention to possible neuropsychological effects of psilocybin and to limitations of the current literature, which will be discussed further below.

1. Cognitive and Emotional Processing Effects in the Healthy Population

Psilocybin appears to cause localized, rather than global, time- and dose-dependent cognitive changes (Barrett et al., 2018; Rucker et al., 2022).

Sensorimotor gating (i.e., prepulse inhibition, PPI) exhibited deficits at short intervals (< 60 ms) between stimuli under the influence of psilocybin (Quednow et al., 2012; Vollenweider et al., 2007). This automatic inhibitory mechanism is responsible for filtering irrelevant stimuli from the brain preventing sensory information overflow, supporting selective attention, and enabling the efficient processing of important information (Ishii et al., 2019; Vollenweider et al., 2007). Both Quednow et al. (2012) and Vollenweider et al. (2007) suggest that sensorimotor gating disruption may be mediated by psilocybin-induced stimulation in serotonin 5-HT2Ar localized in structures such as the striatum or the thalamus. The 'thalamic filter' hypothesis theorizes that cortico-striatal pathways modulate the thalamic gating of sensory data to the cortex. Hence, an overstimulation of 5-HT2Ar could presumably result in deficits of thalamic filtering leading to a sensory overload of the frontal cortex (Vollenweider & Smallridge, 2022).

Actually, increased prefrontal glucose metabolism after psilocybin in-take was evidenced (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997). However, this pattern of *hyperfrontality* may be challenged in view of the low cerebral blood flow (CBF) also generated by psilocybin in healthy subjects (Carhart-Harris, Erritzoe, et al., 2012). Nonetheless, although psilocybin decreases absolute CBF, when assessing regional changes in CBF, psilocybin produces *hyperfrontal* effects (Lewis et al., 2017) making previous literature compatible.

The abovementioned perspectives point to psilocybin consequences regarding the ability to effectively filter and monitor relevant stimuli and resist the distraction that causes attention to shift to a task-irrelevant channel. Sustained attention appears to deteriorate during the psilocybin peak effects (Carter, Burr, et al., 2005; Hasler et al., 2004; Vollenweider et al., 2007). Interpretation for this decrement is based on a lack of ability to suppress distracters (Carter, Burr, et al., 2005). Interestingly, in Vollenweider et al. (2007), sustained attention was positively correlated with PPI capacity providing evidence that deficient filter mechanisms of external stimuli may lead to attentional disturbances. Psilocybin also impaired (visuospatial) attention, as demonstrated by disrupted inhibition of return (IOR), which allows attention to be detached from previously attended locations and thus redirects it to relevant targets (Gouzoulis-Mayfrank et al., 2002). Deficiencies of sensorimotor gating could be associated with IOR deficits.

In addition to automatic inhibition, controlled inhibition also appears to be diminished (Quednow et al., 2012). As highlighted by the authors, this can be explained by the hyper-stimulation of 5-HT2Ar in the prefrontal cortex and anterior cingulate cortex, areas involved in the Stroop task. Thus, the decline seems not to result from effects on working memory (WM) and attention per se, but rather from changes in inhibitory and conflict monitoring processes.

The relationship between WM and attention is not entirely clear. Since WM demands sustained attentional focus and frontal regions are known to be closely engaged in its function (Cohen, 2014; Wittmann et al., 2007), one might presume, however, that once attentional processes are affected, WM would also be impaired. Nevertheless, the evidence reveals inconsistent results concerning psilocybin's impact on WM. While the spatial component of WM is not affected by psilocybin in Carter, Burr, et al. (2005), the opposite is corroborated in Wittmann et al. (2007). The larger sample size and higher psychedelic dose in the latter study could possibly account for this discrepancy. In another perspective, deficits in WM performance were captured by both Barrett et al. (2018) and Umbricht et al. (2003), but the applied paradigms for testing WM differ considerably between studies, with the difference between doses administered being particularly relevant.

Psilocybin dose-dependent alterations in episodic recall and associative learning were demonstrated, as well as overall psychomotor slowing under higher doses (Barrett et al., 2018) – speculatively, these impairments may be a consequence of attentional defects. Particularly, learning and data retrieval from long-term memory are significantly affected by how attention is focused. Thus, impairments on these neuropsychological processes often occur when there are problems with attentional control, mostly involving executive–attention (Cohen, 2014). Paradoxically, 5-HT2A agonism was associated with improved associative learning in a pre-clinical study (Harvey, 2003), yet this should not be uncritically generalized to humans.

Concerning visual processing, serotonergic psychedelics are known to impact it by modulating the activity and connectivity of associated brain regions (Barrett et al., 2020; Kometer et al., 2011). Abnormalities in visual input, as seen with the prolongation of both exclusive visual dominance and transition periods (Carter et al., 2007; Carter, Pettigrew, et al., 2005), can slow the perception of stimuli, which may have been the case in the impairment on spatial orientation ability seen in Barrett et al. (2018). Carter et al. (2007) argue that there is a role for attention in conscious perception, such that manipulation of attention by psilocybin could shed light on understanding perceptual effects.

As stressed by Mason et al. (2021), psilocybin seems to mediate time-dependent changes in specific dimensions of creative thinking. The psychedelic state may promote generation of novel ideas through the DMN. The literature suggests that psilocybin acutely reduces DMN FC (Carhart-Harris, Erritzoe, et al., 2012; Smigielski et al., 2019), however, it may subacutely increase DMN integrity, as seen with DMT (Sampedro et al., 2017), a similar serotonergic psychedelic. DMN disintegration is associated with unconstrained cognition, perhaps a result of increased neuroplasticity in brain regions (Ly et al., 2018; Shao et al., 2021), leaving room for a more flexible thought pattern. Hence, these conclusions could explain the long-term increase in spontaneous creative thinking upon re-augmentation of DMN FC. In reverse, rigid thinking (sub-) acutely decreased, which could be due to an increased connectivity between DMN and the frontoparietal network (Mason et al., 2021), typically anticorrelated resting state networks.

Albeit different constructs within social cognition have been measured, the available literature expresses the potential ability of psilocybin to benefit prosocial behaviors. With morality and cognitive empathy unaffected, psilocybin markedly improved emotional empathy (Pokorny et al., 2017), reduced sensitivity to social exclusion (Preller et al., 2016), and made interpersonal relationships a primary concern rather than economic rewards (Gabay et al., 2018). One possible argument for this is that reduced DMN FC causes a reduction in self-related consciousness having implications in self/other representations and theory of mind (Carhart-Harris et al., 2014). Hence, the fleeting self-dissolution, a key feature of the psychedelic state, associated with alterations in DMN function (Mason et al., 2020) may disturb the barriers between the self and the world and boost feelings of oneness with others and the environment – ultimately contributing to improvements in social cognition and positive changes in psychosocial functioning (Preller & Vollenweider, 2019; Smigielski et al., 2019).

The emotional empathy enhancement might be more pronounced for positive emotions according to the acutely reduction in recognition and processing of predominantly negative emotions (Kometer et al., 2012). Findings in healthy populations suggest an overall reduction in amygdala reactivity (Gill et al., 2022) correlated with an increase in the positive mood (Kraehenmann et al., 2015), which could also explain the diminished reactivity to threat, eventually making negative encounters more bearable. Considering the results together, social behavior could be encouraged and therefore interpersonal contact. The effect of psilocybin on the response to negative affective stimuli was not evidenced by Barrett et

al. (2018) presumably due to a greater involvement of attentional processes in the applied task (see Table 1) than amygdala reactivity.

2. Cognitive and Emotional Processing Effects in the Population with Depression

The present review notably reflects the discrepancy between the amount of studies and range of cognitive/emotional domains investigated with healthy adults and the population with depression. Only cognitive flexibility and emotional recognition were found to be affected by psilocybin intake in depressed subjects.

Patients with MDD revealed an improved cognitive flexibility post-psilocybin therapy, which was maintained for 1-month post-treatment (Doss et al., 2021). This can be linked with the psilocybin-induced increase in the dynamical functional connectivity across the brain in patients with depression (Daws et al., 2022; Doss et al., 2021) facilitating plasticity processes (Ly et al., 2018). Along with such neuronal changes, the fact that the administration of psilocybin is carried out as part of a psychotherapeutic process most likely informs that psychological support and integration after a psychedelic experience occupies a space of special relevance in the edification of a re-signified look at individual experiences and the future (Carhart-Harris, Leech, et al., 2012; Lyons & Carhart-Harris, 2018). Accordingly, a recent study by Barba et al. (2022) evidenced decreases in rumination and thought suppression correlated with ego dissolution and session-linked psychological insight after psilocybin therapy for MDD up to 6-week follow-up.

Psilocybin with psychological support also appears to foster reconnection with one's own and others' emotions. Although studies with healthy individuals state an improvement in emotional recognition towards positive stimuli, the enhancement seems emotionally widespread in patients with TRD (Stroud et al., 2018). Through increased amygdala reactivity to all emotions in the context of depression (Roseman et al., 2018), it is suggested that psilocybin therapy allows confronting and working on negative feelings leading to improvements in depressive symptoms following psilocybin. However, further research is required as the literature is inconsistent about the amygdala's response to emotional stimuli in the case of depression (Ling et al., 2022).

3. Limitations of Available Literature

Despite the attempt to explain the obtained results, several limitations obstruct the elaboration of a safe and reliable integration of the effects of psilocybin on cognition and emotional processing, as well the comparison between the two target populations.

A major challenge resides in the generalizability of the results. Regarding the samples, the heterogeneity among them and the small size stand out, including mostly males and highly educated individuals. A larger inclusion of subjects with previous psychedelic experience may have influenced task performance and put double blindness at risk. Methodologically, both the lack of blinded efficacy evaluation and of use of active placebos, and the strong inconsistency in psilocybin dosages and its route of administration are among the most notable limitations. The lack of control of variables such as expectancy and learning effects, as well as attention difficulties, fatigue, and demotivation possibly due to the psilocybin influence or the duration of the cognitive assessment cannot be disregarded.

Neuropsychological assessment procedures are also a main concern. The application of distinct neuropsychological tools with differences in their nature and administration paradigms in the assessment of the same construct prevent the proper drawing of conclusions. Additionally, the moments of assessment are mostly coincident with the acute phase of the psychedelic experience so that the strength of subjective effects triggered may interfere with task performance. Different dosages may also elicit different cognitive effects. Besides, since the psychedelic state is particularly influenced by the *set* and *setting*, the question arises whether the results in question are context-dependent, with most settings being clinical and aimed at offering comfort and immediate psychological support.

4. Future Directions

Future research should prioritize replication of previous studies, using larger and representative samples (e.g., with different levels of psychedelic experience and distinct baseline cognitive profiles). Conversely, it would be fruitful to establish standardized neuropsychological assessment guidelines. For this, rigorous experiments to estimate which psilocybin dosages and timepoints are associated with greater psychological vulnerability are vital to minimize confounders. Furthermore, the ascertainment of the best instruments to assess each cognitive domain and the definition of dosage standards are critical.

Given the scarcity of studies in the post-acute phase, which hindered comparisons with the outcomes of Rucker et al. (2022), extended follow-up periods are suggested for the

purpose of inferring the durability of cognitive and emotional processing effects. This clarification is a prerequisite for the therapeutic use of psilocybin to become a closer reality.

Especially for the case of depression, more studies are called for on this topic, employing active placebos and strategies to mitigate the high expectations of treatment-effectiveness. Given the influence of the setting, it is of greater importance that psychological intervention be methodologically guided according to simple, manualized, and theoretically clear principles.

Conclusion

This systematic review assessed the state of the art regarding the cognitive and emotional processing effects of psilocybin in the healthy and depressed population. The majority of papers have used non-clinical samples and are remarkably heterogenous from a methodological point of view. Despite these and other important limitations, the reviewed literature suggests that psilocybin acutely alters several cognitive domains, with a localized rather than global focus and in a time-dependent manner.

In healthy individuals, some key impairments were found within the attentional and inhibitory processes, plausibly having critical implications for executive functioning, learning and visual processing. On the contrary, spontaneous creative thinking, emotional empathy, altruistic and positive goal-directed behavior reflect improvements. Therefore, social conduct and cognition may be markedly modulated by psilocybin, pointing to a facilitation in prosocial attitudes and bonding with others and the environment – issues of utmost relevance to study in the clinical population. Greater cognitive flexibility was suggested in patients with depression, which may also have been influenced by psychotherapeutic factors. Additionally, the comparison of the results from both relevant populations proved to be limited, which essentially pointed to differences concerning emotional discrimination.

The existence of diverse theoretical models and inconsistencies in the neurobiological mechanisms of psilocybin complicated the robust interpretation of the described neuropsychological changes in light of the neural mechanisms of psilocybin. Nonetheless, the agonist action of this classic psychedelic on 5-HT2Ar, maximally expressed in the cortex, is hypothesized to be responsible for the changes in cognitive functioning, but current knowledge on this topic is still largely unclear.

The analyses undertaken should be deemed with caution, as the revised matter is still in its infancy. To overcome this problem, more research is needed on cognition and emotional processing during the psychedelic state, mainly in the context of mental illness and with standardized plans. The lack of longitudinal studies explaining and addressing confounding factors is also highlighted, which could improve the understanding of psilocybin's therapeutic potential and neuropsychological changes after treatment, with the ultimate goal of creating safer and more effective psychotherapeutic protocols. On another level, at the basis of all studies with psychedelics, there also lies an opportunity to explore the [neural correlates of] human consciousness.

References

Barba, T., Buehler, S., Kettner, H., Radu, C., Cunha, B. G., Nutt, D. J., Erritzoe, D., Roseman, L., & Carhart-Harris, R. (2022). Effects of psilocybin versus escitalopram on rumination and thought suppression in depression. *BJPsych Open, 8*(5), e163. https://doi.org/10.1192/bjo.2022.565

Barrett, F. S., Carbonaro, T. M., Hurwitz, E., Johnson, M. W., & Griffiths, R. R. (2018). Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: Effects on cognition. *Psychopharmacology, 235*(10), 2915–2927. https://doi.org/10.1007/s00213-018-4981-x

Barrett, F. S., Krimmel, S. R., Griffiths, R., Seminowicz, D. A., & Mathur, B. N. (2020). Psilocybin acutely alters the functional connectivity of the claustrum with brain networks that support perception, memory, and attention. *NeuroImage, 218*, 116980. https://doi.org/10.1016/J.NEUROIMAGE.2020.116980

Carhart-Harris, R. L, & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: Past, present, and future. *Neuropsychopharmacology, 42*(11), 2105–2113. https://doi.org/10.1038/npp.2017.84

Carhart-Harris, R. L. (2019). How do psychedelics work? *Current Opinion in Psychiatry, 32*(1), 16–21. https://doi.org/10.1097/YCO.0000000000000467

Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics. *Pharmacological Reviews, 71*(3), 316–344. https://doi.org/10.1124/PR.118.017160

Carhart-Harris, R. L., & Nutt, D. J. (2017). Serotonin and brain function: A tale of two receptors. *Journal of Psychopharmacology, 31*(9), 1091–1120. https://doi.org/10.1177/0269881117725915

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V, & Nutt, D. J. (2018). Psilocybin with

psychological support for treatment-resistant depression: Six-month follow-up. *Psychopharmacology, 235*(2), 399–408. https://doi.org/10.1007/s00213-017-4771-x

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry, 3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences of the United States of America, 109*(6), 2138–2143. https://doi.org/10.1073/PNAS.1119598109

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., Nutt, D., Axmacher, N., Brooks, S. J., Maclean, K., & Hopkins, J. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience, 8*(20). https://doi.org/10.3389/fnhum.2014.00020

Carhart-Harris, R. L., Leech, R., Williams, T. M., Erritzoe, D., Abbasi, N., Bargiotas, T., Hobden, P., Sharp, D. J., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Implications for psychedelic-assisted psychotherapy: Functional magnetic resonance imaging study with psilocybin. *British Journal of Psychiatry, 200*(3), 238–244. https://doi.org/10.1192/bjp.bp.111.103309

Carter, O. L., Burr, D. C., Pettigrew, J. D., Wallis, G. M., Hasler, F., & Vollenweider, F. X. (2005). Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. *Journal of Cognitive Neuroscience, 17*(10), 1497–1508. https://doi.org/10.1162/089892905774597191

Carter, O. L., Hasler, F., Pettigrew, J. D., Wallis, G. M., Liu, G. B., & Vollenweider, F. X. (2007). Psilocybin links binocular rivalry switch rate to attention and subjective

arousal levels in humans. *Psychopharmacology, 195*(3), 415–424. https://doi.org/10.1007/s00213-007-0930-9

Carter, O. L., Pettigrew, J. D., Hasler, F., Wallis, G. M., Liu, G. B., Hell, D., & Vollenweider, F. X. (2005). Modulating the rate and rhythmicity of perceptual rivalry alternations with the mixed 5-HT 2A and 5-HT 1A agonist psilocybin. *Neuropsychopharmacology, 30*, 1154–1162. https://doi.org/10.1038/sj.npp.1300621

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Cipriani, A., Salanti, G., Furukawa, T. A., Egger, M., Leucht, S., Ruhe, H. G., Turner, E. H., Atkinson, L. Z., Chaimani, A., Higgins, J. P., Ogawa, Y., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P., & Geddes, J. R. (2018). Antidepressants might work for people with major depression: Where do we go from here? *The Lancet Psychiatry, 5*(6), 461–463. https://doi.org/10.1016/S2215-0366(18)30133-0

Cohen, R. A. (2014). *The neuropsychology of attention* (2nd edition). Springer.

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of psilocybin-assisted therapy on major depressive disorder: A randomized clinical trial. *JAMA Psychiatry, 78*(5), 481–489. https://doi.org/10.1001/JAMAPSYCHIATRY.2020.3285

Daws, R. E., Timmermann, C., Giribaldi, B., Sexton, J. D., Wall, M. B., Erritzoe, D., Roseman, L., Nutt, D., & Carhart-Harris, R. (2022). Increased global integration in the brain after psilocybin therapy for depression. *Nature Medicine, 28*(4), 844–851. https://doi.org/10.1038/s41591-022-01744-z

dos Santos, R. G., Osório, F. L., Crippa, J. A. S., & Hallak, J. E. C. (2016). Classical hallucinogens and neuroimaging: A systematic review of human studies:

Hallucinogens and neuroimaging. *Neuroscience and Biobehavioral Reviews*, *71*, 715–728. https://doi.org/10.1016/j.neubiorev.2016.10.026

Doss, M. K., Považan, M., Rosenberg, M. D., Sepeda, N. D., Davis, A. K., Finan, P. H., Smith, G. S., Pekar, J. J., Barker, P. B., Griffiths, R. R., & Barrett, F. S. (2021). Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. *Translational Psychiatry*, *11*(1), 574. https://doi.org/10.1038/s41398-021-01706-y

Forstmann, M., & Sagioglou, C. (2021). New insights into the clinical and nonclinical effects of psychedelic substances: An integrative review. *European Psychologist*. https://doi.org/10.1027/1016-9040/A000447

Gabay, A. S., Carhart-Harris, R. L., Mazibuko, N., Kempton, M. J., Morrison, P. D., Nutt, D. J., & Mehta, M. A. (2018). Psilocybin and MDMA reduce costly punishment in the Ultimatum Game. *Scientific Reports*, *8*(1), 8236. https://doi.org/10.1038/s41598-018-26656-2

Gill, H., Puramat, P., Patel, P., Gill, B., Marks, C. A., Rodrigues, N. B., Castle, D., Cha, D. S., Mansur, R. B., Rosenblat, J. D., & McIntyre, R. S. (2022). The effects of psilocybin in adults with major depressive disorder and the general population: Findings from neuroimaging studies. *Psychiatry Research*, *313*. https://doi.org/10.1016/J.PSYCHRES.2022.114577

Gouzoulis-Mayfrank, E., Schreckenberger, M., Sabri, O., Arning, C., Thelen, B., Spitzer, M., Kovar, K.-A., Hermle, L., Büll, U., & Sass, H. (1999). Neurometabolic effects of psilocybin, 3,4-Methylenedioxyethylamphetamine (MDE) and d-Methamphetamine in healthy volunteers a double-blind, placebo-controlled PET study with [^{18}F] FDG. *Neuropsychopharmacology*, *20*(6).

Gouzoulis-Mayfrank, E., Thelen, B., Maier, S., Heekeren, K., Kovar, K.-A., Sass, H., & Spitzer, M. (2002). Effects of the hallucinogen psilocybin on covert orienting of visual attention in humans. *Neuropsychobiology*, *45*(4), 205–212. https://doi.org/10.1159/000063672

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., Jesse, R., MacLean, K. A., Barrett, F. S., Cosimano, M. P., & Klinedinst, M. A. (2018). Psilocybin-

occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *Journal of Psychopharmacology, 32*(1), 49–69. https://doi.org/10.1177/0269881117731279

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology, 218*(4), 649–665. https://doi.org/10.1007/s00213-011-2358-5

Griffiths, R. R., Richards, W. A., Johnson, M. W., McCann, U. D., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology, 22*(6), 621–632. https://doi.org/10.1177/0269881108094300

Gukasyan, N., Davis, A. K., Barrett, F. S., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., & Griffiths, R. R. (2022). Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of Psychopharmacology, 36*(2), 151–158. https://doi.org/10.1177/02698811211073759

Harvey, J. A. (2003). Role of the serotonin 5-HT2A receptor in learning. *Learning & Memory, 10*(5), 355–362. https://doi.org/10.1101/LM.60803

Hasler, F., Grimberg, U., Benz, M. A., Huber, T., & Vollenweider, F. X. (2004). Acute psychological and physiological effects of psilocybin in healthy humans: A double-blind, placebo-controlled dose–effect study. *Psychopharmacology, 172*(2), 145–156. https://doi.org/10.1007/s00213-003-1640-6

Ishii, D., Takeda, K., Yamamoto, S., Noguchi, A., Ishibashi, K., Tanamachi, K., Yozu, A., & Kohno, Y. (2019). Effect of visuospatial attention on the sensorimotor gating system. *Frontiers in behavioral neuroscience, 13*, 1. https://doi.org/10.3389/fnbeh.2019.00001

Johnson, M. W., Hendricks, P. S., Barrett, F. S., & Griffiths, R. R. (2019). Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. *Pharmacology & Therapeutics, 197*, 83–102. https://doi.org/10.1016/J.PHARMTHERA.2018.11.010

Kometer, M., Cahn, B. R., Andel, D., Carter, O. L., & Vollenweider, F. X. (2011). The 5-HT2A/1A agonist psilocybin disrupts modal object completion associated with visual hallucinations. *Biological Psychiatry*, *69*(5), 399–406. https://doi.org/10.1016/J.BIOPSYCH.2010.10.002

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. X. (2012). Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biological Psychiatry*, *72*(11), 898–906. https://doi.org/10.1016/j.biopsych.2012.04.005

Kraehenmann, R., Preller, K. H., Scheidegger, M., Pokorny, T., Bosch, O. G., Seifritz, E., & Vollenweider, F. X. (2015). Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biological Psychiatry*, *78*(8), 572–581. https://doi.org/10.1016/j.biopsych.2014.04.010

Kraehenmann, R., Schmidt, A., Friston, K., Preller, K. H., Seifritz, E., & Vollenweider, F. X. (2016). The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity. *NeuroImage: Clinical*, *11*, 53–60. https://doi.org/10.1016/j.nicl.2015.08.009

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, *33*(9), 1039–1057. https://doi.org/10.1177/0269881119857204/ASSET/IMAGES/LARGE/10.1177_0269881119857204-FIG1.JPEG

Lewis, C. R., Preller, K. H., Kraehenmann, R., Michels, L., Stämpfli, P., & Vollenweider, F. X. (2017). Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow. *NeuroImage*, *159*, 70–78. https://doi.org/10.1016/j.neuroimage.2017.07.020

Li, W., Mai, X., & Liu, C. (2014). The default mode network and social understanding of others: What do brain connectivity studies tell us. *Frontiers in Human Neuroscience*, *8*(1 FEB). https://doi.org/10.3389/fnhum.2014.00074

Ling, S., Ceban, F., Lui, L. M. W., Lee, Y., Teopiz, K. M., Rodrigues, N. B., Lipsitz, O., Gill, H., Subramaniapillai, M., Mansur, R. B., Lin, K., Ho, R., Rosenblat, J. D., Castle, D., & McIntyre, R. S. (2022). Molecular mechanisms of psilocybin and implications for the treatment of depression. *CNS Drugs, 36*(1), 17–30. https://doi.org/10.1007/s40263-021-00877-y

Lord, L.-D., Expert, P., Atasoy, S., Roseman, L., Rapuano, K., Lambiotte, R., Nutt, D. J., Deco, G., Carhart-Harris, R. L., Kringelbach, M. L., & Cabral, J. (2019). Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. *NeuroImage, 199*, 127–142. https://doi.org/10.1016/j.neuroimage.2019.05.060

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Zarandi, S. S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics promote structural and functional neural plasticity. *Cell reports, 23*(11), 3170–3182. https://doi.org/10.1016/J.CELREP.2018.05.022

Lyons, T., & Carhart-Harris, R. L. (2018). More realistic forecasting of future life events after psilocybin for treatment-resistant depression. *Frontiers in Psychology, 9*. https://doi.org/10.3389/fpsyg.2018.01721

Marks, M. (2021, October 11). *A Strategy for Rescheduling Psilocybin. Scientific American.* https://www.scientificamerican.com/article/a-strategy-for-rescheduling-psilocybin/

Mason, N. L., Kuypers, K. P. C., Müller, F., Reckweg, J., Tse, D. H. Y., Toennes, S. W., Hutten, N. R. P. W., Jansen, J. F. A., Stiers, P., Feilding, A., & Ramaekers, J. G. (2020). Me, myself, bye: Regional alterations in glutamate and the experience of ego dissolution with psilocybin. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-020-0718-8

Mason, N. L., Kuypers, K., Reckweg, J. T., Müller, F., Tse, D., Da Rios, B., Toennes, S. W., Stiers, P., Feilding, A., & Ramaekers, J. G. (2021). Spontaneous and deliberate creative cognition during and after psilocybin exposure. *Translational psychiatry*, *11*(1), 209. https://doi.org/10.1038/s41398-021-01335-5

McGuinness, L. A., & Higgins, J. P. T. (2021). Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods*, *12*(1), 55–61. https://doi.org/10.1002/JRSM.1411

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, *68*(2), 264–355. https://doi.org/10.1124/PR.115.011478

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 1–10. https://doi.org/10.1186/S13643-016-0384-4/FIGURES/6

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*. https://doi.org/10.1136/BMJ.N71

Pokorny, T., Preller, K. H., Kometer, M., Dziobek, I., & Vollenweider, F. X. (2017). Effect of psilocybin on empathy and moral decision-making. *International Journal of Neuropsychopharmacology*, *20*(9), 747–757. https://doi.org/10.1093/ijnp/pyx047

Preller, K. H., & Vollenweider, F. X. (2016). Phenomenology, structure, and dynamic of psychedelic states. *Current topics in behavioral neurosciences*, *36*, 221–256. https://doi.org/10.1007/7854_2016_459

Preller, K. H., & Vollenweider, F. X. (2019). Modulation of social cognition via hallucinogens and "entactogens". *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00881

Preller, K. H., Pokorny, T., Hock, A., Kraehenmann, R., Stämpfli, P., Seifritz, E., Scheidegger, M., & Vollenweider, F. X. (2016). Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(18), 5119–5124. https://doi.org/10.1073/pnas.1524187113

Quednow, B. B., Kometer, M., Geyer, M. A., Vollenweider, F. X., BB, Q., Kometer, M., MA, G., & FX, V. (2012). Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 37*(3), 630–640. https://doi.org/10.1038/npp.2011.228

Roseman, L., Demetriou, L., Wall, M. B., Nutt, D. J., & Carhart-Harris, R. L. (2018). Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. *Neuropharmacology, 142*, 263–269. https://doi.org/10.1016/J.NEUROPHARM.2017.12.041

Roseman, L., Leech, R., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2014). The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Frontiers in Human Neuroscience, 8*(MAY), 204. https://doi.org/10.3389/fnhum.2014.00204

Rucker, J. J., Marwood, L., Ajantaival, R.-L. J., Bird, C., Eriksson, H., Harrison, J., Lennard-Jones, M., Mistry, S., Saldarini, F., Stansfield, S., Tai, S. J., Williams, S., Weston, N., Malievskaia, E., & Young, A. H. (2022). The effects of psilocybin on cognitive and emotional functions in healthy participants: Results from a phase 1, randomised, placebo-controlled trial involving simultaneous psilocybin administration and preparation. *Journal of Psychopharmacology, 36*(1), 114–125. https://doi.org/10.1177/02698811211064720

Sampedro, F., Revenga, M. D. L. F., Valle, M., Roberto, N., Domínguez-Clavé, E., Elices, M., Luna, L. E., Crippa, J. A. S., Hallak, J. E. C., Araujo, D. B. D., Friedlander, P., Barker, S. A., Álvarez, E., Soler, J., Pascual, J. C., Feilding, A., & Riba, J. (2017). Assessing the psychedelic "after-glow" in ayahuasca users: Post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities. *International Journal of Neuropsychopharmacology, 20*(9), 698–711. https://doi.org/10.1093/IJNP/PYX036

Shao, L. X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron, 109*(16), 2535-2544.e4. https://doi.org/10.1016/J.NEURON.2021.06.008

Smigielski, L., Scheidegger, M., Kometer, M., & Vollenweider, F. X. (2019). Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. *NeuroImage, 196*, 207–215. https://doi.org/10.1016/J.NEUROIMAGE.2019.04.009

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *The BMJ, 366*, l4898. https://doi.org/10.1136/BMJ.L4898

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., … Higgins, J. P. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical research ed.), 355*. https://doi.org/10.1136/BMJ.I4919

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., Curran, H. V., & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology, 235*(2), 459–466. https://doi.org/10.1007/S00213-017-4754-Y/FIGURES/2

Umbricht, D., Vollenweider, F. X., Schmid, L., Grübel, C., Skrabo, A., Huber, T., & Koller, R. (2003). Effects of the 5-HT2A agonist psilocybin on mismatch negativity generation and AX-continuous performance task: Implications for the neuropharmacology of cognitive deficits in schizophrenia. *Neuropsychopharmacology, 28*(1), 170–181. https://doi.org/10.1038/sj.npp.1300005

Voineskos, D., Daskalakis, Z. J., & Blumberger, D. M. (2020). Management of treatment-resistant depression: Challenges and strategies. *Neuropsychiatric Disease and Treatment, 16*, 221-234 https://doi.org/10.2147/NDT.S198774

Vollenweider, F. X., & Geyer, M. A. (2001). A systems model of altered consciousness: Integrating natural and drug-induced psychoses. *Brain Research Bulletin, 56*(5), 495–507. https://doi.org/10.1016/S0361-9230(01)00646-3

Vollenweider, F. X., & Smallridge, J. W. (2022). Classic psychedelic drugs: Update on biological mechanisms. *Pharmacopsychiatry, 55*(3). https://doi.org/10.1055/A-1721-2914

Vollenweider, F. X., Csomor, P. A., Knappe, B., Geyer, M. A., & Quednow, B. B. (2007). The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. *Neuropsychopharmacology, 32*(9), 1876–1887. https://doi.org/10.1038/sj.npp.1301324

Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Maguire, P., Stadelmann, O., & Angst, J. (1997). Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 16*(5), 357–372. https://doi.org/10.1016/S0893-133X(96)00246-1

Wittmann, M., Carter, O., Hasler, F., Cahn, B. R., Grimberg, U., Spring, P., Hell, D., Flohr, H., & Vollenweider, F. X. (2007). Effects of psilocybin on time perception and temporal control of behaviour in humans. *Journal of psychopharmacology, 21*(1), 50–64. https://doi.org/10.1177/0269881106065859

World Health Organization. (2021, September 13). *Depression.* https://www.who.int/news-room/fact-sheets/detail/depression

Appendixes

Table 1

Main results of the studies with a healthy sample included in the systematic review

Authors (Year)	Country	Type of Study	Setting	Sample Characteristics	Intervention	Neuropsychological Assessment			Main Findings
				N (male), M_{age} (SD), Level of Education (*n*), Psilocybin's Experience (*n*)	N^{o} dosing sessions, Substances, Follow-Up	Targets of Intervention	Outcome Measures	Time of Assessment	
Barrett et al. (2018)	USA	Double-blind, placebo-controlled, complete crossover-study	Music stimuli and visual stimuli not described ("an esthetic living room-like environment")	20 (9) 28.50 y (n/a) Bachelor's degree or higher (10), associate's degree (4), high school (6) All participants had a history of both classic psychedelic use and dissociative psychedelic use (n_{PSI} not specified)	Five dosing sessions (10-day mean interval) Placebo, PSI (10, 20 and 30 mg/70 kg, p.o.) and DXM (400 mg/70 kg, p.o.) 1-week follow-up after the fifth session	Global cognition	MMSE	120 min after administration	No impairment on global cognition.
						Psychomotor functioning	Circular lights task, and balance task	Baseline and 120, 240, and 360 min after administration	Higher doses of PSI slowed psychomotor performance.
							Motor praxis task (CNB)	Baseline and 120, 180, 240, 300, and 360 min after administration	
						Working memory	Letter N-back task (CNB)	Baseline, 120 min after administration	Dose-dependent impairment on working memory.
						Episodic memory and short-term memory	Word-encoding task	180 minutes after administration	Dose-dependent impairment on short-term and episodic memory.
							Recall, and recognition task	390 minutes after administration	

						Executive functioning and associative learning	DSST	Baseline and 120, 240, and 360 min after administration	Dose-dependent decrease in responses attempted at the peak of PSI effects on the number of trial attempts within 90 s, but no impact on accuracy. Dose-dependent impairment on associative learning.
						Visual perception	PLOT	240 min after administration	No effect on accuracy, but a dose-dependent increase in response time. In general, increased effort for difficult trials.
						Emotional conflict processing	Stroop task		Dose-dependent increase in response time, but no impact on accuracy. No effect on response to negative affective stimuli.
Carter et al. (2005a)	Switzerland	Counterbalanced, double-blind, placebo-controlled, within-subjects study	Not described	8 (5) 27.00 y (2.70) PSI experienced (5)	Four dosing sessions (14-day interval) Placebo, PSI (0.215 mg/kg, p.o.), ketanserin (50 mg, p.o.), and PSI + ketanserin	Working memory	SST (CANTAB)	Baseline, and 120 min after administration	Significant decrease on attentional tracking, but no significant effect on spatial working memory.
						Attention	Multiple-object tracking		
Carter et al. (2005b)	Switzerland	Counterbalanced, double-blind, placebo-controlled, within-subjects study	Not described	12 (6) 26.80 y (3.60) PSI experienced (6)	Three dosing sessions (14-day interval) Placebo and PSI (0.115 and 0.250 mg/kg, p.o.)	Visual perception	Binocular rivalry test	Baseline, and 90, 180, 270, and 360 min after administration	Dose dependent decrease in rivalry rate and rhythmicity.

Carter et al. (2007)	Switzerland	Counterbalanced, double-blind, placebo-controlled, within-subjects study	Not described	10 (6) 26.00 y (2.30) PSI experienced (5)	Four dosing sessions (14-day interval) Placebo, ketanserin (50 mg, p.o.), PSI (0.215 mg/kg, p.o.), and PSI + ketanserin	Visual perception	Binocular rivalry test	Baseline, and 30, 60, 90, 135, 180, 240, 300, 360, and 420 min after administration	Significant reduction in binocular rivalry switching rate. Increase in the proportion of transitional/mixed percept experience.
Gabay et al. (2018)	UK	Open label, within-subjects study	Not described	20 (20) 26.60 y (7.10) PSI experienced (20)	Two dosing sessions (on the same day) Placebo + PSI (2 mg, IV)	Social decision-making and social reward	The Ultimatum Game	Screening and 60 min after administration	Reduced rejection of unfair options.
Gouzoulis-Mayfrank et al. (2002)	Germany	Quasi-randomized, double-blind, placebo-controlled study	Not described	**TG:** 8 (3) 31.40 y (n/a) **CGs:** *MDE* 8 (6) 33.70 y (n/a) *d-methamphetamine* 8 (6) 37.00 y (n/a) *Placebo* 8 (6) 36.40 y (n/a) Higher degree (32)	Single dosing session Placebo, PSI (0.2 mg/kg, p.o., total dose < 15 mg), MDE (2 mg/kg, p.o., total dose < 140 mg) or d-methamphetamine (0.2 mg/kg, p.o., total dose < 17.5 mg, *n*= 4; or 0.4 mg/kg, p.o., total dose < 35 mg, *n*= 4)	Spatial attention	COVAT	60 min pre-drug session and 75–95 min after administration	Overall slowing reaction times after PSI. Slow reaction times in invalid trials at short cue target intervals. Failure of response inhibition in valid trials at long cue target intervals for right visual field targets.

Hasler et al. (2004)	Switzerland	Double-blind, placebo-controlled, within-subjects study	Not described	8 (4) 29.50 y (n/a) Subjects had no or very limited experience with psychoactive drugs (n_{PSI} not specified)	Five dosing sessions (at least 2-week interval) Placebo and PSI [very low dose (VLD) = 0.045 mg/kg, p.o.; low dose (LD) = 0.115 mg/kg, p.o.; medium dose (MD) = 0.215 mg/kg, p.o.; and high dose (HD) = 0.315 mg/kg, p.o.]	Sustained attention	FAIR	140 min after administration	Reduction on attentional capacity after the MD and HD of PSI.
Kometer et al. (2012)	Switzerland	Randomized, double-blind, placebo-controlled, within-subjects study	Not described	17 (11) 26.00 y (4.36) University students/graduates (15), high school (1), apprenticeship (1) PSI experienced (7)	Four dosing sessions (2-week interval) Pre-treatment with placebo or ketanserin (50 mg), and placebo or psilocybin (0.215 mg/kg) (treatment)	Emotional discrimination Emotion inhibition processing	Reading the Mind in the Eyes Test Emotional go/no-go	130 min after administration	Decreased recognition of negative facial expression. Increased goal-directed behavior toward positive compared with negative cues. Enhance of positive, but inhibition of negative sequential emotional effects.
Mason et al. (2021)	Netherlands	Randomized, double-blind, placebo-controlled, parallel-group study	Not described	**TG:** 30 (18) 22.73 y (2.90) **CG:** 30 (17) 23.20 y (3.65) All subjects had a previous experience with a psychedelic substance (n_{PSI} not specified)	Single dosing session Placebo or PSI (0.17 mg/kg, p.o.) 1-week follow-up	Convergent thinking (CT) and divergent thinking (DT)	PCT AUT	Baseline, and 120 min and 7 days after administration Baseline, and 130 min and 7 days after administration	PSI induces a time- and construct-related differentiation of effects on creative thinking. Acute impairment of DT, but an increase in aspects of DT 7 days after PSI ingestion. Acute decline in CT comparing PSI to placebo, but an increase in performance in the PSI group when comparing baseline to the follow-up.

Pokorny et al. (2017)	Switzerland	Randomized, double-blind, placebo-controlled, within-subjects study	Visual stimuli not described ("quiet room")	32 (17) 26.72 y (5.34) PSI experienced (10)	Two dosing sessions (at least 10-day interval) Placebo and PSI (0.215 mg/kg, p.o.)	Moral decision-making Cognitive empathy Emotional empathy	MDT MET	160 min after administration	Increased emotional empathy. No effect on cognitive empathy or moral decision making.
Preller et al. (2016)	Switzerland	Randomized, double-blind, placebo-controlled, crossover study	Not described	21 (12) 26.48 y (4.76)	Two dosing sessions (at least 10-day interval) Placebo and PSI (0.215 mg/kg, p.o.)	Social exclusion	Cyberball task	75 min after administration	Reduction of the feeling of social exclusion.
Quednow et al. (2012)	Switzerland	Randomized, double-blind, placebo-controlled, within-subjects study	Visual stimuli ("calm and comfortable laboratory")	16 (13) 26.70 y (n/a) All are students or academics. PSI experienced (2)	Four dosing sessions (4-week interval) Placebo, PSI (0.260 mg/kg, p.o.), ketanserin (40 mg, p.o.), and PSI + ketanserin	Sensorimotor gating Controlled inhibition	PPI of the acoustic startle response Stroop task	60 min after administration 85 min after administration	Decrease on automatic and controlled inhibition.
Rucker et al. (2022)	UK	Randomized, double-blind, placebo-controlled, between-subjects study	Visual stimuli	**TG:** *PSI 10mg* 30 (16) 36.10 y (9.25) A level/NVQ (1), undergraduate degree (11), master's or postgraduate degree (16), PhD (2) *PSI 25mg* 30 (16)	Single dosing session Placebo or PSI (10 or 25 mg/kg, p.o.) 3-month follow-up	Episodic memory Spatial and working memory Executive functioning, planning	PAL-TEA (CANTAB) SWM-BE (CANTAB) SWM-S (CANTAB)	Baseline, day -1, day 8 and day 29	No clinically relevant negative short- or long-term effects on cognitive functioning or emotional processing.

				36.60 y (10.29) A level/NVQ (2), undergraduate degree (9), master's or postgraduate degree (16), PhD (3) **CG:** 29 (16) 35.60 y (7.69) Undergraduate degree (10), master's or postgraduate degree (15), PhD (4) PSI experienced (33)		Sustained attention Social cognition and emotional processing	RVP-A' (CANTAB) PET, RMET, SSR, SVO, TEQ	Baseline, day -1, day 8 and day 85	
Umbricht et al. (2003)	Switzerland	Randomized, single-blinded, placebo-controlled, within-subjects study	Not described	18 (10) 25.10 y (4.30) University students (16), apprenticeship (2)	Two dosing sessions Placebo and PSI (0.280 mg/kg, p.o.)	Working memory	AX-CPT	Baseline and 70 min after administration	Performance deficits in AX-CPT characterized by a failure to use contextual information.
Vollenweider et al. (2007)	Switzerland	Randomized, double-blind, placebo-controlled, within-subjects study	Visual stimuli ("calm and comfortable laboratory")	16 (7) 26.40 y (n/a) Only three subjects had a psychedelic experience (n_{PSI} not specified)	Four dosing sessions (4-week interval) Placebo and PSI (0.115, 0.215 and 0.315 mg/kg, p.o.)	Sensorimotor gating Sustained attention	PPI of the acoustic startle response FAIR	90 and 165 min after administration 0, 105, 180 and 360 min after administration	Increase in PPI at long ISIs. No effect at medium ISIs. PSI impaired sustained attention, positively correlated with decreased PPI at short ISIs.

Wittmann et al. (2007)	Switzerland	Counterbalanced, double-blind, placebo-controlled, within-subjects study	Not described	12 (6) 26.80 y (3.60) PSI experienced (6)	Three dosing sessions (at least 14-day interval) Placebo and PSI (0.115 and 0.250 mg/kg, p.o.)	Spatial and working memory	SST (CANTAB)	0, 100 and 360 min after administration	Higher dose of PSI impaired SST performance 100 min after administration, compared to placebo. No effect at medium dose.

Note. M_{age}: mean age; SD: standard deviation; N: sample size; PSI: psilocybin; TG: treatment group; CG: control group; N/A: not available; IV: intravenous; P.O.: by mouth, orally; DXM: dextromethorphan; MMSE: the Mini-Mental Status Examination; CNB: the Penn Computerized Neurocognitive Battery; DSST: the Digit Symbol Substitution Task; PLOT: the Penn Line Orientation Test; SST: the Spatial Span Test; CANTAB: the Cambridge Neuropsychological Test Automated Battery; MDE: 3,4-methylenedioxyethylamphetamine; COVAT: the Covert Orienting of Attention Task; FAIR: the Frankfurt attention Inventory; PCT: the Picture Concept Task; AUT: the Alternate Uses Test; MDT: the Moral Dilemma Task; MET: the Multifaceted Empathy Test; PPI: prepulse inhibition; NVQ: national vocational qualification (UK); PAL-TEA: the Paired Associates Learning-Total Errors Adjusted; SWM-BE: the Spatial Working Memory-Between Errors; SWM-S: the Spatial Working Memory-Strategy; RVP-A': the Rapid Visual Information Processing A-prime; PET: the Pictorial Empathy Test; RMET: the Reading the Mind in the Eyes Test; SSR: the Scale of Social Responsibility; SVO: Social Value Orientation; TEQ, the Toronto Empathy Questionnaire; AX-CPT: 'AX'- Type Continuous Performance Test; ISIs: interstimulus intervals.

Table 2

Main results of the studies with a clinical sample included in the systematic review

Authors (Year)	Country	Type of Study	Setting	Diagnosis (Criteria)	Sample Characteristics	Intervention	Neuropsychological Assessment			Main Findings
					N (male), M_{age} (SD), Level of Education (*n*), Psilocybin's Experience (*n*)	N^{o} dosing sessions, Substances, Follow-Up	Targets of Intervention	Outcome Measures	Time of Assessment	
Doss et al. (2021)	USA	Open label, between and within-subjects study	Music stimuli and visual stimuli	MDD (≥17 on the GRID-HAMD)	24 (8): *Immediate treatment group* (*n* = 13) *Delayed treatment group* (*n* = 11) 39.80 y (12.23)	Two dosing sessions (1.6-week interval) PSI (20 and 30 mg/70 kg, p.o.) 1-month follow-up	Cognitive flexibility Response inhibition Selective attention Abstract reasoning	PCET Stroop test Short Penn Verbal Reasoning task	Baseline, and 1 week and 1-month post-treatment	Increase on cognitive flexibility in patients with MDD. No effect on response inhibition, selective attention, and abstract reasoning.
Stroud et al. (2018)	UK	Open-label, between-subjects, pilot study	Visual stimuli ["pre-decorated room (e.g., low lighting, fabric drapes, flowers on bed side table)]	TRD (17+ on the 21 item HAM-D; and who had not benefited from previous pharmacological treatment for at least 6 weeks)	**TG:** 17 (11) 44.94 y (11.51) **CG:** 16 (11) 32.00 y (10.40)	Two dosing sessions (1-week interval) PSI [10 mg (safety session) and 25 mg, p.o.] 1-week follow-up (after the high-dose session)	Social cognition, emotional discrimination	DEER-T	Baseline and 1 week after administration	Enhanced emotion recognition compared to baseline in the patient group, but not in controls.

Note. M_{age}: mean age; SD: standard deviation; N: sample size; PSI: psilocybin. TG: treatment group; CG: control group; P.O.: by mouth, orally; MDD: Major Depressive Disorder; TRD: Treatment Resistant Disorder; GRID-HAMD: the GRID-Hamilton Depression Rating Scale; HAMD: the Hamilton Rating Scale for Depression; PCET: the Penn Conditional Exclusion Test; DEER-T: the Dynamic Emotional Expression Recognition Task.