Psychedelics and cognitive function: A systematic review

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Abstract
Introduction: With the progressive advancement of clinical and experimental trials aimed at investigating the pharmacotherapeutic potential of psychedelic substances, there is also the development of other conceptions of use, not only for the treatment of psychiatric disorders, but also for the improvement of emotional/cognitive functions. Objective: The present study is a systematic review of investigations aimed at evaluating the effects of psychedelics on cognitive functions in healthy volunteers. Methods: A search was performed in PubMed database, using the search terms "psychedelics and cognitive enhancement" and "psychedelics and cognitive performance". Results and conclusions: Of the experimental studies analyzed, only forty-six (46) met the inclusion criteria. The results obtained showed that 3,4-methylenedioxy-methamphetamine (MDMA) was the most studied drug, with eighteen (18) articles. Fourteen (14) articles were published with psilocybin. Lysergic acid diethylamide (LSD) ranked third, with six (6) articles; other two (2) studies focused on investigating the beverage ayahuasca, and another (1) its psychoactive-containing molecule: dimethyltryptamine (DMT). Eight (8) studies investigated the effects of other psychedelic drugs, like S-ketamine, mescaline, 3,4-methylenedioxy-amphetamine (MDE), and ibogaine. Although there were no serious adverse effects resulting from the use of the investigated psychedelic drugs, rigorous assessment of the potential risks of long-term use and of the advantages of the continuous use of these drugs through neuropsychological assessments are still warranted.
Keywords: Psychedelics; Healthy volunteers; Cognitive function.

Resumo
Introdução: Com o recente retorno e progressivo avanço dos ensaios clínicos e experimentais voltados para a investigação do potencial farmacoterapêutico de substâncias psicodélicas, surge o desenvolvimento também de outras concepções de uso, não apenas para o tratamento de transtornos psíquicos, mas também para aprimoramento de funções emocionais/cognitivas. Objetivo: O objeto deste estudo foi realizar uma revisão sistemática de trabalhos que avaliaram a utilização de drogas psicodélicas sobre processos cognitivos em voluntários saudáveis. Método: Foi realizada uma busca na base de dados PubMed, utilizando os termos de busca *"psychedelics and cognitive enhancement"*; e *"psychedelics and cognitive performance"*. Resultados e conclusões: Dos estudos experimentais analisados, verificou-se que somente quarenta e seis (46) preenchiam os critérios de inclusão. Os resultados obtidos mostraram que o metilenodioximetanfetamina (MDMA) foi a droga mais estudada, encontrada em dezoito (18) artigos. Quatorze (14) artigos foram publicados com a psilocibina. Seis (6) artigos investigaram os efeitos da dietilamida do ácido lisérgico (LSD); dois (2) estudos investigaram os efeitos da ayahuasca, e outro (1) de sua molécula psicoativa: a dimetiltriptamina (DMT). Oito (8) artigos investigaram os efeitos de outras drogas psicodélicas: a S-cetamina, mescalina, metilenodioxianfetamina (MDE) e a ibogaína. Embora não tenham sido verificados efeitos adversos graves decorrentes da utilização das substâncias psicodélicas e medicinas tradicionais investigadas, estudos adicionais sobre o potencial de risco de uso a longo prazo e sobre o nível de abrangência das variáveis presentes nas avaliações neuropsicológicas apresentadas ainda são necessários.
Palavras-chave: Substâncias psicodélicas; Voluntários saudáveis; Cognição.

Resumen
Introducción: Con el progresivo avance de los ensayos clínicos y experimentales direccionados a investigar el potencial farmacoterapéutico de las sustancias psicodélicas, también se desarrollan otras concepciones de uso, no sólo para el tratamiento de trastornos psiquiátricos, sino también para la mejora de funciones emocionales/cognitivas. Objetivo: El presente estudio es una revisión sistemática de investigaciones destinadas a evaluar los efectos de los psicodélicos sobre las funciones cognitivas en voluntarios sanos. Métodos: Se realizó una búsqueda en la base de datos PubMed, utilizando

los términos de búsqueda ""*psychedelics and cognitive enhancement*"; y "*psychedelics and cognitive performance*". Resultados y conclusiones: De los estudios experimentales analizados, sólo quarenta y seis (46) cumplieron los criterios de inclusión. Los resultados obtenidos mostraron que la 3,4-metilendioximetanfetamina (MDMA) fue la droga más estudiada, con dieciocho (18) artículos. Se publicaron catorce (14) artículos con psilocibina. La dietilamida del ácido lisérgico (LSD) ocupó el tercer lugar, con seis (6) artículos; otros dos (2) estudios se centraron en investigar la bebida ayahuasca, y outro (1) su molécula que contiene psicoactivos: dimetiltriptamina (DMT). Ocho (8) estudios investigaron los efectos de otras drogas psicodélicas, como S-ketamina, mescalina, 3,4-metilendioxianfetamina (MDE) e ibogaína. Aunque no se produjeron efectos adversos graves derivados del uso de las drogas psicodélicas investigadas, todavía se justifica una evaluación rigurosa de los riesgos potenciales del uso a largo plazo y de las ventajas del uso contínuo de estas drogas mediante evaluaciones neuropsicológicas.
Palabras clave: Sustancias psicodélicas; Voluntarios sanos; Cognición.

1. Introduction

The growth of scientific research with psychedelics, which has been called the "Psychedelic Renaissance" (Carhart-Harris, et al., 2018), has become evident during the last years. Contemporary research with psychedelics applied together with new theoretical-methodological approaches, shows therapeutic efficacy and few adverse side effects on a wide variety of neuropsychiatric disorders, namely: drug addiction (Johnson, et al., 2014; Bogenschutz, et al., 2015), post-traumatic stress disorder (PTSD) (Mithoefer, et al., 2019; Schenberg, et al., 2020; Mitchell, et al., 2021), anxiety disorders (Grob, et al., 2010; Gasser, et al., 2014; Danforth, et al., 2016) and depression (Carthart-Harris, et al., 2016; Ross, et al., 2016). Currently, institutions in several countries have gained legal status to carry out clinical-investigative work on the therapeutic potential of psychedelic drugs. Recently, the US Food and Drug Administration (FDA) assigned 3,4-methylenedioxy-methamphetamine (MDMA) and psilocybin to the "breakthrough therapy" category (Jardim, et al., 2020; Reiff, et al., 2020; Schenberg, et al., 2020), granting these substances the status of "innovative therapies" for the treatments of PTSD and depression, respectively (Rodrigues, 2019).

With the resurgence of studies with psychedelic drugs and the dissemination of successful results in scientific journals, another indication for the use of these drugs emerges: the idea that these substances may promote cognitive/emotional benefits for healthy volunteers. This is the idea that supposedly justifies the use of extremely low dosages over several days, the so-called microdoses (Cameron, et al., 2020). Regarding the motivation underlying the use of microdoses, studies (Fadiman & Korb, 2019; Andersson & Kjellgren, 2019; Hutten, et al., 2020) identified three categories of interest: (a) interest in improving oneself cognitively and/or spiritually; (b) intention to promote well-being (in the sense of promoting health and pleasure or the relief of symptoms, generally related to psychological suffering); (c) as a substitute therapy for psychiatric medication.

Nevertheless, knowledge about the effects of psychedelics on cognitive functions is still relatively limited. Although some psychedelics may improve cognition, in particularly when administered to patients with compromised cognitive functions (Magaraggia, et al., 2021), such association not necessarily applies to non-clinical populations. Therefore, there is an urge to gather evidence from empirical studies looking at the effects of psychedelics in cognitive functions in healthy subjects.

The purpose of the present study was to perform a systematic review of the literature aimed at investigating: 1) which psychedelics have been evaluated for cognitive improvement; 2) the results obtained on different cognitive aspects, i.e. memory, emotional processing, social cognition, creativity; 3) possible side effects.

2. Research Methods and Reporting

The present review was conducted according to the preferred reporting items for systematic reviews (PRISMA) guidelines (Selçuk, 2019). To comply with the principles of these guidelines, we tried to avoid selective reporting by gathering all relevant data that conformed to the specified eligibility criteria described below. All studies published until October 2023 were included, without any language restriction.

2.1 Eligibility criteria

The inclusion criteria were: 1) original articles, comparative studies, and clinical trials that directly dealt with the administration and effects of psychedelics as cognitive enhancers; 2) articles written in any language.

Editorial texts, reviews, comments, conference articles, anecdotal reports and duplicate studies were excluded. In addition, articles that were not conducted with cognitive, psychotechnical and/or neuroimaging tests in their experimental design were withdrawn. Besides, those in which the experiments were conducted on healthy volunteers, as well as those that researchers did not reach knowledge about the concentration of the administered dosage or control of the quality of the drug, were also removed. At last, studies performed with *Cannabis sativa* or cannabinoids were not included in the present review.

2.2 Information sources

The search was conducted in PubMed database, for all kinds of articles published between 1966 to October 2023.

2.3 Search strategy and data collection process

Search strategies consisted in the crossing of the terms psychedelics AND cognitive enhancement, OR psychedelics AND cognitive performance.

The reviewers collected the data independently in three different phases. Phase 1: Titles were carefully read to exclude articles outside the scope of this research. The reviewers were not blinded to authorship information or the name of the journals. Studies that did not deal with the research questions raised by this review were excluded. Phase 2: the reviewers analyzed the abstracts of the remaining studies independently. In this phase, abstracts not addressing the subject of interest, literature reviews, case reports, and congress abstracts were excluded. Phase 3, the full text of the articles selected in phase 2 were assessed. Then, the articles were evaluated by the reviewers to verify whether they met the full inclusion criteria. The studies were excluded, and the reasons recorded. Relevant papers that conformed to the pre-specified eligibility criteria were identified.

After applying the search, inclusion, and exclusion criteria, 46 articles were selected.

2.4 Data items

The following information was compiled to characterize the studies in Table 1: drug(s), authors/year of study, subjects, instruments/measures used to evaluate the performance or cognitive enhancement potential, and main results.

3. Results

3.1 Study Selection

The initial online data search identified one hundred and ninety-three (193) articles. After the exclusion criteria, forty-six (46) articles were selected. The results of the search strategy are shown in Figure 1.

Figure 1 - Flowchart of the search criteria performed.
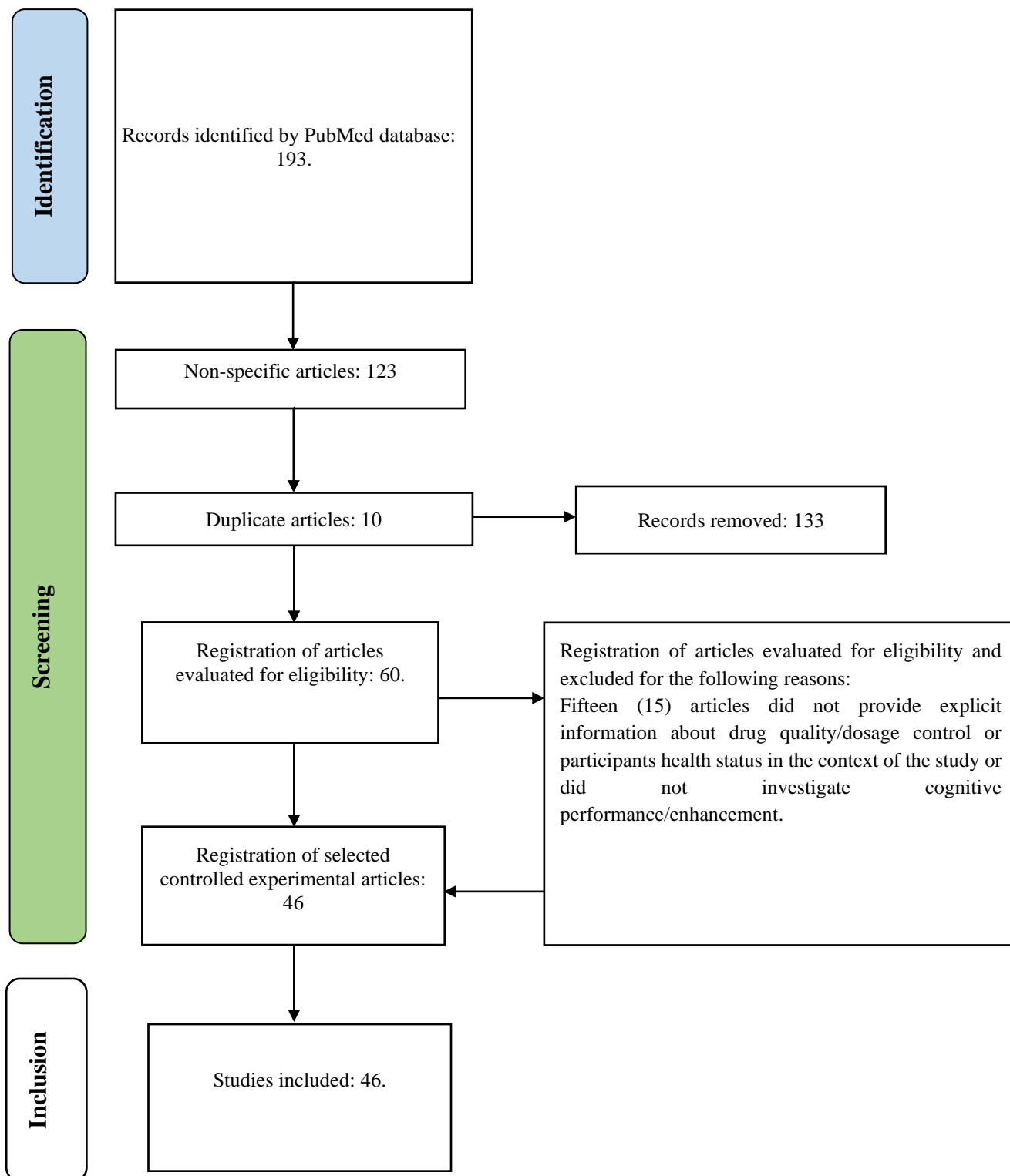
Source: Authors.

3.2 General characteristics of the included studies

Tables 1-4 identify and characterize the included studies. The following drugs were tested for cognitive functions: 3,4-methylenedioxymethamphetamine (MDMA), and its analogue 3,4-methylenedioxyethylamphetamine (MDE), in eighteen (18) and three (3) studies, respectively (Table 1).

Table 1 - 3,4-methylenedioxy-methamphetamine (MDMA) and methylenedioxyamphetamine (MDA).

Drug(s)	Authors/Year	Sample (N/Age/Gender	Methods	Measurements	Results
MDMA	Gabay et al. 2019	20 healthy subjects ± 21-37 years 10M/10F	Randomized, double-blind, placebo-controlled study to investigate the effects of MDMA on social decision-making. Participants played a trust game with trusted and untrusted opponents during fMRI. The density of receptors in the participants' nervous systems using PET imaging was also measured. MDMA and placebo were administered orally in two separate sessions, with a one-week interval between sessions. The order of drug administration was counterbalanced among participants.	Trust game; 5D-ASC; PD; Affective Bias task; MET; ASL fMRI.	The results suggest that MDMA can increase cooperative behavior in social decision-making contexts. This effect was associated with changes in neuronal activity in regions linked to social cognition. However, the study also highlights the context-specific nature of MDMA's effects on decision-making. The study found no evidence to support the hypothesis that MDMA's dopaminergic modulation was responsible for the observed results.
MDMA; MPH; Modafinil	Schmidt et al. 2018a	24 healthy subjects ±19-29 years 12M/12F	Cross-over, double-blind, randomized, within-subject, placebo-controlled study to compare the acute effects of methylphenidate, modafinil, and MDMA on neural correlates of facial fear processing. 60 mg of methylphenidate, 600 mg of modafinil, and 125 mg of MDMA were administered to the subjects while performing an event-related fMRI task to assess neural activation in response to fearful faces. Negative mood states were assessed with the STAI and subjective ratings.	FERT; STAI; AMRS.	Results showed that MDMA, when compared with modafinil, did not increase neuronal activity of the amygdala in responses to fearful faces. The study found no significant effect of methylphenidate or MDMA on brain activation during facial fear processing.
MDMA	Kuypers et al. 2018	20 healthy subjects ±21.2 years 12M/8F	Placebo-controlled within-subject study. Participants were given placebo or the 5-HT2A antagonist ketanserin as a pretreatment, followed by MDMA or placebo as treatment. Participants then completed two behavioral tests (PAST/AAT) that assessed processing of emotional and social stimuli. Self-reported mood and oxytocin concentrations were also identified at various time points throughout the study.	POMS; PAST; AAT.	Results showed that MDMA reduced arousal levels elicited by negative sounds. This effect was neutralized by pre-treatment with ketanserin, indicating the involvement of the 5-HT. MDMA does not increase response towards emotional and social stimuli, but increased positive and negative mood ratings and elevated plasma concentrations of oxytocin. The reduction in arousal levels upon hearing negative sounds was not related to heightened subjective arousal. It is suggested that this decrease in arousal to negative stimuli potentially reflects a decrease in defenses, a process that may play a role in the therapeutic process.
MDMA	Haijen et al. 2018	20 healthy subjects ±21.2 years 12M/8F	Two-by-two double-blind, placebo-controlled within-subject design with pretreatment (ketanserin 40 mg or placebo) preceding the treatment (MDMA 75 mg or placebo) by 30 min. A double-dummy procedure was used to control for differences in Tmax between both drugs.	30-word learning task; NART; GSS; Social behavior tests (Approach Avoidance Test with emotional and social situation stimuli, Processing of Sounds Task) and questionnaires (Dissociative Experiences Scale,	MDMA caused memory impairment in the verbal word learning task. MDMA did not affect endocannabinoid concentrations nor did ketanserin block the MDMA-induced memory impairment. Thus, MDMA-induced memory impairment seems to be unrelated to the endocannabinoid system.

				Clinician Administered Dissociative States Scale, POMS)	
MDMA; MPH; modafinil.	Dolder et al. 2018	24 healthy subjects ± 24.5 years 12M/12F	Double-blind, randomized, crossover study to investigate the acute effects of single doses of MDMA, methylphenidate, modafinil and placebo. The study was developed in four experimental sessions, with at least one week between sessions. Acute drug effects were tested using psychometric scales. The study monitored the autonomic, subjective, endocrine and emotional effects of the drugs.	AMRS; FERT; STAI; ARCI; 5D-ASC; VAS; SADI.	Results suggest that all active drugs produced comparable hemodynamic and adverse effects. However, MDMA produced greater increases in pupil dilation, good subjective effects, drug liking, happiness, confidence, well-being, and changes in consciousness than either methylphenidate or modafinil. MDMA reduced anxiety, but impaired fear recognition and led to incorrect classifications of emotions. In SADI, only MDMA produced sexual arousal-like effects. Only MDMA produced marked increases in cortisol, prolactin and oxytocin.
MDMA; MPH; Modafinil	Schmidt et al. 2017	21 healthy subjects ±21-30 years 10M/11F	The study compared the effects of the three drugs on the neural mechanisms underlying response inhibition in healthy subjects. The methods used in this article were a double-blind, randomized, within-subject placebo-controlled trial. The three drugs were administered while performing an fMRi test related to the Go/No-Go exam to assess brain activation during motor response inhibition.	AMRS; Go/No-go task.	Results suggest that MDMA did not improve inhibitory performance. While the three drugs activated fronto-parietal regions, fMRI results showed that MDMA significantly increased activation in the right middle/inferior frontal gyrus and superior parietal lobule compared with placebo.
MDMA	Kuypers et al. 2016	65 MDMA users and 65 healthy subjects ± 18-28 years 40M/25F	The study compared a control group of healthy volunteers, with no history of drug use, with MDMA users.	WLT-IR; WLT-DR	Results suggest that although memory impairment is clinically present during MDMA use, it is absent during withdrawal. Verbal memory performance of placebo-treated subjects did not differ from controls. History of MDMA use was not predictive of memory impairment. During MDMA use by users, verbal memory was impaired.
MDMA; MPH	Schmid et al. 2015	30 healthy subjects ± 18-32 years 15M/15F	Double-blind, randomized, placebo-controlled, crossover study. The study involved the administration of methylphenidate and MDMA and the evaluation of their effects on subjective sexual arousal through viewing erotic images and on the perception of romantic relationships of unknown couples. Participants were asked to rate their level of sexual arousal when viewing explicit and implicit sexual stimuli and increase the time of presentation of implicit sexual stimuli by pressing the button. Plasma levels of testosterone, estrogen and progesterone were also measured.	SAT; CAT.	Compared with methylphenidate, MDMA did not increase rates of sexual arousal to overt sexual stimuli. However, none of the drugs altered the others' assessment of their romantic relationships. The study also found that plasma levels of testosterone, estrogen and progesterone were not associated with rates of sexual arousal.
MDMA	Kirkpatrick et al. 2015	Study 1: 361 healthy subjects ±34.5 years Both gender (57%F) Study 2: 32 healthy subjects ± 27.6 years 23M/9F	In Study 1, the WTT was administered to participants to examine their performance against measures of personality and socioeconomic status. In Study 2, MDMA-experienced participants completed the WTT after administration of MDMA (0, 0.5, or 1.0 mg/kg) to examine effects on generosity. Drug conditions were administered in randomized order, under double-blind conditions.	NEO-FFI; WTT	Results showed that participants were more generous to a close friend than to an acquaintance or stranger in both studies. In Study 1, WTT generosity was related to family income and the trait "Kindness". In Study 2, MDMA (1.0 mg/kg) increased generosity to a friend but not to a stranger, while MDMA (0.5mg/kg) slightly increased generosity to a stranger, especially among study

					participants. women. Findings suggest that MDMA produces prosocial effects that depend on the social closeness of relationships.
MDMA; MPH	Schmid et al. 2014	30 healthy subjects ± 24.5 years 15M/15F	Double-blind, randomized, placebo-controlled, crossover study to investigate the acute effects of MDMA, methylphenidate, and placebo on various aspects of social cognition. The study used a variety of cognitive tests to assess different dimensions of social cognition. The study also measured the subjective, autonomic, pharmacokinetic, endocrine, and adverse effects of the drugs. Finally, the study combined current and previously published data into a pooled analysis of the effects of MDMA and methylphenidate in a larger sample.	FERT; MET; SVO; MJT; AMRS; 5D-ASC.	Results suggest that MDMA increased emotional empathy for positive emotional situations and tended to reduce recognition of sad faces. MDMA had no effects on cognitive empathy or social cognitive inferences. MDMA produced subjective "empathogenic" effects such as liking the drug, closeness to others, openness, and confidence. MDMA, but not methylphenidate, increased plasma levels of oxytocin and prolactin. None of the drugs influenced moral judgment.
MDMA; Pindolol	Kuypers et al. 2014	20 healthy subjects ±18-26 years 12M/8F	Placebo-controlled within-subject study to investigate the effects of MDMA on empathy and social interaction. The study included four treatment conditions: MDMA (75 mg), with or without pindolol (20 mg), oxytocin nasal spray, or placebo. Participants received the treatments and then rated cognitive and emotional empathy using the RMET and MET tests. Social interaction was assessed using a trust game and a ball-throwing game. Hormone analysis was also performed to measure cortisol and oxytocin levels.	RMET; MET; IRI; Trust Game; SBTGQ; WLT; GSS; POMS; NART	Results showed that MDMA (75 mg) selectively increased emotional empathy, leaving cognitive empathy, trust, and reciprocity unchanged. The effects of MDMA on emotional empathy were not influenced by pindolol or oxytocin. Oxytocin did not affect measures of empathy and social interaction. The Trust Game showed that participants threw more balls to the good player compared to the neutral player.
MDMA	Hysek et al. 2014	32 healthy subjects ± 24.6 years 16M/16F	Cross-over, double-blind, randomized, placebo-controlled study to investigate the acute effects of MDMA on empathy and social behavior in volunteers. Tests were used to assess empathy and social behavior. The study also measured plasma levels of hormones involved in social behavior, including cortisol, prolactin and oxytocin.	VAS; AMRS; MET; IRI; SVO; FERT	Results showed that MDMA increased emotional empathy and social behavior in male participants but impaired the identification of negative emotions on a test (FERT), particularly in female participants. MDMA also increased plasma levels of cortisol, prolactin, and oxytocin. The study did not report any serious adverse effects of MDMA on participants.
MDMA; ethanol; THC	Lansbergen et al. 2011	Study 1: 14 healthy subjects ± 18-29 years 8M/6F Study 2: 14 healthy subjects ± 18-27 years 11M/3F	The aim of the present report was to examine the effects of MDMA alone and in combination with THC or ethanol on ongoing EEG oscillations. Four-way, double-blind, randomized, crossover and placebo-controlled design.	EEG.	Results showed that the attenuation of power when drugs were taken in combination appears to be considerably less than the sum of the drugs alone. There was significant MDMA-alone effects for theta and lower-1 alpha power. Increased individual alpha peak frequency, and theta oscillations and lower-1 alpha oscillations, which overlap the traditional theta frequency band, were attenuated after the administration of MDMA alone.
MDMA	Bedi et al. 2010	21 healthy subjects ± 18-38 years 12M/9F	Four-sessions, within-subject, randomized, double-blind, placebo-controlled design. Self-report data of affective states and tasks to identify emotions from images of faces, pictures of eyes, and vocal cues were collected.	VAS; POMS; FERT; RMET; DANVA-2.	Results showed that MDMA (1.5 mg/kg only) altered a behavioral indicator of social cognition. Specifically, it robustly reduced recognition of fearful faces, without changing recognition of other emotions from facial or vocal cues. MDMA produced self-reports of loving feelings and friendliness but decreased the accuracy of subjects in identifying fear in others. A decreased ability

					to identify negative emotions, particularly threat-related signals such as fear, might facilitate social approach behavior.
MDMA; Pindolol	Hasler et al. 2009	15 healthy subjects ± 20-36 years Only male	Within-subject, double-blind, placebo-controlled study to investigate the effects of MDMA and pindolol on cognitive performance and subjective experiences. The study examined participants under four different conditions: placebo, pindolol, MDMA, and MDMA after pretreatment with pindolol. Cognitive performance was assessed using Cambridge Automated Neuropsychological Test Battery (CANTAB) tasks and subjective experiences were measured using psychometric questionnaires to assess the central dimensions of EAC's, mood and state of anxiety.	AMRS; STAI; 5D-ASC; PAL.	Results showed that MDMA significantly impaired sustained attention and visual-spatial memory but did not affect executive functions. Pindolol pretreatment did not significantly alter MDMA-induced cognitive performance impairment and only exerted a minor modulatory effect on two psychometric scales affected by MDMA treatment ('positive derealization' and 'dreaming').
MDMA; ethanol	Dumont et al. 2008	14 healthy subjects ± 18-29 years 8M/6F	Four-way, double-blind, randomized, crossover, placebo-controlled design.	SDRT; Switch task; Pursuit Task; Point Task; Tangle Task; SDST; BLMRS.	The study demonstrates that the effects of 100mg MDMA on cognitive function are no greater than the effects of a relatively low dose of ethanol. MDMA by itself did not significantly affect subjective alertness. However, MDMA did significantly reduce subjective calmness, for example, subjects felt more excited after the use. Impaired memory function was consistently observed after all drug conditions, whereas impairment of psychomotor function and attention was less consistent across drug conditions.
MDMA	Vollenweider et al. 2005	42 healthy subjects ± 21-38 years 32M/10F	Cross-over, randomized study, where participants received either a placebo or 1.5 mg/kg of MDMA. Decision-making characteristics were evaluated, and results were obtained with error rates of 20%, 50% and 80%. Decision-making characteristics were analyzed using mutual information and mean dynamic entropy. Self-assessment of MDMA-induced psychological state was also obtained.	AMRS; ASC; two-choice prediction task.	Results suggest that acute MDMA administration affects response selection related to success during decision-making. Specifically, MDMA increased the degree to which the previous response predicted the current response and the average predictability of the response sequence with low error rates. MDMA also increased the degree to which the previous stimulus influenced current response selection at all error rates. However, MDMA did not significantly alter basic response characteristics such as latency or response switching. Self-assessment of MDMA-induced psychological state did not predict MDMA-induced decision-making patterns.
MDMA; ethanol	Lamers et al. 2003	12 healthy subjects - 8M/4F	Three-way crossover, double-blind, double-dummy, placebo-controlled study to evaluate the effects of a single dose of MDMA, and alcohol on cognitive function, psychomotor performance, and driving-related task performance.	SDT; TOL; CTT; DAT; OMEDA; MCRT; Word Fluency.	The results showed that a single dose of MDMA improved psychomotor performance such as movement speed and tracking performance in a test (DAT). However, MDMA impaired the ability to predict object motion under divided attention, which may indicate impairment of specific performance skills relevant to driving. There was no effect of MDMA on visual search, planning or semantic memory retrieval. The study found no serious adverse effects and none of the subjects required special care

					during or after the experimental sessions.
MDE	Spitzer et al. 2001	5 healthy subjects - Only males	Randomized double-blind design	WCST; visual pop-out search task; semantic priming task; colour and semantic discrimination task; self-rating scales.	The study demonstrated differential effects on various measures assessing alterations of psychopathology, neuropsychological performance and brain activation patterns after ingestion of (R)- and (S)-MDE. Together with the differential psychological effects of the agent, it is suggested that any future medical applications of MDE within the framework of psychotherapeutic interventions should make use of the (S)-enantiomer only.
MDE; Psilocybin; d-methamphetamine	Gouzoulis-Mayfrank et al. 1999	32 healthy subjects 27-47 years 21M/11F	Double-blind, placebo-controlled neurometabolic design w/ FDG PET study.	Word association task (activation scan) and word repetition task (control scan).	There were no diferences in the total number of overtly spoken words in repetition tasks. In the association task, subjects on psilocybin produced fewer words than the placebo group. Subjects on MDE produced slightly fewer. However, these deficits were not significant. There were no significant deficits between the number of words produced in the three equal parts of the deficit activation periods.
MDE	Schreckenberer et al. 1998	16 healthy subjects	Randomized double-blind trial.	18-FDG PET	The study used 18-FDG PET to measure cerebral glucose deficit and compared the results between the MDE and placebo groups. It was showed a significantly decreased in the bilateral frontal córtex under MDE. However, was concluded that the PET use provides indirect measurements of cerebral glucose deficit and may have limitations in accurately capturing complex metabolic processes in the brain.

Abbreviations: M: male subjects; F: female subjects; mg: milligrams; μg/mcg: micrograms; 5-HT2A: serotonergic receptor; MDMA: 3,4-methylenedioxymethamphetamine; MPH: methylphenidate; THC: Δ9-tetrahydrocannabinol; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; ASC: Alteration of Consciousness Questionnaire; RMET: Reading the Mind in the Eyes Test; SBTGQ: Social Ball Tossing Game Questionnaire; WLT: Word Learning Task; NART: National Adult Reading Test; SDT: Signal Detection Task; TOL: Tower of London; CTT: Critical Screening Test; DAT: Divided Attention Test; OMEDA: Moving Object Estimation Test under Divided Attention; MCRT: Motor Choice Reaction Time; PAL: Pair Associative Learning Task; AMRS: Adjective Mood Rating Scale; MET: Multifaceted Empathy Test; IRI: Interpersonal Reactivity Index; SVO: Social Values Orientation; FERT: Facial Expression Recognition Task; MJT: Moral Judgement Task; AAT: Approach-Avoidance Task; PET: Positron emission tomography; fMRI: Functional magnetic resonance imaging; WTT: Welfare Trade-Off Task; SAT: Sexual Satisfaction Inventory; CAT: Couples Appraisal Task; POMS: Profile of Mood States; PAST: Affective Sound Processing Task; ARCI: Addiction Research Central Inventory; SADI: Sexual Satisfaction and Desire Inventory; PD: The prisoner's dilemma; EAC's: Altered States of Consciousness; BLMRS: Bond and Lader Mood Rating Scale; SDST: Symbol Digit Substitution Test; SDRT: Symbol Digit Recall Test; STAI: State-Trait Anxiety Questionnaire; EEG: Electroencephalogram; VAS: Visual Analogue Scale; NEO-FFI: Neuroticism, Extraversion, Openness-Five Factor, Mood States; PAST: Affective Sound Processing Task; ARCI: Addiction Research Central Inventory; SADI: Sexual Satisfaction and Desire Inventory; PD: The prisoner's dilemma; EAC's: Altered States of Consciousness; BLMRS: Bond and Lader Mood Rating Scale; SDST: Symbol Digit Substitution Test; SDRT: Symbol Digit Recall Test; STAI: State-Trait Anxiety Questionnaire; EEG: Electroencephalogram; ANOVA: analysis of variance; VAS: Visual Analogue Scale; NEO-FFI: Neuroticism, Extraversion, Openness-Five Factor; WCST: Wisconsin Card Sorting Test. Source: Authoors.

Psilocybin was investigated in fourteen (14) studies (Table 2).

Table 2 - Psilocybin.

Drug(s)	Authors/Year	Sample (N/Age/ Gender)	Methods	Measurements	Results
Psilocybin Mescaline; LSD	Ley et al. 2023	32 healthy subjects 25-44 years 16M/16F	Randomized, double-blind, placebo-controlled, cross-over design	VASs; AMRS; 5D-ASC; SOCQ.	The study compared the acute effects of mescaline, LSD, and psilocybin in healthy participants. The subjective effects of the three substances were found to be comparable at psychoactive-equivalent doses. The study found no evidence of qualitative differences in altered states of consciousness induced by equally doses of mescaline, LSD, and psilocybin. The subjective experience did not significantly differ between the three substances. The study supports dose finding for research and psychedelic-assisted therapy, indicating that these substances can be used in a controlled and monitored setting for therapeutic purposes.
Psilocybin	Cavanna et al. 2022	34 healthy subjects ± 18-65 years 23M/11F	Double-blind placebo-controlled experimental study to investigate the acute and short-term effects of microdosing with psilocybin mushrooms. The study measured subjective experience, behavior, creativity, perception, cognition, and neuronal activity in response to a low dose of psilocybin mushrooms (0.5 g of dried mushrooms).	Go/no-go test; Stroop test; BFI; STAI-T; STAI-S; SSS; PANAS; MWQ; PSS; TAS; BIEPS; FSS; CPS; TECA; CFS; RAT; AUT; WK.	Low doses of psilocybin mushrooms may result in noticeable subjective effects and altered EEG rhythms, but without evidence to support increased well-being, creativity, and cognitive function. The reported acute effects were significantly more intense for the active dose compared to placebo, but only for participants who correctly identified their experimental condition. According to the results, the expectation underlies at least some of the anecdotal benefits attributed to microdosing with psilocybin mushrooms.
Psilocybin	Mason et al. 2021	60 healthy subjects	Double-blind, placebo-controlled, parallel-group study. Sixty participants were randomly assigned to receive psilocybin or placebo. Participants were screened for any medical or psychiatric conditions and that they were not taking any substances that could interfere with the study. The effects of psilocybin on creative thinking have been measured using a variety of tests. Brain imaging has also been used to investigate the neural mechanisms underlying psilocybin's effects on creative thinking.	PCT; AUT; 5D-ASC; fMRi.	Psilocybin induced a differentiation of effects related to time and the construction of creative thinking. Acutely, psilocybin increased ratings of spontaneous creative insights while decreasing deliberate task-based creativity. Seven days after psilocybin, the number of new ideas increased. Furthermore, the study found that acute and persistent effects were predicted by connectivity within and between networks of the default mode network.
Psilocybin	Smigielski et al. 2020	17 healthy subjects ± 25.1 years 9M/8F	Double-blind, placebo-controlled, within-subject design with a counterbalanced order of administration. A verbal self-monitoring task involving vocalizations and participant identification of real-time auditory source- (self/other) and pitch-modulating feedback. Subjective experience and task performance were analyzed, with time-point-by-time-point assumption-free multivariate randomization statistics applied to the spatiotemporal dynamics of event-related potentials.	5D-ASC; EEG.	The study found that psilocybin induce shifts in perception and alter self-referential processing. Also, it was showed that psilocybin abolishes distinctiveness of self-related scalp configurations via P300-related mechanisms. Moreover, psilocybin affected self-other processing by modulating the activity in the supragenual cingulate cortex and insula.
Psilocybin	Prochazkova et al. 2018	38 healthy subjects	The study investigated the effects of microdosing	RPM; PCT; AUT.	Results showed that convergent and divergent thinking performance improved after a non-

		±31.5 years 23M/15F	psychedelic mushrooms on creativity-related problem-solving tests. The study was conducted during a microdosing event organized by the Dutch Psychedelic Society. Participants were tested once before taking a microdose and once while waiting for the effects to manifest. Two creativity-related problem-solving tasks were used to assess convergent and divergent thinking performance, respectively. Changes in fluid intelligence were also assessed. The mushrooms were subsequently analyzed to quantify active psychedelic alkaloids, including psilocin, psilocybin, norbaeocystin, and baeocystin. The study was unblinded, meaning participants were aware they were taking a microdose.		blind microdose of psychedelic mushrooms, while fluid intelligence was unaffected. The effect of time point was significant, due to better performance in the second than in the first session. The study provides quantitative support for the cognitive-enhancing properties of microdosed psychedelics, but future research is needed to confirm these preliminary findings in more rigorous placebo-controlled study designs. Based on these preliminary results, the authors speculate that psychedelics may affect cognitive metacontrol policies by optimizing the balance between cognitive persistence and flexibility.
Psilocybin; DXM	Barrett et al. 2018	20 healthy subjects ± 28.5 years 9M/11F	Double-blind, placebo-controlled, within-subject study in which participants completed neuropsychological assessments during five blind drug administration sessions (10, 20 and 30 mg/70 kg psilocybin; 400 mg/70 kg DXM; and placebo). The study evaluated effects across several cognitive as well as subjective domains that have been reported elsewhere.	6-point confidence scale; Circular lights task; balance task; CNB; Stroop Test; PLOT; DSST; MMSE; mpraxis task; word-encoding and recognition task; letter n-back task	Psilocybin exerted D-D effects across multiple cognitive domains, including psychomotor performance, working memory, episodic memory, associative learning, and visual perception. However, there was no evidence of psychological impairment or delirium with psilocybin or DXM. DXM had greater effects than all doses of psilocybin on balance, episodic memory, response inhibition, and executive control. The study reported no significant adverse effects of psilocybin or DXM on cognitive function.
Psilocybin	Pokorny et al. 2017	32 healthy subjects ±20-38 years 17M/15F	Double-blind, randomized, placebo-controlled, within-subject design.	MET; MDT; IRI; 5D-ASC; PANAS.	The study found that psilocybin increased emotional empathy but did not affect cognitive empathy or moral behavior in healthy subjects. Furthermore, the increase in emotional empathy scores was predicted by the changed meaning of percepts scores, as measured by the 5D-ASC scale. These findings suggests that psilocybin have potential therapeutic benefits for individuals with déficits in social skills and empathy.
Psilocybin	Kometer et al. 2013	15 healthy subjects ≅ 26 years 11M/4F	Double-blind, placebo-controlled, within-subject, randomized design.	5D-ASC; EEG	Psilocybin strongly decreased prestimulus parieto-occipital alpha power values, thus precluding a subsequent stimulus-induced alpha power decrease. Furthermore, psilocybin strongly decreased N170 potentials associated with the appearance of visual perceptual alterations, including visual hallucinations. All of these effects were blocked by pretreatment with the 5-HT2A antagonist ketanserin, indicating that activation of 5-HT2A receptors by psilocybin profoundly modulates the neurophysiological and phenomenological indices of visual processing.
Psilocybin	Carhart-Harris et al. 2012a	15 healthy subjects ≅ 34 years 10M/5F (ASL) 13M/2F (BOLD)	Functional MRI (fMRI) techniques and a protocol to designed to image the transition from normal waking consciousness to the psychedelic state.	ASL perfusion, BOLD	Psilocybin significantly decreased brain blood flow and venous oxygenation in a manner that correlated with its subjective effects, and significantly decreased the positive coupling of two key structural hubs. It is therefore possible that phasic or

					shortterm effects of psilocybin show some rebound that is detected by longer-term changes in glucose metabolism. The pharmaco-physiological interaction results were particularly intriguing, revealing significant decreases in the positive coupling between the the posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC) after psilocybin. The results suggest decreased activity and connectivity in the brain's connector hubs, permitting an unconstrained style of cognition.
Psilocybin	Carhart-Harris et al. 2012b	10 healthy subjects ≅ 31 years 9M/1F	Placebo-controlled cross-over study.	Fifteen memory cues were presented in a blocked paradigm, interleaved with rest and an auditory attention task with two functional magnetic resonance imaging scans (fMRI) separated by seven days.	Robust activations to autobiographical memory cues were found after both placebo and psilocybin, but greater late phase sensory activations and more intense subjective effects were seen after psilocybin. Greater activations were observed in the bilateral auditory cortex, somatosensory cortex, superior parietal cortex, left visual association regions and the occipital pole after psilocybin, and post-hoc tests confirmed that visual and other sensory regions were uniquely activated under psilocybin. These effects may have implications for the use of psilocybin in psychotherapy.
Psilocybin	Wittmann et al. 2007	12 healthy subjects - -	Double-blind experimental study to investigate the effects of psilocybin on temporal processing. The study employed tests of temporal reproduction, sensorimotor synchronization, and rhythm tapping to evaluate the impact of psilocybin on timing performance. Various tests were used to evaluate the subjective effects of psilocybin. The study also assessed spatial working memory and conscious experience to control for cognitive and subjective changes.	SSP; 5D-ASC; AMRS.	Psilocybin significantly impairs the ability to reproduce intervals lasting longer than 2.5 seconds, to synchronize interbeat intervals longer than 2 seconds, and causes subjects to be slower at their preferred beat rate. These objective effects on time performance were accompanied by working memory impairments and subjective changes in conscious state, i.e., increased reports of 'depersonalization' and 'derealization' phenomena, including disturbances in the subjective 'sense of time'. The study suggests that the serotonergic system is selectively involved in processing interval durations longer than 2 to 3 seconds and in voluntary control of movement speed.
Psilocybin	Hasler et al. 2004	8 healthy subjects 22-44 years 4M/4F	The study investigated the effects of administering different doses of psilocybin to participants and measuring the effects on various psychological and physiological parameters. The study was based on a double-blind, placebo-controlled experiment, and the different doses of psilocybin were administered in random order. Psychological parameters were assessed using several tests. Physiological parameters measured included blood pressure, electrocardiogram, and plasma levels of various hormones and clinical chemical parameters.	5D-ASC; AMRS; FAIR.	The results of the article showed that psilocybin increased the D-D shape scores of all core dimensions of the EACs. Only one subject reacted with transient anxiety to the high dose of psilocybin. Compared to placebo, medium and high doses of psilocybin led to a 50% reduction in performance on the FAIR test. "General inactivation," "emotional arousal," and "dreaminess" were the only domains of the AMRS scale showing increased scores after medium and high doses of psilocybin. Mean arterial pressure was moderately elevated 60 minutes after administration of the high dose of psilocybin. Neither electrocardiogram nor body temperature were affected by any dose of psilocybin. Plasma levels of thyroid-stimulating hormone, adrenocorticotropic hormone, and cortisol were elevated during the peak effects of high-dose psilocybin, while plasma prolactin levels increased after medium and high doses of psilocybin.
Psilocybin;	Gouzoulis-Mayfrank et al. 1999	32 healthy subjects 27-47 years	Double-blind, placebo-controlled neurometabolic design w/ FDG PET study.	Word association task (activation scan)	There were no diferences in the total number of overtly spoken words in repetition tasks. In the association task, subjects on psilocybin

MDE; d-methamphetamine		21M/11F		and word repetition task (control scan).	produced fewer words than the placebo group. Subjects on MDE produced slightly fewer. However, these deficits were not significant. There were no significant deficits between the number of words produced in the three equal parts of the deficit activation periods.
Psilocybin Dextro-amphetamine	Duke; Keeler, 1968	8 healthy subjects - Only male	Randomized double-blind, placebo-controlled trial	Trail Making Test	The study shows that psilocybin produces a deficit in performance as compared to placebo. In addition, the demonstration that psilocybin significantly impairs performance of the complex task as compared to the simple task suggests that drug induced muscular incoordination is not responsible for decrements in performance.

Abbreviations: M: male subjects; F: female subjects; mg: milligrams; 5-HT2A: serotonergic receptor; MDE: 3,4-methylenedioxyethylamphetamine; LSD: lysergic acid diethylamide; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; n-back task: Continuous Performance Task; AMRS: Adjective Mood Rating Scale; MET: Multifaceted Empathy Test; IRI: Interpersonal Reactivity Index; PANAS: Positive and Negative Affect Scale; DXM: dextromethorphan; D-D: dose-dependent; PLOT: Penn Line Orientation Test; DSST: Digit Symbol Substitution Task; MMSE: Mini Mental State Examination; BOLD: blood-oxygen level-dependent; PCT: Picture-Concept Task; AUT: Alternative Uses Task; BFI: Five Personalities Inventory; STAI: State-Trait Anxiety Questionnaire; SSS: Short Suggestionability Scale; MWQ: Distraction Scale; PSS: Perceived Stress Scale; FSS: Flow State Scale; CPS: Creative Personality Scale; TECA: Cognitive-Affective Empathy Test; CFS: Cognitive Flexibility Scale; RAT: Remote Association Test; WK: Wallach-Kogan Test; EEG: Electroencephalogram; VAS: Visual Analogue Scale. Source: Authors.

Lysergic acid diethylamide (LSD-25) appeared in six (6) studies analyzed (Table 3).

Table 3 - Lysergic acid diethylamide (LSD).

Drug(s)	Authors/Year	Sample (N/Age/Gender)	Methods	Measurements	Results
LSD Mescaline Psilocybin	Ley et al. 2023	32 healthy subjects 25-44 years 16M/16F	Randomized, double-blind, placebo-controlled, cross-over design	VASs; AMRS; 5D-ASC; SOCQ.	The study compared the acute effects of mescaline, LSD, and psilocybin in healthy participants. The subjective effects of the three substances were found to be comparable at psychoactive-equivalent doses. The study found no evidence of qualitative differences in altered states of consciousness induced by equally doses of mescaline, LSD, and psilocybin. The subjective experience did not significantly differ between the three substances. The study supports dose finding for research and psychedelic-assisted therapy, indicating that these substances can be used in a controlled and monitored setting for therapeutic purposes.
LSD	De Wit et al. 2022	56 healthy subjects ± 19-35 years 37M/19F	Double-blind controlled study to investigate the effects of repeated low doses of LSD on mood, cognitive performance and responses to emotional tests. The study involved four 5-hour drug administration sessions separated by 3-4 days, followed by a drug-free follow-up session 3-4 days after the last session. Participants were randomly assigned to one of three groups: placebo, 13 µg LSD, or 26 µg LSD. The drug's effects were measured using subjective assessments, cognitive and emotional tests.	POMS; PANAS; DASS; ARCI; 5-ASC; End-of-Session Questionnaire; Drug Effects Questionnaire	Repeated low doses of LSD (13 or 26 µg) produced no significant changes in participants' mood or cognitive performance. LSD (26 µg) produced modest subjective effects, including ratings of enhancement in 'feeling a drug high' and stimulant-like and LSD-like effects, but did not improve mood or affect performance on psychomotor or emotional tests. No residual effects were detected on mood or test performance in the drug-free follow-up session. The study concluded that, in the context of a controlled environment and with a limited number of administrations, repeated low doses of LSD are safe but produce negligible changes in mood or cognition in healthy individuals.
LSD	Hutten et al. 2020	24 healthy subjects ± 22.8 years 12M/12F	Placebo-controlled, within-subject study to evaluate the acute effects of three different doses of LSD (5, 10, and 20 mcg) on measures of cognition, mood, and subjective experience. Participants completed a battery of cognitive tests and questionnaires to assess	PVT; DSST; CCT; POMS; VAS; 5D-ASC; EDI; GSS.	Results showed that low doses of LSD (5, 10, and 20 mg) had selective and beneficial effects on mood and cognition in most observations. Positive effects included an improvement in positive mood, friendliness, excitement, and a decrease in lapses in attention. Negative effects included an increase in confusion and anxiety. Psychedelic-induced changes in waking consciousness were also present. Overall, the study demonstrated that low doses of LSD can have positive effects on mood and cognition, but more research is needed to determine the long-term effects and safety of microdosing with LSD.

Drug(s)	Authors/Year	Sample (N/Age/Gender)	Method	Measurements	Results
			their mood and subjective experience up to 6 hours after LSD administration.		
LSD	Schmidt et al. 2018b	18 healthy subjects ±25-58 years 9M/9F	Double-blind, randomized, placebo-controlled, crossover study. The study administered LSD (100 µg) and placebo to participants and evaluated response inhibition with tests (Go/No-Go) and fMRi. The study also used the 5D-ASC questionnaire to measure LSD-induced "visual hallucinations."	5D-ASC; Go/No-go Task; fMRI.	The results showed that LSD administration impaired inhibitory performance and reduced neuronal activity in several regions, including the right middle temporal gyrus, superior/middle/inferior frontal gyrus, left anterior cingulate and superior frontal cortex, and left postcentral gyrus and cerebellum. The study also found that parahippocampal activation during response inhibition was differentially related to inhibitory performance after placebo and LSD administration. Finally, activation in the left superior frontal gyrus under LSD exposure was negatively related to LSD-induced cognitive and visual imagery impairments. These findings suggest that activation of 5-HT2A by LSD leads to a disruption of inhibitory processing mediated by the hippocampal prefrontal cortex, which may subsequently promote LSD-induced visual image formation.
LSD	Roseman et al. 2016	10 healthy subjects - 6M/4F	Subjects attended to two scanning days (LSD and placebo) at least 2 weeks apart in a balanced order, within-subjects design.	RSFC; ASL; BOLD; ASC.	The study found that under the influence of LSD, the visual cortex behaves as if it is processing spatially localized visual information. LSD altered eyes-closed functional connectivity within the early visual cortex in a retinopic fashion. Patches of visual cortex with congruent retinotopic representation showed greater resting-state functional connectivity (RSFC) than patches with incongruent representations.
LSD	Goldberger, L., 1966	42 healthy subjects - -	Randomized double-blind, placebo-controlled trial	Digit Span; Iowa Silent Reading Test; Robinson Tests; Word-naming; Serial Sevens; Simple Rhyming.	Results showed no similarity between isolation and LSD effects, at least on a quantitative basis. Therefore, the quality and intensity differed: the loss of time sense, and concentration difficulties would be more profound in LSD. The study conclude that eight (8) hours of isolation does not produce significant group effects of either impairment or improvement, at least not with the kinds of tests so far employed.

Abbreviations: M: male subjects; F: female subjects; µg/mcg: micrograms; 5-HT2A: serotonergic receptor; LSD: lysergic acid diethylamide; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; ASC: Alteration of Consciousness Questionnaire; RSFC: Resting-state functional connectivity; BOLD: blood-oxygen level-dependent; ASL: Arterial Spin Labelling; fMRI: Functional magnetic resonance imaging; MLG: Generalized Linear Model; ANOVA: analysis of variance; GSS: Groeninger Sleep Scale; EDI: Ego Dissolution Inventory; PVT: Psychomotor Vigilance Task; DSST: Digit Symbol Substitution Task; POMS: Profile of Mood States; CCT: Cognitive Control Test; VAS: Visual Analogue Scale; PANAS: Positive and Negative Affect Scale; DASS: Depression, Anxiety and Stress Scale; ARCI: Addiction Research Central Inventory; AMRS: Adjective Mood Rating Scale; SOCQ: States of Consciousness Questionnaire. Source: Authors.

Traditional indigenous medicine and other substances were also investigated: mescaline (2 studies), S-ketamine (1 study), ketamine (1 study), dimethyltryptamine (DMT) (1 study), ibogaine (1 study), and ayahuasca (2 studies) (Table 4).

Table 4 - Ayahuasca and N,N-dimethyltryptamine (DMT), Ketamine, Ibogaine and Mescaline.

Drug(s)	Authors/Year	Sample (N/Age/Gender)	Method	Measurements	Results
Ayahuasca	Rossi et al. 2023	17 healthy subjects ± 20-36 years -	Proof-of-concept, randomized, double-blind, placebo-controlled design evaluated the effects in social cognition variables, subjective measurements, safety, and tolerability after administration of CBD or placebo, followed by a single dose of ayahuasca.	REFE task; MET; VAMS.	The study found significant reductions in reaction times for emotion recognition tasks in both the ayahuasca and CBD groups without significant differences between the groups. Both groups showed significant reduction in anxiety, sedation, cognitive deterioration, and discomfort. The study suggests that both drugs could be applied to clinical populations with anxiety disorders, and further trials with larger samples are needed to confirm these findings.
Ayahuasca	Rocha et al. 2021	22 healthy subjects ± 28.5 years 15M/7F	Randomized, double-blind, placebo-controlled, parallel-group study. The study evaluated the effects of a single dose of ayahuasca during a cognitive test of emotion recognition in facial expressions, as well as subjective effects, tolerability measures and plasma BDNF levels. The test was performed before and after drug ingestion, and	REFE.	Results showed that a single dose of ayahuasca did not significantly modify the recognition of emotions in facial expressions compared to placebo. The study also found that ayahuasca was well tolerated, mainly producing nausea, gastrointestinal discomfort and vomiting. Participants reported visual effects, tranquility/relaxation, and well-being, with few reports of anxiety and transient confusion. No significant effects were observed on cardiovascular measures and BDNF levels. The study also found a significant deterioration of

			again at various times up to 3 months after drug ingestion. The study also evaluated the stability of ayahuasca alkaloids during the study period.		alkaloids, especially for dimethyltryptamine (DMT), dependent on metabolization time.
DMT; S-ketamine	Daumann et al. 2010	14 healthy subjects ± 26-42 years 8M/6F	An event-related, randomized, double-blind, crossover, fMRi study was designed to investigate the effects of DMT and S-ketamine during alert states. A target detection test with visual and auditory cues was used to capture neuronal correlates of phasic alertness. The effects of DMT and S-ketamine on alertness in participants were investigated using a target detection test with visual and auditory cues.	HRS; APZ-OAV.	Results showed that DMT administration led to decreased neuronal activation during task performance, particularly in extrastriate regions during visual alerting and in temporal regions during auditory alerting. In contrast, S-ketamine administration led to increased cortical activation in the left insula and precentral gyrus in the auditory modality.
Ketamine	Lofwall et al. 2006	18 healthy subjects ± 24 years 8M/10F	Single doses of intramuscular injections of ketamine or placebo were administered to participants in a double-blind, placebo-controlled, crossover study. The effects of ketamine on memory, working memory, time estimation, psychomotor performance, and subjective experience were assessed repeatedly for 5 hours after drug administration. Various cognitive tests were used to evaluate the effects of ketamine on memory, attention, and psychomotor performance. The study also evaluated the subjective effects of ketamine using questionnaires.	n-back task; VAS; 6-point confidence scale; Goodman Kruskal gamma correlation; HRS; M-Scale; Episodic Memory Task; DSST.	Results showed that ketamine selectively impaired encoding while sparing retrieval (Episodic Memory Task), working memory while sparing attention, and Digit Symbol Substitution Test (DSST) speed while sparing accuracy. Ketamine did not significantly impair recognition or source memory, metamemory, or time estimation. The study also found that memory measures were less sensitive to the effects of ketamine than subjective or psychomotor measures. The subjective effects lasted longer than memory and most psychomotor impairments. Overall, the study suggests that ketamine produces selective, transient, dose- and time-related effects on memory, attention, psychomotor performance, and subjective experience.
Ibogaine	Forsyth et al. 2016	21 healthy subjects ± 20-40 years Only male	Randomized, double-blind, placebo-controlled study with participants who received a single dose of 20 mg of ibogaine after 6 days of pre-treatment with paroxetine, double-blind or placebo. The study evaluated the influence of ibogaine on psychological variables that reflect mood and cognitive functions using a battery of psychometric tests.	The article does not specify the evaluation method but reports that responses were compared to a battery of psychometric tests and subjective mood ratings performed before and 2 hours after ibogaine dosing. Psychological tests were chosen based on the responsiveness to opioid and serotonergic ligands.	Results suggest that a single 20 mg dose of ibogaine had minimal influence on psychological tests and mood assessments. The ability to selectively ignore distracting spatial information showed some evidence of modulation; however, this effect was limited to the least challenging condition, which casts doubt on the reliability of this result. The study was unable to identify stimulant effects after single doses of 20 mg of ibogaine.
Mescaline; LSD; Psilocybin	Ley et al. 2023	32 healthy subjects 25-44 years 16M/16F	Randomized, double-blind, placebo-controlled, cross-over design	VASs; AMRS; 5D-ASC; SOCQ.	The study compared the acute effects of mescaline, LSD, and psilocybin in healthy participants. The subjective effects of the three substances were found to be comparable at psychoactive-equivalent doses. The study found no evidence of qualitative differences in altered states of consciousness induced by equally doses of mescaline, LSD, and psilocybin. The subjective experience did not significantly differ between the three substances. The study

					supports dose finding for research and psychedelic-assisted therapy, indicating that these substances can be used in a controlled and monitored setting for therapeutic purposes.
Mescaline	Halpern et al. 2005	3 groups of the Navajo ethnic group, in which: 61 belong to the NAC religion and consume peyote regularly. 36 individuals with alcohol dependence, but sober for 2 months. 79 individuals who use peyote, alcohol, or another substance. ± 18-45 years Only male	The study recruited three groups of Navajo Indians, including NAC members who regularly ingested peyote, individuals with alcohol dependence, and a comparison group reporting minimal use of any substance. The researchers then administered a screening interview and ten neuropsychological tests of memory and attentional/executive functions to each participant. The study was a cross-sectional design, and all assessments were conducted on the Navajo Nation reservation.	Stroop test; RMHI; WRAT-3; WAIS- R; ROCF; WCST; WMS; RPM; Trails Make A and B	The results of the article showed that Navajo Indians who regularly ingested peyote in a religious setting did not exhibit significant cognitive impairments compared to those with minimal substance use. However, individuals with past alcohol dependence showed significant deficits on the RMHI and two neuropsychological measures. The study suggests that peyote use in a religious context may not have long-term residual psychological or cognitive effects.

Abbreviations: M: male subjects; F: female subjects; mg: milligrams; µg/mcg: micrograms; CBD: Cannabidiol; DMT: N,N-dimethyltryptamine; LSD: lysergic acid diethylamide; BDNF: brain-derived neurotrophic factor; REFE: Facial Expression Emotion Recognition Test; MET: Multifaceted Empathy Test; APZ-OAV: Mental Abnormality Status Test; VAMS: Visual Analog Mood Scale; HRS: Hallucinatory Rating Scale; fMRI: Functional magnetic resonance imaging; n-back task: Continuous Performance Task; VAS: Visual Analogue Scale; DSST: Digit Symbol Substitution Task; 5-HT2A: serotonergic receptor; 5D-ASC: 5-Dimensional Altered States of Consciousness Rating Scale; WAIS- R: Wechsler Adult Intelligence Scale – Revised; RMHI: Mental Health Status Assessment Inventory; RPM: Raven Progressive Matrices; WRAT-3: Wide Range Achievement Test-3; ROCF: Rey-Osterreith Complex Figure Test; WMS: Wechsler Memory Scale; RSFC: Resting-state functional connectivity; NAC: Native American Church; AMRS: Adjective Mood Rating Scale; SOCQ: States of Consciousness Questionnaire. Source: Authors.

Eleven (11) studies compared psychedelic serotoninergic drugs with each other, or with another type of drug, like modafinil, pindolol, ethanol, methylphenidate (MPH), Δ9-tetrahydrocannabinol (THC), among others.

Thirty-six (36) studies investigated male and female subjects, with prevalence for male subjects. Five (5) studies were performed with male subjects. The ages of the subjects ranged from 18-65 years of age. Thirty-six (36) articles chose the double-blind, randomized, placebo-controlled clinical trial strategy as their main evaluation method (Ley, et al., 2023; Rossi, et al., 2023; De Wit, et al., 2022; Cavanna, et al., 2022; Rocha, et al., 2021; Mason, et al., 2021; Holze, et al., 2021; Smigielski, et al., 2020; Gabay, et al., 2019; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Haijen, et al., 2018; Dolder, et al., 2018; Barrett, et al., 2018; Schmidt, et al., 2017; Pokorny, et al., 2017; Forsyth, et al., 2016; Kirkpatrick, et al., 2015; Schmid, et al., 2015; Schmid, et al., 2014; Hysek, et al., 2014; Kometer, et al., 2013; Lansbergen, et al., 2011; Daumann, et al., 2010; Bedi, et al., 2010; Hasler, et al., 2009; Dumont, et al., 2008; Wittmann, et al., 2007; Lofwall, et al., 2006; Hasler, et al., 2004; Lamers, et al., 2003; Spitzer, et al., 2001; Gouzoulis-Mayfrank, et al., 1999; Schreckenberger, et al., 1998; Duke & Keeler, 1968; Goldberger, L., 1966). Some studies added other interventions to research in order to more rigorously assess the levels of safety or effectiveness of the aspects studied, for example: sixteen (16) studies used crossing techniques (cross-over design) to compare the effects of different treatments or interventions in the same group of participants (Ley, et al., 2023; Holze, et al., 2021; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Dolder, et al., 2018; Schmid, et al., 2015; Schmid, et al., 2014; Hysek, et al., 2014; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Daumann, et al., 2010; Dumont, et al., 2008; Lofwall, et al., 2006; Vollenweider, et al., 2005; Halpern, et al., 2005; Lamers, et al., 2003).

Thirteen (13) studies used within-subject procedures (Smigielski, et al., 2020; Hutten, et al., 2020; Schmidt, et al., 2018a; Kuypers, et al., 2018; Haijen, et al., 2018; Barrett, et al., 2018; Schmidt, et al., 2017; Pokorny, et al., 2017; Roseman, et al., 2016; Kuypers, et al., 2014; Kometer, et al., 2013; Bedi, et al., 2010; Hasler, et al., 2009), in which each participant is exposed to all independent variable levels in random order. This intervention allows each participant to serve as their own control, thus

increasing the statistical power of the study and reducing the effects of individual differences between participants. Three (3) studies used dose-response/dose-effect design techniques to gradually assess psychological and physiological effects (Holze, et al., 2021; Barrett, et al., 2018; Hasler, et al., 2004). Two (2) studies used the double-dummy technique, in which the inactive placebo has similar perceptual effects to the studied drug, for example: smell or taste, with the intention of further reducing the possibility of bias (Haijen, et al., 2018; Lamers, et al., 2003). Three (3) studies used the counterbalanced technique (Smigielski, et al., 2020; Gabay, et al., 2019; Vollenweider, et al., 2005), in which the order of presentation of the experimental conditions is systematically varied between participants to ensure that each condition displayed an equal number of times in each position.

3.3 Main results

Tables 1-4 also present the main results found. Forty-six (46) studies were selected and included different cognitive and subjective task-based evaluations with healthy subjects. Fifteen (15) studies used the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), to assess the subjective effects of hallucinogenic substances in experimental sessions. The 5D-ASC is a standardized questionnaire composed of 94 items to be answered on visual analogue scales where there are items that address concepts about: experience of unity with the whole, spiritual experience, state of bliss, perspicacity, disincarnation, control and cognition impaired, anxiety, complex images, elementary images, audiovisual synesthesia and altered meaning of perceptions (Ley, et al., 2023; De Wit, et al., 2022; Mason, et al., 2021; Holze, et al., 2021; Smigielski, et al., 2020; Hutten, et al., 2020; Gabay, et al., 2019; Schmidt, et al., 2018b; Dolder, et al., 2018; Pokorny, et al., 2017; Schmid, et al., 2014; Kometer, et al., 2013; Hasler, et al., 2009; Wittmann, et al., 2007; Hasler, et al., 2004). Ten (10) studies used the Adjective Mood Rating Scale (AMRS), which assesses mood states based on a self-assessment with the help of adjectives (Ley, et al., 2023; Schmidt, et al., 2018a; Dolder, et al., 2018; Schmidt, et al., 2017; Schmid, et al., 2014; Hysek, et al., 2014; Hasler, et al., 2009; Wittmann, et al., 2007; Vollenweider, et al., 2005; Hasler, et al., 2004). The Visual Analog Scale (VAS) test was repeatedly used in seven (7) studies to assess subjective effects related to sociability, including categories such as: "feeling happy", "open" and "close to others" (Ley, et al., 2023; Holze, et al., 2021; Hutten, et al., 2020; Dolder, et al., 2018; Hysek, et al., 2014; Bedi, et al., 2010; Lofwall, et al., 2006). The Multifaceted Empathy Test (MET), which is a task that assesses different aspects of empathy, classified as: "cognitive and emotional", was the instrument used in six (6) studies (Rossi, et al., 2023; Gabay, et al., 2019; Pokorny, et al., 2017; Schmid, et al., 2014; Kuypers, et al., 2014; Hysek, et al., 2014). Four (4) studies also applied the psychometric test State/Trait Anxiety Questionnaire (STAI), used to measure emotional states of anxiety, and in one (1) study the STAI-T, which evaluates trait anxiety, and the STAI-S, which measures state anxiety, were used (Cavanna, et al., 2022; Schmidt, et al., 2018a; Dolder, et al., 2018; Hasler, et al., 2009). Also, the Facial Expression Emotion Recognition Test (FERT), which assesses the effects of substances on the recognition of basic facial emotions (i.e., happiness, sadness, anger, and fear) (Schmidt, et al., 2018a; Dolder, et al., 2018; Schmid, et al., 2014; Hysek, et al., 2014), as well as the mood self-assessment questionnaire Profile of Mood States (POMS), used to assess various mood states, such as tension, depression, anger, vigor, fatigue, and confusion (De Wit, et al., 2022; Hutten, et al., 2020; Kuypers, et al., 2018; Kuypers, et al., 2014; Bedi, et al., 2010); and the Positive and Negative Affect Scale (PANAS), a standardized questionnaire used to measure positive and negative affect, understood as two independent dimensions of mood (De Wit, et al., 2022; Cavanna, et al., 2022; Holze, et al., 2021; Pokorny, et al., 2017). The n-back task, or Continuous Performance Test, which consists of the sequential visual presentation of single letters, where subjects need to press a button when a target stimulus appears – the definition of the target differs in relation to the experimental conditions –, which appeared in two other articles (Barrett, et al., 2018; Lofwall, et al., 2006). The Interpersonal Reactivity Index (IRI), a self-assessment questionnaire used to measure notions of empathy (Pokorny, et al., 2017; Kuypers, et al., 2014; Hysek, et al., 2014); the Stroop Test, a neuropsychological test that measures concepts of selective attention and cognitive flexibility (Cavanna, et al., 2022; Barrett, et al., 2018; Halpern, et al., 2005); and the Go/No-go task, a computerized

test used to assess inhibitory control by the ability to inhibit an overbearing response to digital stimuli (Cavanna, et al., 2022; Schmidt, et al., 2018b; Schmidt, et al., 2017) were also adopted in three studies. In addition, the following instruments were used: Alternative Uses Task (AUT), used to assess the notion of "divergent thinking" (Cavanna, et al., 2022; Mason, et al., 2021; Prochazkova, et al., 2018); Moral Dilemma Task (MDT), a test that measures the extent to which research participants prioritize utilitarian (maximizing the greater good) or deontological (following rules and moral principles) considerations in their decision-making (Pokorny, et al., 2017); Social Value Orientation (SVO), which assesses an individual's social preferences, specifically their tendency to cooperate or compete with others in social situations. The test assesses an individual's willingness to share resources and make decisions that benefit themselves and others (Schmid, et al., 2014; Hysek, et al., 2014); Picture Concept Task (PCT), which is an instrument used to measure creative thinking, through notions of divergent and convergent thinking (Mason, et al., 2021; Prochazkova, et al., 2018); Digit symbol substitution task (DSST), which deals with neuropsychological assessment used to measure executive function, mental flexibility and associative learning (Hutten, et al., 2020; Barrett, et al., 2018; Lofwall, et al., 2006); Groninger Sleep Scale (GSS), this scale helps to assess the quality and quantity of sleep from the previous night (Hutten, et al., 2020; Haijen, et al., 2018; Kuypers, et al., 2014); Hallucinogenic Rating Scale (HRS), a self-rating scale on the psychological effects experienced by hallucinogenic drugs (Daumann, et al., 2010; Lofwall, et al., 2006); The Trust Game, which was used to assess the ability to infer another person's mental state and their ability to cooperate to make beneficial choices (Gabay, et al., 2019; Kuypers, et al., 2014); The Tower of London (TOL), a neuropsychological test used to assess planning and problem-solving skills (Lamers, et al., 2003). Apart from behavioral and subjective measurements, seventeen (17) of the selected studies also used neuroimaging methods such as functional magnetic resonance imaging (fMRi), positron emission tomography (PET), and Arterial Spin Labeling (ASL) to evaluate brain activity after drug or placebo administration (Ley, et al., 2023; Cavanna, et al., 2022; Mason, et al., 2021; Smigielski, et al., 2020; Gabay, et al., 2019; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Schmidt, et al., 2017; Roseman, et al., 2016; Carhart-Harris, et al., 2012a; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Daumann, et al., 2010; Daumann, et al., 2003; Spitzer, et al., 2001; Gouzoulis-Mayfrank, et al., 1999; Schreckenberger, et al., 1998). One (1) study (Kirkpatrick, et al., 2015) applied a five-variable personality trait test, the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI), which intended to examine scales of neuroticism, extraversion, openness, agreeableness, and conscientiousness.

In some studies (Mason, et al., 2021; Dolder, et al., 2018; Forsyth, et al., 2016), the cognitive tests used were not specifically detailed in the information provided. However, the procedures mostly focused on measuring working memory, selective attention, verbal memory, psychological well-being, and associative memory using fMRI or self-rating scales of psychological states. In one study (Hasler, et al., 2009), measures were applied with the intention of assessing cognitive performance. These are part of the battery of neuropsychological tests developed by the University of Cambridge, the CANTAB – Cambridge Neuropsychological Test Automated Battery. It is a battery of digital tests that aims to assess different cognitive domains, including attention, memory, and executive functions.

Some studies used criteria to ensure that the recruited subjects could be considered healthy: a) The practice of abstinence by the participants was requested in twenty-eight (28) of the analyzed studies (Ley, et al., 2023; Rossi, et al., 2023; De Wit, et al., 2022; Rocha, et al., 2021; Mason, et al., 2021; Holze, et al., 2021; Hutten, et al., 2020; Gabay, et al., 2019; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Kuypers, et al., 2018; Haijen, et al., 2018; Schmidt, et al., 2017; Pokorny, et al., 2017; Roseman, et al., 2016; Schmid, et al., 2015; Kirkpatrick, et al., 2015; Schmid, et al., 2014; Kuypers, et al., 2014; Hysek, et al., 2014; Kometer, et al., 2013; Carhart-Harris, et al., 2012a; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Bedi, et al., 2010; Dumont, et al., 2008; Lofwall, et al., 2006; Vollenweider, et al., 2005). Depending on the conditions of each methodological procedure, the abstinence time varied between hours before the tests started and could reach up to 3 months. In general, abstinence from licit drugs, such as alcohol, nicotine and caffeine were required. b) Two (2) articles did not admit subjects who

had gone through episodes of suicide attempts (De Wit, et al., 2022; Pokorny, et al., 2017); c) One (1) study left out people who had a criminal history (Lamers, et al., 2003); d) Another did not include people who had a formal job during the night period (Kirkpatrick, et al., 2015). e) Interestingly, some studies considered polydrug-using participants as healthy people (Kuypers, et al., 2018; Haijen, et al., 2018; Kuypers, et al., 2014; Lansbergen, et al., 2011; Lamers, et al., 2003); f) Eight (8) studies had as exclusion criteria volunteers who consumed more than 10 cigarettes per day (Dolder, et al., 2018; Schmidt, et al., 2018a; Schmidt, et al., 2017; Kirkpatrick, et al., 2015; Schmid, et al., 2015; Schmid, et al., 2014; Hysek, et al., 2014; Lofwall, et al., 2006). Broadly speaking, researchers considered participants healthy based on their medical (cardiopathies, hypertension, chronic diseases, chemical dependency, traumas) and psychiatric history, acquired either through self-report, interviews or through physical and laboratory examination.

The participation of female volunteers who were pregnant or breastfeeding was excluded for safety reasons in twenty-one (21) articles (Ley, et al., 2023; Rossi, et al., 2023; De Wit, et al., 2022; Rocha, et al., 2021; Holze, et al., 2021; Hutten, et al., 2020; Schmidt, et al., 2018b; Haijen, et al., 2018; Barrett, et al., 2018; Schmidt, et al., 2017; Pokorny, et al., 2017; Roseman, et al., 2016; Schmid, et al., 2015; Kirkpatrick, et al., 2015; Kuypers, et al., 2014; Carhart-Harris, et al., 2012a; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Bedi, et al., 2010; Lofwall, et al., 2006; Lamers, et al., 2003). The menstrual cycle conditions of female volunteers were mentioned in twelve (12) articles (De Wit, et al., 2022; Mason, et al., 2021; Holze, et al., 2021; Hutten, et al., 2020; Dolder, et al., 2018; Schmidt, et al., 2017; Kirkpatrick, et al., 2015; Schmid, et al., 2014; Hysek, et al., 2014; Hasler, et al., 2009; Vollenweider, et al., 2005; Hasler, et al., 2004).

Thirty-four (34) studies had participants who had previous experiences with psychedelic substances at least one time in life (Rossi, et al., 2023; Ley, et al., 2023; De Wit, et al., 2022; Cavanna, et al., 2022; Rocha, et al., 2021; Mason, et al., 2021; Holze, et al., 2021; Hutten, et al., 2020; Gabay, et al., 2019; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Prochazkova, et al., 2018; Kuypers, et al., 2018; Dolder, et al., 2018; Haijen, et al., 2018; Barrett, et al., 2018; Schmidt, et al., 2018; Pokorny, et al., 2017; Roseman, et al., 2016; Schmid, et al., 2015; Kirkpatrick, et al., 2015; Schmid, et al., 2014; Kuypers, et al., 2014; Hysek, et al., 2014; Carhart-Harris, et al., 2012a; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Bedi, et al., 2010; Hasler, et al., 2009; Dumont, et al., 2008; Wittmann, et al., 2007; Halpern, et al., 2005; Hasler, et al., 2004; Lamers, et al., 2003).

Five (5) studies addressed the phenomenon of microdosing, specifically analyzing the practice with the use of psilocybin mushrooms (2) and microdoses of LSD (3), apart from using batteries of cognitive tests in order to assess various self-reported measures of psychological traits such as mood, anxiety, depression, stress, well-being, and mindfulness (De Wit, et al., 2022; Cavanna, et al., 2022; Holze, et al., 2021; Hutten, et al., 2020; Prochazkova, et al., 2018).

Twenty-eight (28) articles highlighted the use of the "washout period" technique, that is, a rest interval between testing sessions to ensure that the effects of the previous treatment disappeared before the next test was administered and the participants did not develop a possible tolerance (Ley, et al., 2023; De Wit, et al., 2022; Cavanna, et al., 2022; Holze, et al., 2021; Smigielski, et al., 2020; Hutten, et al., 2020; Schmidt, et al., 2018a; Schmidt, et al., 2018b; Kuypers, et al., 2018; Haijen, et al., 2018; Barrett, et al., 2018; Dolder, et al., 2018; Pokorny, et al., 2017; Schmidt, et al., 2017; Schmid, et al., 2015; Kirkpatrick, et al., 2015; Schmid, et al., 2014; Hysek, et al., 2014; Kometer, et al., 2013; Carhart-Harris, et al., 2012b; Lansbergen, et al., 2011; Dumont, et al., 2008; Wittmann, et al., 2007; Lofwall, et al., 2006; Vollenweider, et al., 2005; Halpern, et al., 2005; Spitzer, et al., 2001; Duke & Keeler, 1968).

Sixteen (16) studies also used other substances to verify the potential for performance or cognitive enhancement in comparison or interaction with another psychedelic. Among the most used drugs are: modafinil, methylphenidate, alcohol, and dextromethorphan (DXM) (Rossi, et al., 2023; Dolder, et al., 2018; Haijen, et al., 2018; Barrett, et al., 2018; Kuypers, et al., 2018; Schmidt, et al., 2018a; Schmidt, et al., 2017; Schmid, et al., 2015; Schmid, et al., 2014; Kuypers, et al., 2014; Lansbergen,

et al., 2011; Daumann, et al., 2010; Hasler, et al., 2009; Dumont, et al., 2008; Lamers, et al., 2003; Gouzoulis-Mayfrank, et al., 1999).

Exams to certify the consumption of other drugs, mostly made from urine, hair, and saliva analyses, were also performed in thirty-four (34) studies (Ley, et al., 2023; De Wit, et al., 2022; Cavanna, et al., 2022; Mason, et al., 2021; Holze, et al., 2021; Rocha, et al., 2021; Hutten, et al., 2020; Gabay, et al., 2019; Barrett, et al., 2018; Dolder, et al., 2018; Schmidt, et al., 2018a; Kuypers, et al., 2018; Pokorny, et al., 2017; Schmidt, et al., 2017; Roseman, et al., 2016; Kuypers, et al., 2016; Forsyth, et al., 2016; Kirkpatrick, et al., 2015; Schmid, et al., 2015; Kuypers, et al., 2014; Schmid, et al., 2014; Hysek, et al., 2014; Kometer, et al., 2013; Carhart-Harris, et al., 2012a; Lansbergen, et al., 2011; Bedi, et al., 2010; Daumann, et al., 2010; Hasler, et al., 2009; Dumont, et al., 2008; Wittmann, et al., 2007; Lofwall, et al., 2006; Vollenweider, et al., 2005; Hasler, et al., 2004; Lamers, et al., 2003). In general, moderate use of marijuana (Cannabis) was accepted.

Of the forty-six (46) selected articles, the race/ethnicity of the participants were mentioned only in five (5) articles (De Wit, et al., 2022; Hutten, et al., 2020; Barrett, et al., 2018; Kirkpatrick, et al., 2015; Bedi, et al., 2010). Among the juxtaposed racial and ethnic categories, there were: 454 Caucasians; 8 Asians; 4 Blacks; 14 Mestizos; 7 Hispanic and 1 Indian.

It is also possible to note that the form of recruitment of participants was carried out mostly within the spaces where the scientific studies themselves were projected, that is, within the Universities. The presence of volunteers who came from academic spaces was verified in nineteen (19) articles (Holze, et al., 2021; Hutten, et al., 2020; Kuypers, et al., 2018; Barrett, et al., 2018; Dolder, et al., 2018; Schmidt, et al., 2018b; Haijen, et al., 2018; Pokorny, et al., 2017; Schmidt, et al., 2017; Kuypers, et al., 2016; Schmid, et al., 2015; Schmid, et al., 2014; Kuypers, et al., 2014; Hysek, et al., 2014; Hasler, et al., 2009; Wittmann, et al., 2007; Vollenweider, et al., 2005; Hasler, et al., 2004; Lamers, et al., 2003). Other forms of recruitment were based on contact in the dance scene, mostly in raves, online advertisements, or social networks and "word of mouth".

4. Discussion

The present study is a systematic review of investigations aimed at evaluating the effects of psychedelics in cognitive functions in healthy volunteers. Of the experimental studies analyzed, only forty-six (46) met the inclusion criteria. The results obtained showed that MDMA was the most studied drug, with eighteen (18) articles (Gabay, et al., 2019; Dolder, et al., 2018; Haijen, et al., 2018; Kuypers, et al., 2018; Schmidt, et al., 2018a; Schmidt, et al., 2017; Kuypers, et al., 2016; Schmid, et al., 2015; Kirkpatrick, et al., 2015; Schmid, et al., 2014; Kuypers, et al., 2014; Hysek, et al., 2014; Lansbergen, et al., 2011; Bedi, et al., 2010; Hasler, et al., 2009; Dumont, et al., 2008; Vollenweider, et al., 2005; Lamers, et al., 2003). Fourteen (14) articles were published with psilocybin (Ley, et al., 2023; Cavanna, et al., 2022; Mason, et al., 2021; Smigielski, et al., 2020; Prochazkova, et al., 2018; Barrett, et al., 2018; Pokorny, et al., 2017; Kometer, et al., 2013; Carhart-Harris, et al., 2012a; Carhart-Harris, et al., 2012b; Wittmann, et al., 2007; Hasler, et al., 2004; Gouzoulis-Mayfrank, et al., 1999; Duke & Keeler, 1968). There were six (6) studies performed with LSD (Ley, et al., 2023; De Wit, et al., 2022; Hutten, et al., 2020; Schmidt, et al., 2018b; Roseman, et al., 2016; Goldberger, L., 1966). Other two (2) studies (Rossi, et al., 2023; Rocha, et al., 2021) focused on investigating the effects of ayahuasca, and one (1) its psychoactive-containing molecule, DMT (Daumann, et al., 2010). Eight (8) studies investigated the effects of other psychedelic drugs: S-ketamine (Daumann, et al., 2010) and ketamine (Lofwall, et al., 2006), mescaline (Ley, et al., 2023; Halpern, et al., 2005), 3,4-methylenedioxy-amphetamine (MDE) (Spitzer, et al., 2001; Gouzoulis-Mayfrank, et al., 1999; Schreckenberger, et al., 1998), and ibogaine (Forsyth, et al., 2016).

Results from the studies performed with each one of these substances are discussed in the next sections.

4.1 MDMA

Schmid and coworkers (2014) used the FERT to investigate whether healthy volunteers developed empathy for situations they considered positive. MDMA enhanced emotional empathy for positive emotionally charged situations and tended to reduce the recognition of sad faces. However, the drug had no effects on cognitive empathy in the MET or social cognitive inferences in the Movie for the Assessment of Social Cognition (MASC). MDMA produced subjective 'empathogenic' effects, such as drug liking, closeness to others, openness, and trust.

In other studies, MDMA also produced effects classified as "empathogenics", ie. pupil dilation, subjective effects related to well-being, drug liking, closeness to others, openness, happiness, confidence, sexual arousal, changes in consciousness (Dolder, et al., 2018; Schmid, et al., 2014) and psychomotor performance (Lamers, et al., 2003). Interesting, MDMA reduced arousal levels elicited by negative sounds (Kuypers, et al., 2018). One article (Hysek, et al., 2014) found that MDMA increased "emotional empathy" and social behavior in male participants but impaired the identification of negative emotions on the FERT, particularly in female participants. In contrast, the results of another study showed that although MDMA, at a low dose (75 mg), induced greater empathy, attitudes such as trust, and reciprocity remained unchanged (Kuypers, et al., 2014).

Another finding (Gabay, et al., 2019) showed that MDMA can increase cooperative behavior in social decision-making contexts when playing with trusted opponents. This effect was associated with changes in neuronal activity in regions linked to social cognition. Nevertheless, the study highlights the context-specific nature of MDMA's effects on decision-making. Also, the study found no evidence to support the hypothesis that MDMA's dopaminergic modulation was responsible for the observed results. Similarly, Kirkpatrick and coworkers (2015) suggest that MDMA produces prosocial effects that depend on the social closeness of relationships.

Bedi and coworkers (2010) found that MDMA (1.5 mg/kg) altered a behavioral indicator of social cognition. Specifically, it robustly reduced recognition of fearful faces, without changing recognition of other emotions from facial or vocal cues. MDMA also produced self-reports of loving feelings and friendliness but decreased the accuracy of subjects in identifying fear in others.

Another study (Schmidt, et al., 2018a) compared the effects of MDMA, modafinil and methylphenidate in negative emotional processing in healthy subjects and used fMRI to evaluate brain activation. Fearful faces induced significant activation in various brain regions, including the amygdala, fusiform gyrus, anterior cingulate and orbitofrontal cortex, calcarine sulcus, dorsal striatum, and insula and inferior frontal gyrus. Modafinil increased brain activation in response to fearful faces within the limbic-cortical-striatal-pallidal-thalamic circuit relative to placebo. The drug also increased amygdala responses to fearful faces compared with MDMA, thus suggesting the positive behavioral and neurobiological effects of MDMA on emotional processing.

MDMA was also shown to increase positive and negative mood ratings and elevate plasma concentrations of oxytocin (Kuypers, et al., 2018; Schmid, et al., 2014; Hysek, et al., 2014), prolactin (Schmid, et al., 2014; Hysek, et al., 2014), and cortisol (Hysek, et al., 2014). In addition, Haijen and coworkers (2018) demonstrated that MDMA did not affect endocannabinoid concentrations, and that the MDMA-induced memory impairment which has consistently been demonstrated in human placebo-controlled studies seems to be unrelated to the endocannabinoid system.

Lansbergen and coworkers (2011) showed that the combined ingestion of MDMA and THC affects induces continuous electroencephalographic (EEG) oscillations differently than the sum of each drug alone, indicating potential interactions between these substances. The changes in continuous EEG oscillations observed may be related to the impairment of task performance often reported following drug ingestion, highlighting the importance of considering EEG measurements when evaluating the cognitive effects of drug use.

One study (Schmidt, et al., 2017) showed that MDMA did not improve inhibitory performance, although fMRI results indicated that MDMA significantly increased activation in the right middle/inferior frontal gyrus and superior parietal lobule

compared with placebo. Additionally, it significantly reduced subjective calmness, i.e subjects felt more excited after the use (Schmidt, et al., 2017).

The previous history of MDMA use was not predictive of memory impairment, but during MDMA use, verbal memory was impaired (Kuypers, et al., 2016). Other results also showed that MDMA can significantly impair the level of sustained attention and visual-spatial memory, but no evidence was found that the substance negatively affected functions related to thought and emotions, when compared with modafinil and methylphenidate (Hasler, et al., 2009). The drug had no effects on visual perception, planning ability and semantic memory retrieval (Lamers, et al., 2003). However, Dumont and coworkers (2008) consistently observed impaired memory function after drug conditions, whereas impairment of psychomotor function and attention was less consistent across the drug conditions.

Adverse effects were found after administration of the substance, as we could see, the main side effects reported were lack of appetite, dry mouth, headache, negative subjective effects linked to fear (Dolder, et al., 2018) and significant impairments in attention and memory, for example, in the ability to predict movements under divided attention (Lamers, et al., 2003).

Taken together, the results gathered above show no conclusive evidence that MDMA can improve cognition or on which regions encephalic disorders are specifically related to their effects (Kuypers, et al., 2018; Kirkpatrick, et al., 2015; Vollenweider, et al., 2005). One of the studies even explicitly warns that the use of the substance for cognitive enhancement purposes is not recommended, as there is no rigorous assessment of the potential risks of long-term use (Vollenweider, et al., 2005).

4.2 3,4-methylenedioxyethylamphetamine (MDE)

Gouzoulis-Mayfrank and coworkers (1999) investigated the neurometabolic effects of MDE, psilocybin, and d-methamphetamine in healthy volunteers. In the MDE group, frontal hypometabolism was more pronounced, except for the anterior cingulate, which showed hyperactivity. The drug showed less attenuation of cognitive activation-related increases in left frontocortical regions compared to psilocybin, indicating a potentially milder effect on cognitive function. Cognitive disturbances were associated with both diminished activity in the bilateral frontal region and increased activity in the right anterior cingulate.

Spitzer and coworkers (2001) investigated differential effects of (R)- and (S)-MDE on measurements of psychopathology, neuropsychological performance, and brain activation. Results showed that (S)-MDE induced increases in mood, impairments in cognition and activated the right frontal cortex. (R)-MDE, on the other hand, increased depression, visual feature processing, and activated the visual cortical and left frontal areas. The authors concluded that the entactogenic effects of MDE are likely to be caused by the (S)-enantiomer, while (R)-MDE seems to respond for the neurotoxic effects of the drug. A significant decrease in bilateral frontal cortex activity after MDE treatment was also found. However, the authors argue that PET provides indirect measurements of cerebral glucose deficits and may have limitations in accurately capturing complex metabolic processes in the brain (Schreckenberger, et al., 1998).

4.3 Psilocybin

One of the earlier studies included in the present review was performed by Duke & Keeler (1968). The authors showed that both psilocybin and dextro-amphetamine produced a deficit in cognitive performance as compared to placebo. Psilocybin significantly impaired performance of a complex task as compared to a simple task, suggesting that drug-induced muscular incoordination was not responsible for decrements in performance.

Several years later, Gouzoulis-Mayfrank and coworkers (1999) showed that psilocybin increased regional metabolic glucose utilization (rMRGlu) in distinct right hemispheric frontotemporal cortical regions, particularly in the anterior cingulate, and decreased rMRGlu in the thalamus, suggesting a potential impact on cognitive functioning.

In the beginning of the years 2000, Hasler and coworkers (2004) showed that the altered states of consciousness induced by psilocybin, in a dose-dependent manner, are generally well tolerated and integrated by healthy individuals. However, it should be noted that some participants reported adverse effects such as anxiety, confusion, and changes in time perception and working memory (Wittmann, et al., 2007; Hasler, et al., 2004).

Psilocybin also significantly decreased cerebral blood flow and venous oxygenation in a way that correlated with its subjective effects (Carhart-Harris, et al., 2012a). The pharmacophysiological interaction results revealed significant reductions in positive coupling between the posterior cingulate cortex and the medial prefrontal cortex following ingestion (Carhart-Harris, et al., 2012a). It was suggested that decreased activity and connectivity in the brain's connecting centers allows for an unconstrained style of cognition (Carhart-Harris, et al., 2012a).

Carhart-Harris and coworkers (2012b) also showed greater sensory activation and more intense subjective effects after psilocybin when compared to placebo. Greater activations were observed in the bilateral auditory cortex, somatosensory cortex, superior parietal cortex, left visual association regions and the occipital pole after psilocybin. The drug also induced changes in perception and altered self-referential processing, affecting self-other processing by modulating activity in the supragenual cingulate cortex and insula (Smigielski, et al., 2020).

Kometer and coworkers (2013) used EEG to investigate psilocybin effects on alpha waves oscillations that regulate cortical excitability and early visual-evoked P1 and N170 potentials in healthy human subjects. Results showed that the drug strongly decreased pre-stimulus parieto-occipital alpha power values, thus preventing a subsequent stimulus-induced decrease in alpha power (Kometer, et al., 2013). Furthermore, psilocybin strongly decreased N170 potentials associated with the onset of visual perceptual changes, including visual hallucinations (Kometer, et al., 2013). These effects were blocked by pretreatment with the serotonin (5-HT) 2A antagonist ketanserin, indicating that activation of 5-HT2A receptors by psilocybin modulates neurophysiological and phenomenological indices of visual processing (Kometer, et al., 2013).

Pokorny and coworkers (2017) showed that psilocybin significantly increased explicit and implicit emotional empathy in healthy human subjects compared to placebo. The study also found that psilocybin did not significantly affect cognitive empathy or moral behavior, thus suggesting that the effects of psilocybin on social cognition are specific to emotional empathy and may not directly influence moral decision-making. The findings of this study highlight the potential therapeutic applications of psilocybin in improving social skills and empathy.

Convergent and divergent thinking performance was found to be improved after a non-blind microdose of psychedelic mushrooms, while fluid intelligence was unaffected (Prochazkova, et al., 2018). Better performance was found in a second session when compared to the first session. According to the authors, these results provide quantitative support for the cognitive-enhancing properties of microdosed psychedelics (Prochazkova, et al., 2018).

Barrett and coworkers (2018) reported that psilocybin exerted dose-dependent effects on several cognitive functions, including psychomotor performance, working memory, episodic memory, associative learning, and visual perception. There was no evidence of psychological impairment or delirium with psilocybin.

Another study (Mason, et al., 2021) found that there were no reports of adverse effects during a psilocybin trial. However, some research participants reported mild and brief symptomatic syndromes, for example: changes in mood, perception and thought processes. These effects were generally well tolerated and disappeared within a few hours after administration of the substance.

Cavanna and coworkers (2022) found that low doses of psilocybin mushrooms can result in noticeable subjective effects. EEG results showed altered theta rhythms, associated with memory and attention processes, but without evidence to support the improvement of well-being, creativity and other cognitive functions. Additionally, according to the study (Cavanna, et al, 2022), anticipation plays a role, to some extent, in some of the anecdotal benefits attributed to microdosing psilocybin mushrooms.

Other studies (Mason, et al., 2021; Barrett, et al., 2018; Wittmann, et al., 2007) showed that psilocybin did not produce cognitive enhancement, but affected memory, perception, and creative thinking performances in several neuropsychological assessments, therefore suggesting that it is premature to consider that psilocybin contributes to cognitive enhancement.

4.4 LSD

Goldberger (1966) evaluated effects on cognitive performance of LSD, placebo, and social isolation. The loss of the sense of time was more profound and the difficulties in concentrating more debilitating and widespread with LSD when compared to placebo. On the other hand, eight hours of isolation did not produce significant group effects of impairment or improvement.

Schmidt and coworkers (2018b) showed that LSD administration impaired inhibitory performance and reduced neuronal activity in several regions, including the right middle temporal gyrus, superior/middle/inferior frontal gyrus, left anterior cingulate and superior frontal cortex, and left postcentral gyrus and cerebellum. The study also found that parahippocampal activation during response inhibition was differentially related to inhibitory performance after placebo and LSD administration. Additionally, activation in the left superior frontal gyrus under LSD exposure was negatively related to LSD-induced cognitive and visual imagery impairments (Schmidt, et al., 2018b).

Roseman and coworkers (2016) found that under the influence of LSD, the visual cortex behaves as if it is processing spatially localized visual information. This result suggests that LSD induces changes in the visual system that mimic the processing of visual stimuli even when there is no external visual input. In addition, activation in the left superior frontal gyrus under LSD exposure was also found to be negatively related to LSD-induced cognitive impairments and visual perceptions (Roseman, et al., 2016).

Hutten and coworkers (2020) observed few adverse effects during the use of low doses of LSD, such as confusion and anxiety, fatigue and increased blood pressure and heart rate and body temperature. These effects were mild and transient. Flashback phenomena were also reported in some participants after LSD administration (Ley, et al., 2023).

Results obtained by De Wit, et al., (2022) considered that, in the context of a controlled environment and in a limited number of administrations, low (13 or 26 μg) and repeated doses of LSD are safe but produce no significant changes in mood or cognition in healthy participants. In contrast, Hutten, and coworkers (2020) showed that low doses of LSD (5, 10 and 20 μg) exerted selective and beneficial effects on mood and cognition in most observations. Also, positive effects included an improvement in positive mood, friendliness, arousal, and a decrease in attention lapses.

Ley and coworkers (2023) found no evidence of qualitative differences in altered states of consciousness induced by equally strong doses of LSD, mescaline, and psilocybin. The subjective experience did not significantly differ between the three substances. The study supports dose finding for research and psychedelic-assisted therapy, indicating that LSD can be used in a controlled and monitored setting for therapeutic purposes.

4.5 Ayahuasca and DMT

Two studies investigated the effects of ayahuasca in cognitive functions (Rocha, et al., 2021; Rossi, et al, 2023). Rocha and coworkers (2021) aimed to assess the acute and prolonged effects of a single dose of ayahuasca on the recognition of emotions in facial expressions in healthy volunteers. The trial included a facial recognition task performed before and after drug intake, subjective effects assessment, tolerability measures, and measurement of brain-derived neurotrophic factor plasma levels (BDNF). The results showed that ayahuasca did not significantly modify FERT results compared to placebo. No significant effects were observed on cardiovascular measures and BDNF. The study also highlighted the time-dependent deterioration of

ayahuasca alkaloids, particularly DMT. Some participants reported feeling visual effects, tranquility/relaxation, and well-being (Rocha, et al., 2021).

Ayahuasca also reduced reaction times for emotion recognition and empathy, improving (faster) emotional processing and inducing an anxiolytic effect (Rossi, et al., 2023). Results also suggest that the acute administration of ayahuasca can have both positive and negative effects on neuropsychological performance. In general, ayahuasca was well-tolerated, with mainly nausea, gastrointestinal discomfort, and vomiting reported as side effects, and produced typical psychedelic/hallucinogenic effects (Rossi, et al., 2023; Rocha, et al., 2021).

Daumann and coworkers (2010) investigated the effects of DMT on cognitive measurements and neurobiological activation. It was also demonstrated that the administration of DMT alone led to a decrease in the blood oxygenation level-dependent (BOLD) response during the performance of an alerting task, particularly in extrastriate regions during visual alerting and in the temporal regions during an auditory stimulus (Daumann, et al., 2010). However, the study did not specifically assess outcomes for cognitive enhancement, so further research is needed to better understand the effects of ayahuasca on psychological functions (Rocha, et al., 2021). Thus, it is not clear that DMT, present in ayahuasca, can improve cognition (Rocha, et al., 2021; Daumann, et al., 2010).

4.6 Ketamine

One article (Lofwall, et al., 2006) showed that ketamine produces selective and brief pharmacological effects (dose-dependent) on cognitive functions related to memory, attention, psychomotricity, and subjective experience. Although concrete evidence that ketamine can produce cognitive-enhancing effects was not provided, no evidence was found that the drug produces significant harm.

Daumann and coworkers (2010) also showed that the administration of S-ketamine led to increased cortical activation in the left insula and in the precentral gyrus, responsible for motor, auditory and emotional activities.

4.7 Ibogaine

Forsyth and coworkers (2016) investigated the effects of ibogaine in healthy male volunteers that received a single 20 mg dose of ibogaine after 6 days pretreatment with double-blind paroxetine or placebo. The authors used a battery of psychometric tests and subjective mood ratings performed before and 2h after ibogaine. Results showed that ibogaine did not alter psychological evaluation and mood ratings.

4.8 Mescaline

Ley and coworkers (2023) found no evidence of qualitative differences in altered states of consciousness induced by equally doses of mescaline, LSD, and psilocybin. The subjective effects of the three substances were found to be comparable at psychoactive-equivalent doses. Furthermore, adverse effects were reported. Mescaline caused slightly more subacute adverse effects (12-24 h) than LSD and psilocybin.

Another study (Halpern, et al., 2005) showed that people of Navajo ethnicity, who regularly ingested peyote in a religious setting, did not exhibit significant cognitive impairments compared to those with minimal substance use.

5. Conclusion

Taken together the results from the present study indicate that although several pieces of evidence suggest that the use of psychedelics may improve cognitive performance, there are still important limitations regarding the differences in the procedures adopted, small sample sizes, and insufficient range of testing in healthy volunteers. These limitations make it

challenging to capture the full spectrum of experiences people might have in natural settings or with varying dosages. Assessing effects across multiple dosages and different stages of the psychedelic experience could provide a more comprehensive understanding of their impacts. This could encompass variations in intensity, duration, and potential therapeutic or adverse effects at different points of the experience. To conclude, the results from the present review suggest that, although there were no serious adverse effects resulting from the use of the psychedelic drugs investigated, further studies on the use of psychedelics with the aim of improving cognitive enhancement in healthy people are still warranted.

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