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The Cognitive Effects of Classic Psychedelic Drugs

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Abstract

Introduction. Classic psychedelic drugs are increasingly investigated as a psychopharmacological aid for psychotherapeutic approaches. These drugs are used in various dosages, from sub-perceptual microdoses to fully perceptual macrodoses, to elicit diverse acute and subacute effects. Those effects are thought to be highly dependent on personal and environmental extra-pharmacological factors. ***Methods.*** This systematic review coalesced the results of 43 studies that used neuropsychological tests of cognition and highlights differences among dosages, time of testing, and extra-pharmacological factors. ***Results.*** Acutely classic psychedelics impair attention, working memory, and executive functions, while improving social cognition and creativity. In contrast, classic psychedelic users are not subacutely influenced on any domain in comparison to non-users, while traditional, regular users of the classic psychedelic Ayahuasca are better on some domains. A clinical sample with social anxiety disorder, showed cognitive improvements after the acute drug effects. ***Discussion.*** By now, it is well-established that classic psychedelics acutely impair performance on cognitive measures. Therefore, future neuropsychological research should further assess their potential efficacy in treating cognitive deficits of clinical populations with a particular focus on the under-investigated extra-pharmacological factors (i.e., personality, motivation, expectation, and intention).

Keywords: Psychedelics, Cognition, Set, Setting, Microdosing

Mental Health Crisis & Lack of Psychiatric Innovations

Neuropsychiatric disorders (NPD), including mental, neurological, and substance use disorders are increasingly amounting for the Global Disease Burden, as their contribution has risen from 7.3% in 1990 to 10.4% in 2010 (Catalá-López et al., 2013; Patel et al., 2016, p. 30f). The COVID-19 pandemic is negatively impacting the general public's mental health, as about one-third of the global population is currently experiencing significant levels of anxiety, depression and/or psychological distress (Necho et al., 2021). Additionally, the global climate crisis is at the detriment of public mental health, and there is increasing evidence that not only extreme weather events can have posttraumatic-stress disorder as a consequence, but also that a significant proportion of the population are experiencing harmful levels of anxiety due to their perception of climate change (Clayton, 2021). Despite these indications of a global mental health crisis, the development of new psychiatric medications has massively decelerated from 49 new psychiatric drugs approved by the US Food and Drug Administration between 1996 and 2006 to just 22 new approvals between 2007 and 2016 (Schenberg, 2018). Furthermore, current psychopharmacological interventions, such as antidepressants, are of questionable clinical efficacy, highlighting the need for psychopharmacological innovations (Jakobsen et al., 2018). Therefore, research on Classic Psychedelics (CPs) for the treatment of several NPDs gained renewed attention in recent years and evidence for their clinical utility is growing at an accelerating pace (Murnane, 2018; Reiff et al., 2020, p. 2).

Psychedelic Revival in Science – Clinical Evidence & Safety

CPs are psychoactive substances that share agonist (or partial agonist) activity at the serotonergic 2A receptor underlying their psychedelic (i.e. mind-manifesting) effects (Johnson et al., 2019, p. 2). CPs can be categorized into two structural categories, the first being tryptamines, including psilocybin, lysergic acid diethylamide (LSD), and

dimethyltryptamine (DMT), and the second being phenethylamines, including mescaline (Johnson et al., 2019, p. 2).

Various indigenous cultures appear to have used ayahuasca (a plant brewed beverage containing DMT and monoaminoxidase inhibitors), psilocybin-containing mushrooms, and mescaline-containing cacti for sacramental use in religious and/or healing contexts since ancient times (Johnson et al., 2019, p. 3). Western scientists have investigated psychedelic substances in more than 1000 clinical trials including around 40,000 patients between 1950 and the mid-1960s, which was terminated by European and US governments due to concerns about the general public's psychedelic use and its associations with the anti-establishment movement of the 1960s (Murnane, 2018; Reiff et al., 2020). Recent clinical trials on CPs' therapeutic efficacy indicated their possible utility in treating various NPDs, including psychological distress associated with life-threatening diseases (Fuentes et al., 2020; Johnson et al., 2019), treatment-resistant depression (Johnson et al., 2019), obsessive-compulsive disorder (OCD; Moreno et al., 2006), and substance use disorders (SUD; Johnson et al., 2019). In addition to this evidence for CPs' therapeutic efficacy in treating disorders of psychological origin, they also might be efficacious for treating disorders of neurological origin, such as cluster headaches (Schindler et al., 2015). There are several first and second phase clinical trials investigating CPs' efficacy for treating cluster headaches (CH; Knudsen, G.M., NCT04280055; D'Souza, D.C., NCT02981173; Liechti, M., NCT03781128) migraine headaches (D'Souza, D.C., NCT03341689; Yale University, NCT04218539), and concussion headaches (D'Souza, D.C. & Schindler, E., NCT03806985).

Despite CPs being physiologically well tolerated and of low addiction potential, their use encompasses psychological risks (Johnson et al., 2008). The most common of these is to experience overwhelming distress during the drug action, commonly referred to as "bad trips", that can elicit dangerous behaviors, which can actually be well controlled in a medically supervised setting (Johnson et al., 2008). Less common, but more severe,

psychological consequences that can be triggered by CPs are prolonged psychosis and Hallucinogen Persistent Perception Disorder (HPPD), of which the latter describes the persistent re-experiencing of perceptual alterations along with clinically significant distress and/or functional impairment after the acute CP effects are over (Johnson et al., 2008). Both, the positive, as well as the negative possible consequences could have an impact on cognitive functioning, as the disorders that can result from CP use, as well as the disorders that might be treatable with CPs can include a cognitive dimension (American Psychiatric Association, 2013; Donders, 2005, p. ix). For instance, psychotic disorders, that can be triggered by CPs, are associated with a wide-variety of cognitive deficits, that can significantly impact psycho-social functioning (Grau et al., 2016). On the contrary, major depressive disorders, OCD, SUD, and CH, which might be treatable with PAP are also associated with wide-ranging cognitive deficits of variable severity (Abramovitch et al., 2019; Dresler et al., 2012; Ramey & Regier, 2019; Semkovska et al., 2019).

RDoC – Dimensionality of Symptoms & Nonspecific Treatments

While the American Psychiatric Association (APA) acknowledges a cognitive dimension to NPDs, they still adhere to the categorical approach to diagnoses in their current Diagnostic and Statistical Manual of Mental Disorders (DSM-VR), alike the current World Health Organization's International Classification of Diseases (ICD-10). In contrast, the National Institute of Mental Health (NIMH) has shifted towards a dimensional symptom classification to promote transdiagnostic research with their development of the Research Domain Criteria (RDoC) since 2009 (Clark et al., 2017; Cuthbert, 2020). The RDoC is a translational framework that is intended to move towards research on functional dimensions of behavior and cognitive/affective processes that range from normal to abnormal, as opposed to the reductionistic diagnostic cut-offs of the DSM and ICD (Cuthbert, 2020). While the APA defines cognition as "all forms of knowledge and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem-solving" and "an individual

percept, idea, memory, or the like", the NIMH's RDoC domain of cognitive systems contains the six domains, namely attention, perception, declarative memory, language, cognitive control, and working memory.

Furthermore, the specificity, with which the DSM/ICD diagnostic categories direct specific treatments, is contradictory to the emerging evidence that the efficacy of psychopharmacological interventions, such as antidepressant medications, are not entirely disorder-specific, but rather show some efficacy for various disorders (Clark et al., 2017). Similarly, CPs seem to have some therapeutic efficacy across a wide-range of disorders (Johnson et al., 2019). Some of the common psychopharmacological interventions have damaging side-effects to overall health, that might be overseen when only looking at studies of physiological safety and efficacy of symptom reduction (Clark et al., 2017). Therefore, it is essential to also elucidate the efficacy of CPs on cognition, and identify risk factors for cognitive side-effects, as is intended by this systematic review. Current psychopharmacological interventions require the regular, often daily, intake of the medication, with the consequence of frequent non-adherence to the medication regimen that is associated with the client's beliefs of its ineffectiveness and perceptions of its side-effects (Semahegn et al., 2018; Wheeler et al., 2014). The tolerability of current antidepressant medications can be increased by combining it with psychotherapy, but Psychedelic-assisted Psychotherapy (PAP) bypasses the non-adherence issue of pharmacotherapy, as the administration of the CP is limited in frequency with enduring significant symptom-reductions occurring after just two therapeutically supervised sessions of drug intake (Greenway et al., 2020; Griffiths et al.; 2016; Ross et al., 2016; Johnson et al., 2019). Similar to, for example, the gold-standard treatment for Major Depressive Disorders (MDD), which combines psychotherapy with an antidepressant psychopharmaceutical agent, PAP is also integrating pharmacotherapy, in this case with psychedelic drug, and psychotherapeutic interventions, such as cognitive-behavioral therapy (Greenway et al., 2020). Hereby, the latter

serves to prepare the client before the CP experience, and, subsequently, as a translational framework to integrate the insights gained during the CP session (Greenway et al., 2020).

Cognitive Risks of Illicit CP Use, Motivations and Dosage Differences

The therapeutic framework and medical supervision are also helpful in reducing the psychological risks that are associated with the illicit, uncontrolled use of CPs (Johnson et al., 2008). It was recommended to exclude those with a personal or family history of psychotic disorders or bipolar disorders from CP research due to their increased risks for adverse consequences. Despite these exclusionary criteria only being introduced in the early 1960s, the rates of psychotic reactions, suicide attempts, and suicides in LSD research of the 1950s and 1960s are comparable to those of conventional psychotherapy (Johnson et al., 2008; Passie et al., 2008; Rucker et al., 2018).

The dangers of illicit, uncontrolled intake of CPs by a layman without any cultural background of sacramental CP use are, in contrast to the low risks associated with CP administration by a psychotherapist or psychiatrist, not to be neglected (Johnson et al., 2008). While psychotic reactions after CP use are only lasting days in controlled research settings, such adverse reactions can last up to months after uncontrolled CP use (Johnson et al., 2008). While the cognitive domain of HPPD is not well researched, first-episode and recent-onset Psychotic disorders are associated with a wide-variety of cognitive deficits, that can significantly impact psycho-social functioning (Grau et al., 2016). On the contrast, the disorders, such as MDD, OCD, SUD, and cluster headaches, that might be treatable with PAP are also associated with wide-ranging cognitive deficits of variable severity (Abramovitch et al., 2019; Dresler et al., 2012; Ramey & Regier, 2019; Semkovska et al., 2019).

Therefore, despite CPs being longest known substances of the psychedelic class of substances and CP research having initiated more than 125 years ago, their effects' on cognition still remain unclear and paradoxical (Carhart-Harris et al., 2016; Swanson, 2018).

Swanson (2018) identified four key features of 19th & 20th century theories concerning psychedelics' effects. Firstly, the adaptive mechanism of constrained perception, emotion, cognition, and self-reference is inhibited and thus elicit diverse effects. Secondly, if this adaptive mechanism is either not enough or too highly constrained, it can produce certain pathologies. Thirdly, psychedelic effects share common features with psychotic disorders due to the weakened constraints. Lastly, the temporary weakening of these constraints are the exact mechanism by which psychedelic effects can be therapeutically useful (Swanson, 2018). Thus, psychedelics appear to be the class of substances whose effects depend the most on extra-pharmacological factors (EPFs; Hartogsohn, 2017). EPFs thought to influence CPs' effects include personality, preparation, expectancy, physical-, social- and cultural-setting, motivation, and intention, all of which would need to be extensively controlled to objectively assess their clinical efficacy (Hartogsohn, 2016; Labate & Cavnar, 2013).

Motivations and intentions for illicit CP use are varying, but seem to be partially dose-dependent. While some are using "normal", perceptual dosages (i.e. macrodosing) to broaden consciousness, have a spiritual experience, and/or to experience nature, others are partaking in the increasing trend of "microdosing" with no intention to experience perceptual effects, but rather to improve cognition, (Kettner et al., 2019; Lea et al., 2020).

Contrary to that, normal dosages were shown to impair cognition, as performance on measures of working memory and directed attention were inhibited by CPs' immediate effects (Swanson, 2018). Like the acute effects, after effects also diverge, as some CP use results in a Psychotic Disorder with cognitive deficits as sequelae, while other studies indicated positive effects on cognition, including increases in creativity-related traits, cognitive flexibility, mindfulness, and the personality trait openness (American Psychiatric Association, 2013; Murphy-Beiner & Soar, 2020; Swanson, 2018).

To assess the full spectrum of CPs' cognitive effects, this systematic review includes clinical and non-clinical populations and various cognitive outcome measures, so that it

adheres to the RDoC guidelines. A comparison of extra-pharmacological factors is conducted to compare environmental circumstances that might be beneficial or harmful. As cognitive functioning during the acute CP effects seem to diverge cognitive functioning after the drug action, the time of measurement will also be included as a comparator. Lastly, to account CP users' differences in intentions, the dosage will be compared to investigate the differences in cognitive effects of micro-dosing and common, perceptual dosages.

This master thesis aims to synthesize the literature on the acute and after-effects of normal and micro-dosages classic psychedelics on cognitive functions in clinical and nonclinical samples. A main focus will be on their variability across extra-pharmacological factors, as far as they are mentioned in the included studies. Finally, this review will give directions to improve testing the cognitive effects of psychedelics.

Methods

The research questions were formulated using the PICOT framework (Table 1). The reporting of the literature search and screening was conducted using the Preferred Reporting in Systematic Reviews and Meta Analyses (PRISMA) guidelines.

Table 1 - PICOT criteria

Population	Psychedelic use in nonclinical and clinical populations, incl. those diagnosed with psychological distress associated with life-threatening diseases, treatment-resistant depression, and substance use disorders.
Intervention	Classic Psychedelics, including psilocybin (incl. psilocybin mushrooms), dimethyltryptamine (DMT; incl. ayahuasca brews), lysergic acid diethylamide (LSD), and mescaline (incl. peyote/san pedro cacti)
Comparison	1) Extra-pharmacological Factors 2) Dosage (Microdosing vs. Normal/Full dosage) 3) Timeframe (Acute measure vs. Subacute measure)
Outcomes	Cognitive/Neuropsychological Functioning
Timeframe	Acute effects vs. After effects (i.e., Subacute)

Search strategy

The literature databases PubMed (1964 - 2021) and PsycInfo (1960 - 2021) were chosen to conduct this systematic review. Filters were added on both databases for the exclusion of animal studies and reviews (on PsycInfo, also exclusion of meta-analyses). Search terms were

entered n both databases in adherence to the research question's two main concepts of psychedelics and cognitive/neuropsychological functioning. Followingly, search terms were grouped to the referred concepts and placed in brackets, with the Boolean operator term "OR" separating words or group of words in each concept. The final search strategy was consisting of the concepts and respective search terms organized in the following way, using the Boolean operators "AND" and "OR": ((neuropsychological assessment) OR (cogniti*)) AND ((psychedelics) OR (hallucinogens) OR (psychotomimetic)) NOT ((animals) OR (reviews)). The full search strings for both databases can be found in the appendix. The year and language of publication, characteristics of human subjects, and type of psychedelic drug were not specified in the search query to prevent exclusion of relevant results. This search strategy yielded 1125 results on July 6th 2021, of which 148 were duplicates, and 977 were screened for eligibility using the website Rayyan.

Study selection

Reports were included, if they fulfilled the following inclusion criteria: (1) the study subjects were human; (2) the subjects used or were given a classic psychedelic substance; (3) the study included an objective, quantitative assessment on one or more neuropsychological or cognitive domain(s)

Studies were excluded, if they did not fulfill one of the inclusion criteria. Additionalexclusion criteria were: (1) the type of hallucinogen was not specified; (2) the study was inaccessible; (3) the study was a case study, review, or meta-analysis.

Data extraction

The relevant data that was extracted from 42 studies included: (1) sample size; (2) clinical or non-clinical sample, incl. possible diagnoses and symptom severity; (3) geographical/cultural origin of sample; (4) mean age of sample and standard deviation; (5) type, dosage, and timing of classic psychedelic drug; (6) previous psychedelic use of study sample; (7) study design and focus; (8) cognitive or neuropsychological assessment measure;

(9) time of assessment; (10) environmental characteristics during acute drug effects; (11) type, dosage, and timing of possible other drug use/administration; (12) illicit use or controlled administration of substances; (13) findings on neuropsychological or cognitive outcome measures; (14) relevant findings on other outcome measures.

Results

PRISMA 2009 Flow Diagram

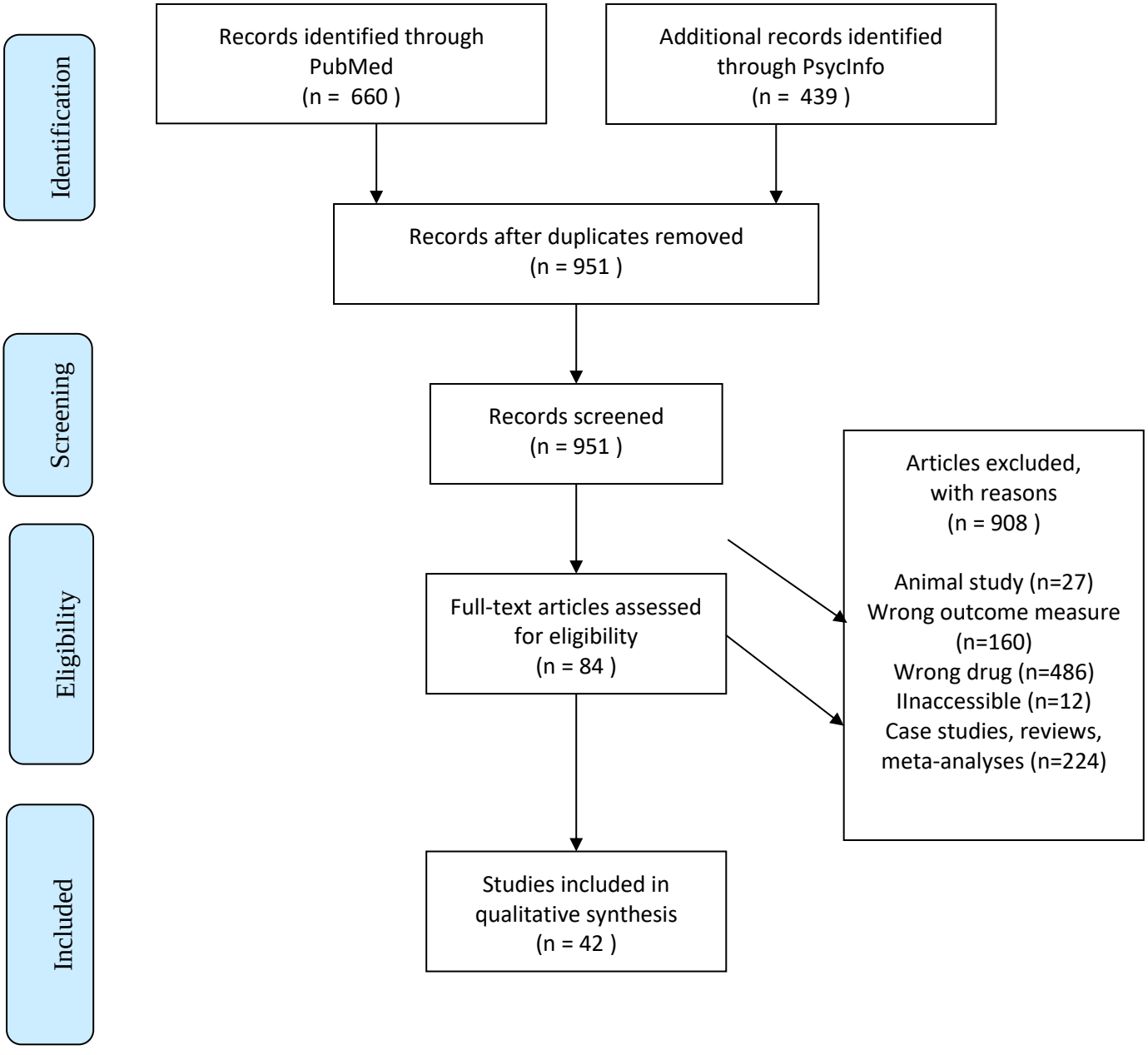

Table 1

Overview of studies which measured during acute drug effects

Study	Sample	Substance & Dosage	Design of Study	Constructs Addressed	Methodology	Conclusions
Daumann et al. (2010)	14 healthy volunteers (M=8, F=6), mean age: 32.1 (range: 26-42)	DMT & Placebo; S-Ketamine & Placebo; all conditions i.v.; Placebo & drug conditions on same day 2-3 h apart, both drugs at least 14 days apart	Double-blind, placebo-controlled, within-subject design	Phasic Alertness (A)	Target-Detection Task with Visual Targets and Visual, Auditory or no warning cues	DMT ↓ Alertness (specifically attention) compared to Placebo; No significant differences betw. DMT & S-Ketamine
Dolder et al. (2016)	40 healthy participants; Study 1 (n=24) M=12, F=12, mean age: 33±11; Study 2 (n=16) M=8, F=8, mean age: 29±6	LSD (Study 1: 100µg p.o.; Study 2: 200µg p.o.) and Placebo; at least 7 days apart	Pooled data from similar placebo-controlled, double-blind, random-order, crossover studies	Emotion Recognition (SC); Cognitive & Emotional Empathy (SC); Social Behavior (SC)	Facial Emotion Recognition Task; Multifaceted Empathy Test; Social Value Orientation Test	LSD ↑ explicit and implicit emotional empathy, ↓ recognition of sad and fearful faces, ↑ desire to be with other people, ↑ prosocial behavior
Duerler et al. (2020)	24 healthy volunteers (M=18, F=6), mean age: 25.25±3.72	LSD (100µg p.o.), LSD (100µg p.o.) + Ketanserin, and Placebo; at least 3 weeks apart	Double-blind, randomized, placebo-controlled, within-subject design	Social Influence Processing, Social decision-making (SC)	Social Influence Paradigm (Aesthetic quality of street art: Per session 20 initial ratings & follow-up after receiving feedback about the supposed group norm)	LSD ↑ adaptation to the opinion of others, but only if similar to one's own.
Family et al. (2016)	10 healthy volunteers with prior psychedelic experiences (M=9, F=1), mean age: 34.2±7.4	LSD (40 to 80µg i.v.), and Placebo; at least 1 week apart	Single-blind, randomized, placebo-controlled, within-subject design	Semantic processing, Lexical/Word Retrieval (L)	Picture-Naming Task (categories: body parts, clothing, vehicles)	LSD & Placebo conditions had similar reaction times. LSD ↑ substitution errors for semantically similar, but not semantically different words. Suggests that LSD ↑ spread of semantic network activation.
Goldberger (1966)	42 paid unemployed actors (n.a. age & gender), healthy on gross	LSD (100µg p.o.), Perceptual Isolation, or Placebo	Double-blind, placebo-controlled, between-subjects design	WM; Language Comprehension (L); Phonological Awareness (L); Verbal Fluency (L);	Digit Span; Comprehension of Long & Short Passages adapted from Iowa Silent Reading Test; Robinson	LSD ↓ all measures, except the Digit Span Test compared to Perceptual Isolation & Placebo Conditions

	pathological screening			Concentration (A)	Rhyming & Simple Rhyming; Word Naming with 3 or 4 Letters; Serial Sevens	
Gouzoulis-Mayfrank et al. (2006)	15 healthy volunteers (M=9, F=6), mean age: 38 (range: 28-53), no stressful life events in past 4 weeks	DMT (low dosage & high dosage, i.v.) and S-Ketamine (KET; low dosage & high dosage, i.v.); dosages 2-4h apart; drugs 2-4 weeks apart	Randomized, double-blind, crossover design with pseudorandomized order	Visual Attention, Reaction times, Inhibition of Return; Endogenous: Conscious, directed attention shifting (EF); Exogenous: Automatic visual attention (A)	Covert Orienting of Visual Attention Task (COVAT) with endogenous cues & no cues and exogenous cues & no cues	DMT & KET dose-dependent ↓ reaction times (DMT>KET), DMT ↓ alerting of spatially neutral cues, DMT & low-dose KET ↓ inhibition of return (automatic inhibition of attention towards redundant sensory information), suggesting pre-disposal to positive psychotic symptoms
Hasler et al. (2004)	8 healthy participants (M=4, F=4), mean age: 29.5 (range: 22-44)	Psilocybin (very-low dose: 45mcg/kg, low dose: 0.115mg/kg, medium dose: 0.215mg/kg, high dose: 0.315mg/kg; p.o.) and Placebo; at least 2 weeks apart	Randomized, double-blind, placebo-controlled, within-subject design	Sustained Attention (A)	Frankfurt Attention Inventory	Medium & high dosages of Psilocybin ↓ sustained attention, while very-low & low dosages did not. May be confounded with drug-induced lack of motivation to perform well in this task.
Kometer et al. (2012)	17 healthy volunteers (M=11, F=6), mean age: 25±4.36, mostly university students	Psilocybin (0.215mg/kg p.o.) or Placebo after pretreatment with Placebo (PP) or Ketanserin (KP); conditions at least 2 weeks apart	Double-blind, within-subject, placebo-controlled randomized design	Facial Emotional Recognition (SC); Goal-directed behavior towards emotional cues (SC)	Reading the Mind in the Eyes Test (German adaptation); Emotional Go-Nogo Task	Psilocybin ↓ recognition of negative facial expressions, ↑ behavior towards positive relative to negative cues. Psilocybin biases emotional processing to positive relative to negative information.
Kuypers et al. (2016)	26 healthy, spiritual Ayahuasca group members: G1 (n=15; W=10, M=5; mean age: 37.4±5.8) & G2 (n=11; W=7, M=4; mean age: 52±13)	Ayahuasca (DMT, harmine, tetrahydroharmine, and harmaline); DMT content and mean intake of G1 > G2; at least 2 days Ayahuasca	Quasi-experimental design	Creativity (Convergent and Divergent Thinking)	Picture Concept Task (PCT); Pattern-Line Meanings Task (PLMT)	Ayahuasca ↓ convergent thinking, ↑ divergent thinking on PCT. No significant differences on PLMT.

		abstinent before study				
Pokorny et al. (2017)	22 healthy volunteers (M=13, F=11), mean age: 26.63±5.33	Psilocybin (0.215mg/kg p.o.) and Placebo; at least 10 days apart	Double-blind, randomized, placebo-controlled within-subject design	Implicit & Explicit Emotional Empathy, Cognitive Empathy (SC); Hypothetical moral decision-making (SC)	Multifaceted Empathy Test; Moral Dilemma Task	Psilocybin ↑ implicit & explicit emotional empathy independent of stimuli valence (positive/negative), no significant difference in cognitive empathy and hypothetical moral decision-making.
Pokorny et al. (2019)	25 healthy volunteers (M=19, F=6), mean age: 25.24±2.79	LSD (100µg p.o.), LSD (100µg) + Ketanserin (40mg), and Placebo; at least 2 weeks apart	Double-blind, randomized, placebo-controlled, within-subject design	EF; Spatial WM; Risk-based decision-making (EF)	Intra-/Extra-Dimensional Shift Task (computerized analog of Wisconsin Card Sorting Test); Spatial Working Memory Task; Cambridge Gambling Task	LSD ↓ executive functions, cognitive flexibility, working memory compared to Placebo, but no significant difference in quality of decision-making and risk-taking. Ketanserin normalized all LSD-induced cognitive deficits.
Preller et al. (2018)	24 healthy human participants (M=18, F=6), mean age: 25.42±3.69	LSD (100µg p.o.), LSD + Ketanserin, and Placebo; 2 weeks apart	Double-blind, randomized, counterbalanced design	SC: Joint Attention (Self-initiated vs. Other-initiated)	Social Interaction Task	LSD ↓ response to self-initiated compared to other-initiated social interactions, suggesting reduced self-referential processing (self-other differentiation). LSD ↓ joint attention. No differences between LSD + Ketanserin and Placebo conditions.
Schmidt et al. (2017)	18 healthy volunteers (M=9, F=9), mean age: 31±9	LSD (100µg p.o.) and Placebo; at least 7 days apart	Double-blind, randomized, placebo-controlled, cross-over design	Response Inhibition (EF)	Go/No-Go Task	LSD ↓ inhibitory performance, ↓ response to go trials, and ↑ reaction times.
Smigielski et al. (2020)	17 healthy individuals (M=9, F=8), mean age: 25.1±4.1	Psilocybin (0.23mg/kg p.o.) and Placebo; at least 2 weeks apart	Double-blind, placebo-controlled, within-subject crossover design	Self-monitoring, Self-Other Differentiation, Self-referential processing (SC)	Self-Monitoring task involving speech production with feedback varying in source (self vs other) and pitch on voice recognition	Psilocybin ↓ probability of attributing the "self" voice to "self" significantly more than the probability of attributing the "other" voice as "other". Suggests aberrations in self-experience, lessened ego-centricity, and a state of "selflessness" that other studies previously described about Psilocybin.
Umbricht et al. (2003)	18 healthy volunteers (M=10, F=8), mean age:	Psilocybin (0.28mg/kg) and Placebo, on separate days	Single-blind, randomized, placebo-controlled,	Sustained & selective attention, cognitive control,	AX-Continuous Performance Task (AX-CPT)	Psilocybin ↓ AX-CPT performance, particular ↓ in using contextual information, whereas no change in the use of non-

	25.1±4.3, University students (n=16) & employed (n=2)		within-subject design	response inhibition (A & EF)		contextual information was found. Psilocybin did not alter mismatch negativity, suggesting that the maintenance of contextual information is not adversely affected.
Vollenweider et al. (1998)	Healthy volunteers recruited from staff of University of Zürich: G1 (n=15; F=7, M=8; mean age: 29.7±5.3) & G2 (n=10; F=5, M=5; mean age: 28.4±4)	Psilocybin (0.25mg/kg) or Placebo, after Pretreatment with Ketanserin, Haloperidol or Risperidone (each condition: n=5 of G1); or with Placebo or Ketanserin (each condition: n=5 of G2); 1 month apart	Placebo-controlled within-subject design	Spatial WM	Visual-Manual Delayed Response Task (DRT)	Psilocybin ↓ spatial working memory. This could be completely prevented by serotonin receptor 5-HT2A (Ketanserin & Risperidone pretreatment conditions), but not dopamine receptor D2 (Haloperidol pretreatment condition) antagonism.
Mason et al. (2021)	60 healthy participants (M=35, F=25), mean age: 22.97±3.28; allocated to Psilocybin or Control group (n=30 each)	Psilocybin (0.17mg/kg p.o) or Placebo	Balanced randomized, placebo-controlled, double-blind, parallel-group design	Creativity (Convergent and Divergent Thinking)	Picture Concept Task (PCT); Alternative Uses Task (AUT)	Psilocybin ↓ convergent thinking (d=0.85, p<0.01) and divergent thinking, incl. fluency (d=0.84, p<0.01) and originality (d=0.65, p=0.02) on the PCT. Psilocybin ↓ fluency (d=0.8, p<0.01) on AUT.
Barrett et al. (2018)	20 healthy hallucinogen users (F=11, M=9), mean age: 28.5 (range: 22-43)	Psilocybin (0.143mg/kg, 0.29mg/kg, 0.43mg/kg p.o.), Dextromethorphan (high-dosed dissociative, 400mg), and Placebo; mean days between conditions: 10 (range: 3-21)	Double-blind, placebo-controlled, complete-crossover design	Psychomotor Performance (O); Visual Perception (O); WM; episodic memory, associative learning (ML); A & EF; Overall Cognitive Impairment (GC)	Circular Lights, Balance, & Penn Motor Praxis Tasks; Penn Line Orientation Task; Penn letter n-back Task; Word Encoding, Recall, and Recognition Task with 36 target & 36 lure words; Digit Symbol Substitution Task; Mini Mental Status Examination	Psilocybin did not induce global cognitive impairment, but dose-dependently ↓ psychomotor performance, working memory, episodic memory, associative learning, and visual perception.

Quednow et al. (2011)	16 healthy participants (M=13, F=3), mean age: 29.7 (range: 24-39)	Psilocybin (0.260mg/kg p.o.), Ketanserin (40mg p.o.), Psilocybin + Ketanserin, and Placebo; at least 4 weeks apart	Placebo-controlled, crossed, counterbalanced, double-blind design	Selective attention & Controlled inhibition (A & EF)	Stroop Color-Word Test	Psilocybin ↓ controlled inhibition, and ↑ response latencies. Ketanserin attenuated these Psilocybin-induced alterations.
Spitzer et al. (1996)	8 healthy males, mean age: 39.4	Psilocybin (0.2mg/kg p.o.) and Placebo	Double-blind placebo-controlled within-subject design	Direct and indirect semantic priming (L), reaction times (A)	Lexical decision paradigm (two alternative versions)	Psilocybin ↑ reaction times, but low error rates. No significant difference in direct semantic priming. Psilocybin ↑ indirect semantic priming, suggesting a broadening of consciousness or enhancement of creativity.
Wittman et al. (2007)	12 healthy volunteering students from Uni Zürich (F=6, M=6), mean age: 26.8±3.6	Psilocybin (0.115mg/kg, 0.25mg/kg) and Placebo; at least two weeks apart	Double-blind, placebo-controlled, within-subject design	Temporal Processing, Timing Performance (O); Sensorimotor synchronization (O); Motor Control (O); Spatial WM	Temporal Reproduction of 500hz sound of short- and long-intervals; Mates Sensorimotor synchronization; Mates Tapping Speed; Spatial Span Test from Cambridge Neuropsychological Test Automated Battery	Psilocybin alters time perception and temporal control of behavior, as indicated by ↓ reproduction of sound intervals (>3sec.), ↓ synchronization of motor response (finger tap) to sound (>2sec.), and ↓ preferred tapping tempo. No differences were found on shorter durations of sound intervals, suggesting interactions with cognitive dimensions of temporal processing, such as short-term, attention, or decision-making mechanisms, rather than basic pacemaker/accumulator brain mechanism. High-dosed Psilocybin ↓ short-term memory during peak drug effects.
Dos Santos et al. (2021)	17 volunteers with social-anxiety disorder (F=15, M=2), mean age: 24.9 (range: 19-32); Ayahuasca G (n=9) & Control G (n=8); Undergraduate students (n=15) & Private	Ayahuasca (2ml/kg p.o.) or Placebo; Drug was donated by Traditional Ayahuasca Church	Randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial	Emotion Recognition (SC)	Recognition of Emotions in Facial Expressions (derived from Ekman & Friesen)	Ayahuasca did not significantly alter reaction times or accuracy of emotion recognition compared to Placebo.

	psychiatric clinic (n=2)					
Mendes Rocha et al. (2021)	20 healthy volunteers, mean age: 31.8 (range: 21-55); randomly allocated to Ayahuasca G (F=7, M=3) or Control G (F=5, M=5)	Ayahuasca (1ml/kg p.o.) or Placebo; Drug was donated by Traditional Ayahuasca Church	Randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial	Emotion Recognition (SC)	Recognition of Emotions in Facial Expressions (derived from Ekman & Friesen)	Ayahuasca did not significantly alter reaction times or accuracy of emotion recognition compared to Placebo.
Bouso et al. (2013)	24 Ayahuasca users (F=12, M=12), mean age: 46 (range: 29-62); occasional user G (n=13) & long-term experienced user G (n=11)	Ayahuasca (100ml p.o.)	Mixed between- and within-subject design with counterbalanced order of test administration	Verbal WM; Selective attention, cognitive flexibility, conflict monitoring, resistance to interference (A & EF); Planning, inhibition, impulsivity (EF)	Sternberg Working Memory Task (SWMT); Stroop Color-Word Test (SCWT); Tower of London (TOL)	Ayahuasca ↓ verbal working memory (SWMT), and ↓ stimulus-response interference (SCWT), as indicated by ↑ speed with unaffected accuracy. Ayahuasca ↓ executive functions (TOL) only in occasional users, suggesting that experienced long-term users developed compensatory mechanisms for Ayahuasca's detrimental effects on Executive Functions.

F Female, *M* Male; *G* Group; *p.o.* per oral, *i.v.* intravenous, *A* Attention & Alertness, *EF* Executive Functions & Cognitive Control, *SC* Social Cognition, *ML* Memory & Learning, *L* Language, *WM* Working Memory, *GC* Global Cognition, *O* Other cognitive functions, *sign.* significantly, ± Standard Deviation, ↑ increase, ↓ decrease, *WAIS* Wechsler Adult Intelligence Scale

Table 2

Overview of studies which measured after acute drug effects

Study	Sample	Substance & Dosage	Design of Study	Constructs Addressed	Methodology	Conclusions
Mason et al. (2021)	60 healthy participants (M=35, F=25), mean age: 22.97±3.28; allocated to Psilocybin G or Control G (n=30 each)	Psilocybin (0.17mg/kg p.o) or Placebo	Balanced randomized, placebo-controlled, double-blind, parallel-group design	Creativity (Convergent and Divergent Thinking)	Picture Concept Task; Alternative Uses Task	Psilocybin ↑ divergent thinking, incl. novelty and ↓ convergent thinking at 7-day follow-up compared to Placebo. Suggested that the difference in convergent thinking might be due to an impaired learning effect during Psilocybin.
Dos Santos et al. (2021)	17 volunteers with social-anxiety disorder (F=15, M=2), mean age: 24.9 (range: 19-32); Ayahuasca G (n=9) & Control G (n=8); Undergraduate students (n=15) & Private psychiatric clinic (n=2)	Ayahuasca (2ml/kg) or Placebo; Drug was donated by Traditional Ayahuasca Church	Randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial	Emotion Recognition (SC)	Recognition of Emotions in Facial Expressions (derived from Ekman & Friesen)	Significant effect of time (↑ reaction time, and ↑ accuracy) was found in the Ayahuasca group, but not in the Placebo group.
Mendes Rocha et al. (2021)	20 healthy volunteers, mean age: 31.8 (range: 21-55); randomly allocated to Ayahuasca G (F=7, M=3) or control G (F=5, M=5)	Ayahuasca (1ml/kg p.o.); Drug was donated by Traditional Ayahuasca Church	Randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial	Emotion Recognition (SC)	Recognition of Emotions in Facial Expressions (derived from Ekman & Friesen)	Significant effect of time (↑ reaction time, and ↑ accuracy) was found in both groups, suggesting a learning effect, possibly up to a ceiling effect.
Barbosa et al. (2016)	30 US-members of a Brazilian syncretic Christian Ayahuasca church (M=16, F=14), age range: 22-67; Non-Ayahuasca	Ayahuasca; Ceremonies within past 12-months (range: 20-62; median = 32.5)	Cross-sectional, case-controlled design	Verbal intelligence (L); Visual attention (A); Selective attention, cognitive flexibility, inhibition (A & EF); Sustained Attention (A); Verbal	Nelson Adult Reading Test; Trail Making Test; Stroop Color-Word Test (Golden Version); Conners' Continuous Performance Test II; California Verbal	No significant group differences on any of the cognitive measures, except that Ayahuasca ↑ verbal learning with proactive interference (CVLT). Additional evidence that regular Ayahuasca use has no long-term effects on cognitive functioning. Measures were done after at least 6 days of Ayahuasca abstinence.

	using control G (n=27)			Retention, Retrieval, & Recognition (ML & L), Vulnerability to Proactive Interference (EF)	Learning Test (CVLT)	
Bouso et al. (2012)	127 regular Ayahuasca users of Brazilian Ayahuasca churches located in Jungle and Urban Settings (F=65, M=62), mean age 36.74±13.07 ; Non-Ayahuasca using religious control G (n=115)	Ayahuasca; at least twice per month for past 15 years; Control group: Less than 6 lifetime Ayahuasca experiences	Between-group comparison with age, sex, and education matched control group	Selective attention, conflict monitoring (A & EF); Strategic planning, organized searching, cognitive set-shifting, goal-oriented behavior, impulse inhibition (EF); WM	Stroop Color Word Test; Wisconsin Card Sorting Test; Letter-Number Sequencing from WAIS III	Ayahuasca ↑ on most subscales of all tests, suggesting no prefrontal impairment due to Ayahuasca use. This might be due to Ayahuasca users' motivation to demonstrate its safety to researchers.
Bouso et al. (2015)	22 regular Ayahuasca users of the Santo Daime church (M=6, F=16), mean age: 40.9±12.6; Non-Ayahuasca using matched-controls (n=22)	Ayahuasca; at least 50 times in past 2 years; no ayahuasca use at least 2 weeks prior testing	Between-group comparison with age, sex, education, verbal IQ and fluid IQ matched control group	WM; Planning, set-shifting, response inhibition (EF); Set-shifting (EF)	Two-back Task; Wisconsin Card Sorting Test; Switching Task	Ayahuasca ↑ on most subscales of dual-back task and non-switch trials of task-switching tests. No other significant differences between groups. Indicates no worse neuropsychological performance nor evidence of neuropsychological toxicity in Ayahuasca group.
Culver & King (1974)	24 LSD/mescaline-using Dartmouth senior class students; age range: 20-25	LSD and/or Mescaline, untested, use of at least once per month for past 12 months, no use before college	Between-group comparison with age, verbal SAT, mathematical SAT, and MMPI matched control groups (one cannabis user & one with no cannabis or LSD/mescaline use)	Intelligence (GC); L; WM; Visual attention (A)	WAIS (Verbal, Performance, & Full-scale IQ; Subtests: Comprehension, Vocabulary, Similarities, Information, Speech Perception; Digit Span); Trail Making Test	LSD/Mescaline users performed within normal limits, but ↓ than the cannabis-using group and the control group. Alcohol use was not accounting for these differences.

Doering-Silveira et al. (2005)	Brazilian adolescents; Ayahuasca-consuming group (n=40) from syncretic Christian Ayahuasca church (M=22, F=18), mean age: 16.52±1.34; control group (n=40)	Ayahuasca; at least 24 times in past 2 years, but at least 20 days of Ayahuasca abstinence prior to study	Between-group comparison matched by sex, age, race, and educational level	Visual attention, scanning, psychomotor speed (A); Selective attention & cognitive flexibility (A & EF); ML; Sustained attention, reaction time, vigilance (A); Verbal learning & memory (L & ML); WM; EF	Trail Making Test; Stroop Color-Word Test (Victoria Version); Rey-Osterrieth Complex Figure Test; Conners' Continuous Performance Test II; WHO-UCLA Auditory Verbal Learning Test; WAIS III Subtests (Digit Span; Digit Symbol Substitution; Symbol Search; Object Assembly)	No significant group differences on any of the measures, except Ayahuasca ↓ learning & encoding trials of WHO-UCLA Auditory Verbal Learning Test. This was within average range when compared to normative adolescent data. Indicates no injurious effects of Ayahuasca on adolescents using it in ceremonial setting with their families.
Grob et al. (1996)	15 male long-term members of a Brazilian syncretic church that uses Ayahuasca	Ayahuasca; frequent, repeated ingestion over at least 10 years	Between-group comparison with age, sex, ethnicity, and level of education matched control group	Auditory-Verbal Encoding, Storage, and Retrieval (L & ML)	WHO-UCLA Auditory Learning Verbal Memory Test (translated from English to Portuguese)	Ayahuasca users ↑ on recall of words on fifth learning trial, and almost all other scales, although non-significantly. Indicates overall high cognitive functioning and no cognitive deterioration in long-term Ayahuasca users.
Halpern et al. (2005)	Navajo Native Americans (ages 18-45): G1: Peyote-using Native American Church Members (n=61); G2: Individuals with past-alcohol dependence (n=36); G3: Individuals with minimal substance use (n=79); Gs sign. differed in sex (G1: F = 75%; G2: F = 44%, G3:	Mescaline-containing cactus (Peyote); Group 1: at least 100 times, Group 2 & 3: <5 times); other hallucinogen use <10 times in all three groups	Cross-sectional design with investigator blinded to group status	ML; EF; ML; A & EF; GC; A; L; WM; EF	Rey-Osterrieth Complex Figure Test; Wisconsin Card Sorting Test; Nonverbal portions of Wechsler Memory Scale; Stroop Color-Word Test; Ravens Progressive Matrices; Trail Making Test; WAIS Subtests (Vocabulary; Digit Span; Digit Symbol Substitution; Block Design)	No significant differences on any of the measures between Peyote-using Group (1) and group with minimal substance use (3). Total lifetime Peyote use showed no significant associations with neuropsychological measures. These results may not generalize to illicit hallucinogen users.

	F = 82%) and age (G2 > G3); similar level of education					
Kaasik & Kreegipuu (2020)	30 Estonian Ayahuasca users (F=15, M=15), mean age: 38.7±9.8; Control G (n=30): Estonian non-users matched by gender, age, and level of education	Ayahuasca (usually 30-60ml, but up to 120ml), probably some participants dosed repeatedly	Cross-sectional case-controlled design	GC; GC	Montreal Cognitive Assessment (Estonian Version); Raven Standard Progressive Matrices (24-item computer version)	No significant differences on cognitive ability or fluid intelligence between both groups. Also not significantly correlated with past 12-month or lifetime use of Ayahuasca.
Murphy-Beiner & Soar (2020)	48 healthy adult volunteers with psychedelic interest (F=26, M=22), mean age: 38.48±7.21, predominantly white and highly-educated	Ayahuasca; lifetime past ayahuasca experiences: 0 (12,5%), 1-5 (20.8%), 6-10 (29.2%), >10 (37.5%; total years of ayahuasca use: 0-9; 1 participant used it 2 weeks before study, all others did not use it for 1 month+	Controlled, observational, within-subject design	Selective attention, conflict monitoring, and resistance to interference (A & EF); Set-shifting, problem-solving, response inhibition (EF)	Stroop Color-Word Test (SCWT); Wisconsin Card Sorting Test (WCST)	Significant increase in correct responses between pre- and post-ayahuasca on the WCST, not influenced by previous ayahuasca intake. No significant effect on reaction times was found (WCST). SCWT interference (congruent vs. Incongruent trials) showed no significant effect, but errors on incongruent trials were significantly reduced after Ayahuasca. A limit to these conclusions is that both tests are very prone to learning effects.
O'Shaughnessy et al. (2021)	8 Spanish-speaking male addiction treatment center inpatients, motivated for treatment	Ayahuasca; repeated ingestion over at least 2 months treatment period, along with other traditional indigenous healing methods (diet & social seclusion) and Western psychotherapeutic and biomedical approaches.	Observational design with repeated measures	GC; A; L; ML	Repeated Battery for the Assessment of Neuropsychological Functioning Update (Total Scale; Attention Subscale; Language Subscale; Delayed Memory Subscale)	Mean score increases on all neuropsychological measures from intake to treatment, however paired samples t-test intake vs treatment was only significant for total scale and delayed memory.
Vardy & Kay (1983)	21 psychiatric inpatients who	LSD, untested & unknown dose; 34.6%	Between-group comparison with age,	Intelligence (GC); WM; A & EF; L; L; L; ML	WAIS (Verbal, Performance & Full-Scale	Both groups had highly similar subtest scatter profiles on the WAIS, only the comprehension subtest

	experienced LSD-induced psychosis (M=17, F=4) mean age: 19.81±3.09	one to five times, 7.7% six to ten times, 57.7% eleven to one-hundred times	education, demography matched control group with 3- to 5-year follow-up		IQ; Subtests: Digit Span; Digit Symbol Substitution; Information; Comprehension; Similarities; Vocabulary); Bender Visual Retention Test	was worse in the LSD group, while the digit span test was worse in the schizophrenic group, verbal IQ > performance IQ in both groups and could not distinguish them; No differences in visual-motor performance between groups, both highly impaired
Wright & Hogan (1972)	20 volunteering LSD users (F=5, M=15), mean age: 20.15 (range: 17-24)	LSD (100-300µg), mean nr. of LSD experiences= 29.3	Between-group comparison with age, sex, education, and intelligence matched control group	Intelligence (GC); L; WM; A & EF; Visual attention (A)	WAIS (Verbal, Performance, Full-scale IQ; Subtests: Comprehension, Vocabulary, Similarities, Information, Speech Perception; Digit Span; Digit Symbol Substitution); Trail Making Test	Overall, no significant differences between LSD users and control group; No "brain" or cognitive dysfunctions in LSD users
Uthaug et al. (2018)	Ayahuasca ceremony participants (n=57): G1: Dutch (n=30; F=18, M=12), 7 reported a psychological disorder; G2: Colombian (n=27; F=18, M=9), 6 reported a psychological disorder	Ayahuasca: Colombia and Dutch samples varied considerably in DMT, harmine, and harmaline concentrations; Past experiences with Ayahuasca: 56.7% of G1 & 59.3% of G2	Mixed within-subject and between-group observational design	Creativity (Convergent and Divergent Thinking)	Picture Concept Task (3 parallel versions composed of the Wechsler Preschool and Primary School Intelligence Scale and the Wechsler Intelligence Scale for Children	Convergent thinking increased by 9% and 29% at the morning after and 4-weeks after ayahuasca intake, respectively, whereas only the latter was significant. Divergent thinking on the other hand did not change significantly. It might be that both convergent and divergent thinking coincide, as divergent thinking was previously shown to increase during acute effects, whereas this study shows an increase of convergent thinking at 4-week follow-up.

F Female, *M* Male; *G* Group; *p.o.* per oral, *i.v.* intraveneous, *A* Attention & Alertness, *EF* Executive Functions & Cognitive Control, *SC* Social Cognition, *ML* Memory & Learning, *L* Language, *WM* Working Memory, *GC* Global Cognition, *O* Other cognitive functions, *sign.* significantly, ± Standard Deviation, ↑ increase, ↓ decrease, *WAIS* Wechsler Adult Intelligence Scale, *WHO-UCLA* World Health Organization - University of California Los Angeles

Time Frame: Acute Effects vs. After Effects

The first research question, to compare the acute and after-effects of CPs, was reduced to the usual dosages of psychedelics as the effects of CP microdoses will be discussed below. Twenty-one studies measured cognition during the acute psychedelic effects, thirteen studies measured cognition after the acute psychedelic effects (i.e. subacute), and three measured both during and after acute psychedelic effects. These will be described per cognitive dimension (i.e. social cognition, creativity, attention/alertness, executive functions, working memory, memory/learning, language, others). Cognitive tests were categorized into these dimensions according to the cognitive functions mentioned by the studies or by the manual, in case they were not mentioned or contradictive.

Social Cognition

Social cognition was measured during the acute effects of a CP by eight studies (Dolder et al., 2016; Dos Santos et al., 2021; Duerler et al., 2020; Kometer et al., 2012; Mendes Rocha et al., 2021; Pokorny et al., 2017; Preller et al., 2018; Smigielski et al., 2020), and subacutely by two studies (Dos Santos et al., 2021; Mendes Rocha et al., 2021). Kometer et al. (2012) found Psilocybin to acutely decrease recognition of negative emotions and increase behavior towards positive relative to negative emotional cues. Self-other differentiation was reduced by the acute effects of LSD and Psilocybin (Preller et al., 2018; Smigielski et al, 2020). Furthermore, Dolder et al. (2016) found LSD to acutely increase prosocial behavior, while Duerler et al. (2020) found LSD to acutely increase the social adaptation of opinions similar to one's own. Implicit and explicit emotional empathy, as measured by the Multifaceted Empathy Test, was increased during the acute effects of LSD and Psilocybin (Dolder et al, 2016; Pokorny et al., 2017). Two studies found emotion recognition, as measured by the Recognition of Emotions in Facial Expressions Task, not to be acutely affected by Ayahuasca, but found a significant increase over time with follow-up assessments until 3-months after intake (Dos Santos et al., 2021; Mendes Rocha et al., 2021). Of the eight

acutely measuring studies six found an effect and two found no effect on social cognition. Both subacute studies found positive effects on social cognition.

Creativity

Creativity was measured by two studies during the effects of a CP (Kuypers et al., 2016; Mason et al., 2021), and subacutely by two studies (Mason et al., 2021; Uthaug et al., 2018). Tests applied were the Picture Concept, the Alternative Uses, and the Pattern-Line Meanings Task. Convergent thinking was found to be decreased by acute CP effects, while divergent thinking was acutely increased by Psilocybin and decreased by Ayahuasca (Kuypers et al., 2016; Mason et al., 2021). At 7-days post-Psilocybin, Mason et al. (2021) found divergent thinking to be increased and convergent thinking to be decreased. Conversely, Uthaug et al. (2018) found no effect on divergent thinking 1-day and 4-week after Ayahuasca, but a significant increase of convergent thinking at 4-week follow-up.

Attention & Alertness

Nine studies assessed attention or alertness during the acute psychedelic effects (Daumann et al., 2010; Goldberger, 1966; Gouzoulis-Mayfrank et al., 2006; Hasler et al., 2004; Umbricht et al., 2003; Spitzer et al., 1996; Bouso et al., 2013; Quednow et al., 2011; Barrett et al., 2018) and nine studies assessed it after the acute drug effects were over (Barbosa et al., 2016; Culver & King, 1974; Doering-Silveira et al., 2005; Murphy-Beiner & Soar, 2020; O'Shaughnessy et al., 2021; Wright & Hogan, 1972; Halpern et al., 2005; Bouso et al., 2012; Vardy & Kay, 1983). Acute measures of attention were the Serial Sevens, the Target-Detection, Covert Orienting of Visual Attention, AX-Continuous Performance, Digit Symbol Substitution (DSST), Stroop Color-Word Tests, the Frankfurt Attention Inventory, and the Lexical Decision Paradigm. All nine studies found significant reductions on their measures of attention during the acute effects of a CP (Daumann et al., 2010; Goldberger, 1966; Gouzoulis-Mayfrank et al., 2006; Hasler et al., 2004; Umbricht et al., 2003; Spitzer et al., 1996; Bouso et al., 2013; Quednow et al., 2011; Barrett et al., 2018).

Tests of attention after the acute effects of a CP were the Stroop Color-Word (SCWT), Digit Symbol Substitution, Conner's Continuous Performance, Trail Making Tests (TMT), and the Attention Subscale of the Repeated Battery for the Assessment of Neuropsychological Functioning. Six studies did not find any differences on attention between CP users and controls (Barbosa et al., 2016; Doering-Silveira et al., 2005; O'Shaughnessy et al., 2021; Wright & Hogan, 1972; Halpern et al., 2005; Vardy & Kay, 1983). Three studies did not find differences on the SCWT between regular Ayahuasca or Peyote users and controls (Halpern et al., 2005; Doering-Silveira et al., 2005; Barbosa et al., 2016). Contrary to that, Bouso et al. (2012) found the SCWT performance of regular Ayahuasca-users to be better than that of controls. Furthermore, Murphy-Beiner & Soar (2020) found a significantly reduced number of errors in the incongruent condition of the SCWT 24-hours post-Ayahuasca. In contrast, Culver & King (1974) found their LSD/mescaline-using group to have significantly worse TMT performance compared to controls, but their performance was within normal limits. Another four studies did not find any attentional differences on the TMT between regular LSD-using, Ayahuasca-using, or Peyote-using groups, and controls (Barbosa et al., 2016; Doering-Silveira et al., 2005; Halpern et al., 2005; Wright & Hogan, 1972). All nine acutely measuring studies found significant impairments of attention. Of the nine subacutely measuring studies two found significantly positive, one found significantly negative, and six found no effects on attention.

Executive Functions & Cognitive Control

Seven studies measured executive functions during the acute effects of a CP (Gouzoulis-Mayfrank et al., 2006; Pokorny et al., 2019; Barrett et al., 2018; Bouso et al., 2013; Schmidt et al., 2017; Umbricht et al., 2003; Quednow et al., 2011), and eight studies measured it after the acute CP effects were over (Barbosa et al., 2016; Bouso et al., 2012; Bouso et al., 2015; Doering-Silveira et al., 2005; Halpern et al., 2005; Murphy-Beiner & Soar, 2020; Wright & Hogan, 1972; Vardy & Kay, 1983). Measures used to assess executive functions acutely were

the Covert Orienting of Visual Attention Task, Tower of London (ToL), AX-Continuous Performance Task, Go/No-Go Task, Intra-/Extra-Dimensional Shift Task (IEDST), Cambridge Gambling Task (CGT), Digit Symbol Substitution Task, and Stroop Color-Word Test (SCWT). Four studies only found significant impairments on their measures of executive functions during the acute effects of a CP (Gouzoulis-Mayfrank et al., 2006; Barrett et al., 2018; Schmidt et al., 2017; Quednow et al., 2011). Bouso et al. (2013) found the ToL performance of occasional, but not of experienced, Ayahuasca users to be significantly impaired. Furthermore, they found significantly decreased response latencies with unaffected accuracy on the SCWT from pre-Ayahuasca scores to scores during Ayahuasca. In contrast, Quednow et al. (2011) found significantly increased response latencies and errors on the SCWT in their Psilocybin condition compared to Placebo. Pokorny et al. (2019) found LSD-related decreased executive performance on the IEDST, but no impact on risk-based decision making on the CGT.

Executive functioning tests applied after acute CP effects were over included the Stroop Color-Word (SCWT), Digit Symbol Substitution (DSST), Wisconsin Card Sorting (WCST), Switching (ST), and California Verbal Learning Tests (CVLT). Three studies did not find performance differences on the SCWT between regular Ayahuasca- or Peyote-users and controls (Barbosa et al., 2016; Doering-Silveira et al., 2005; Halpern et al., 2005). On the other hand, Bouso et al. (2012) found better SCWT performance, including better inhibitory performance, in their regular Ayahuasca-using group compared to controls. Also, Murphy-Beiner & Soar (2020) found significant improvements in SCWT performance from pre- to 24-hour-post-Ayahuasca scores. On the DSST, three studies found no significant differences between LSD-, Peyote-, and adolescent Ayahuasca-users and controls (Halpern et al., 2005; Doering-Silveira et al., 2005; Wright & Hogan, 1972). In contrast, Vardy & Kay (1983) found their group with an LSD-induced psychosis to exhibit an impaired DSST performance similar to that of a schizophrenic comparison group. Bouso et al. (2012) found the

performance of regular Ayahuasca-using groups on the WCST to be significantly better than controls. Murphy-Beiner & Soar (2020) also found the WCST performance of Ayahuasca users to be significantly improved 24 hours after Ayahuasca use. The WCST performance of regular Peyote-users was not significantly different from that of controls (Halpern et al., 2005). Similarly, Bouso et al. (2015) only found a trend towards a better WCST performance in regular Ayahuasca-users compared to controls, but on the Switching Task the performance of the Ayahuasca group was significantly better than that of the controls. Also, Barbosa et al. (2016) found regular Ayahuasca users to be significantly better than controls on the interference list of the California Verbal Learning Test, which indicates a lower susceptibility to proactive interference. All seven acutely measuring studies found significant executive functioning impairments. Of the eight subacutely measuring studies four found no significant differences, and four found significantly better executive functioning in CP users.

Working Memory

There are six studies that measured working memory during the acute effects of a CP (Goldberger, 1966; Pokorny et al., 2019; Vollenweider et al., 1998; Barrett et al., 2018; Wittman et al., 2007; Bouso et al., 2013), and seven studies that measured it after the acute CP effects were over (Bouso et al., 2012; Bouso et al., 2015; Doering-Silveira et al., 2005; Halpern et al., 2005; Vardy & Kay, 1983; Culver & King, 1974; Wright & Hogan, 1972). Working memory tests applied during the acute CP effects included the Spatial Span, Letter-n-Back, Spatial Working Memory, Sternberg Working Memory, Visual-Manual Delayed Response, and Digit Span Tasks. Five studies reported significant working memory impairments during the acute effects of a CP (Pokorny et al., 2019; Vollenweider et al., 1998; Barrett et al., 2018; Wittman et al., 2007; Bouso et al., 2013). In contrast, the Digit Span Task solely used by Goldberger (1966) was not significantly influenced by the acute effects of LSD compared to placebo.

Four studies used the Digit Span Task (DST) after the acute effects of a CP found no

differences to the performance of controls (Halpern et al., 2005; Doering-Silveira et al., 2005; Culver & King, 1974; Wright & Hogan, 1972). Vardy & Kay (1983) found a significantly better DST performance in the group suffering from LSD-induced psychosis compared to the schizophrenic comparison group. Regular Ayahuasca users scored significantly better than controls on the Letter-Number Sequencing and Two-Back Tasks, indicating a better working memory performance (Bouso et al., 2012; Bouso et al., 2015). Five of the six acutely measuring studies found significant working memory impairments, while one did not find an effect. Of the seven subacutely measuring studies four found no differences, and three found significantly better working memory performance.

Memory & Learning

The dimension of memory and learning was measured by one study during the acute effects of a CP (Barrett et al., 2018), while six studies measured it subacutely (Barbosa et al., 2016; Grob et al., 1996; Halpern et al., 2005; O'Shaughnessy et al., 2021; Vardy & Kay, 1983; Doering-Silveira et al., 2005). Barrett et al. (2018) found Psilocybin to acutely and dose-dependently reduce episodic memory function on the Word Encoding, Recall, and Recognition Task.

Regarding studies that measured memory after the acute CP effects, four studies did not find differences between regular Ayahuasca users and controls, assessed with the California Verbal Learning Test, the World Health Organization/University of California at Los Angeles Auditory Verbal Learning Test, the Rey-Osterrieth Complex Figure Test, and the Wechsler Memory Scale (Barbosa et al., 2016; Grob et al., 1996; Halpern et al., 2005; Doering-Silveira et al., 2005). In contrast, Vardy & Kay (1983) found no significant difference on the Bender Visual Retention Test between patients with an LSD-induced psychosis and schizophrenic patients. On the other hand, O'Shaughnessy et al. (2021) used the Repeated Battery for the Assessment of Neuropsychological Functioning Update and found the performance on the delayed memory subscale to be significantly improved from intake to treatment in a group of

people with substance-use disorders in an addiction treatment center which uses Ayahuasca. The one acutely measuring study found a significant impairment on memory. Of the six subacute studies five did not find any differences and one found positive effects on memory function.

Language

Three studies have measured language during the acute effects of a CP (Family et al., 2016; Goldberger, 1966; Spitzer et al., 1996), and seven have measured it after the acute effects of the CP (Barbosa et al., 2016; Doering-Silveira et al., 2005; O'Shaughnessy et al., 2021; Wright & Hogan, 1972; Culver & King, 1974; Halpern, 2005; Grob et al., 1996; Vardy & Kay, 1983). Goldberger (1966) employed a Comprehension of Long and Short Passages Test, a Word Naming Test, the Robinson Rhyming Test, and a Simple Rhyming Test, and found that the group acutely under the influence of LSD to have a significantly lower performance compared to the placebo group else than the Short Passage Comprehension Subtest. Spitzer et al. (1966) used a Lexical Decision Paradigm and found a significant increase of indirect semantic priming in the group acutely under the influence of Psilocybin, but no significant difference in direct semantic priming between the Psilocybin group and the Placebo group. Similarly, Family et al. (2016) found significantly more substitution errors for semantically similar, but not semantically different words, and similar reaction times on the Picture-Naming Task in their LSD condition compared to the Placebo condition, suggesting that LSD increases the spread of semantic network activation.

Barbosa et al. (2016) employed the Nelson Adult Reading Test and the California Verbal Learning Test to a group of regular Ayahuasca users and found no differences to controls. Similarly, Doering-Silveira et al. (2005) and Grob et al. (1996) employed the World Health Organization – University of California Los Angeles Auditory Verbal Learning Test and found no differences between their regular Ayahuasca user groups and control groups on most trials. Culver & King (1974) did not find any differences on the language-related

Wechsler Adult Intelligence Scale (WAIS) subtests (Comprehension, Vocabulary, Similarities, Information, Speech Perception) between LSD users and controls. Wright & Hogan (1972) also did not find significant differences between LSD users and controls on these measures, else than that the LSD users performed significantly worse on the WAIS Comprehension and significantly better on the WAIS Information subtests. Also, Halpern et al. (2005) found no difference between regular Peyote users and a comparison group on the WAIS Vocabulary Test. Vardy & Kay (1983) found a subjects with an LSD-induced psychosis and schizophrenic subjects to have similar performances on the WAIS Information, WAIS Vocabulary, and WAIS Similarities, but found a significantly worse WAIS Comprehension performance in the LSD-psychotic group. O'Shaughnessy et al. (2021) found no difference between performance at intake and performance at follow-up of people with substance use disorders in an Ayahuasca treatment center on the language subscale of the Repeated Battery for the Assessment of Neuropsychological Functioning Update. All three acutely measuring studies found an effect on language function. Of the seven subacutely measuring studies two found a significant difference in language function, while five studies did not.

Other Cognitive Functions

Regarding tests that assess other cognitive functions, Barrett et al. (2018) applied the Circular Lights Task, the Balance Task, and the Penn Motor Praxis, as well as the Penn Line Orientation Tasks and found acute Psilocybin effects to dose-dependently impair gross motor performance, such as balance and hand-eye-coordination, and induced psychomotor slowing without impairing accuracy, but to not influence spatial orientation. Wittman et al. (2007) employed the Mates Sensorimotor Synchronization, and Tapping Speed Tasks, and an Auditory Temporal Reproduction Task of short- and long-intervals to people under the influence of Psilocybin or placebo. They found Psilocybin to decrease the reproduction of sound intervals of less than three seconds, synchronization of motor response to sound less

than two seconds, and reduced preferred tapping tempo, which can be concluded in that Psilocybin alters time perception and temporal control of behavior (Wittmann et al., 2007).

Global Cognitive Ability

There is one study that employed measures of global cognitive ability during the acute effects of a CP (Barrett et al., 2018), and six studies that measured it after the acute effects of a CP (Culver & King, 1974; Kaasik & Kreegipuu, 2020; Vardy & Kay, 1983; Wright & Hogan, 1972; Halpern et al., 2005; O'Shaughnessy et al., 2021). The performance on the Mini Mental Status Examination was not significantly impaired in subjects under the influence of Psilocybin (Barrett et al., 2018).

Four studies did not find significant differences in global cognition between Ayahuasca-, Peyote-, and LSD-using groups and controls, as measured by the Montreal Cognitive Assessment, Raven's Standard Progressive Matrices, and the Wechsler Adult Intelligence Scale (WAIS; Kaasik & Kreegipuu, 2020; Halpern et al., 2005; Culver & King, 1974; Wright & Hogan, 1974). Also, Vardy & Kay (1983) applied the WAIS and did not find significant differences on verbal, performance, and full-scale IQ between an LSD-induced psychosis group and a schizophrenic group. In contrast, O'Shaughnessy et al. (2021) employed the Repeated Battery for the Assessment of Neuropsychological Functioning Update on a group of people with substance use disorders and found significant improvement from intake assessment to an assessment during or after a treatment in a specialized Ayahuasca center.

Table 3

Overview of studies that used CP microdoses

Study	Sample	Substance & Dosage	Design of Study	Constructs Addressed	Methodology	Conclusions
Hutten et al. (2020)	24 healthy recreational psychedelic users (F=12, M=12); mean age: 22.8±3, majority Caucasian (n=21), mostly students in higher education	LSD (0, 5, 10, 20 μg; min. 5 days washout between randomized administrations)	Double-blind placebo-controlled within-subject design	Sustained Attention (A); A & EF; Cognitive Control (EF)	Psychomotor Vigilance Task (PVT); Digit Symbol Substitution Task (DSST); Cognitive Control Task (CCT)	Speed of Information Processing reduced, while retained accuracy (DSST; 20mcg); Majority showed enhanced attention (PVT; 5, 20mcg); Cognitive Control unaffected (CCT)
Szigeti et al. (2021)	191 participants, mostly educated, middle-aged (mean age: 33.5±9.4), healthy males (M=70%, F=29%, Other=1%); randomized to placebo, half-half (2 weeks placebo, 2 weeks microdose), or microdose conditions	Psychedelic Microdose, twice per week for 4 weeks; reported substances (not tested): 61% LSD, 24% Psilocybin mushrooms, 14% LSD analogue, 1% DOB or LSA; average dose: LSD/LSD analogues (13μg+-5.5) & Psilocybin mushrooms (0.2g+-0.12)	Naturalistic, randomly assigned, self-blinding, prospective online citizen-science	Spatial WM; Visual Memory (M & L); visual representation (O); deductive reasoning (O); planning (EF); A	Spatial Span Test; Paired Associates Test; Rotations Test; Odd one out Test; Spatial Planning Test; Feature Match Test	Neither accumulative (from baseline to week 5), nor acute (2-6 hours after drug intake) cognitive improvements were found and no significant differences between groups were found on any of the measures. The placebo effect underlies microdosing-related self-reported cognitive improvements.
Bershad et al. (2019)	20 healthy young adults (F=12, M=8), age range: 18-40	LSD (6.5μg, 13μg, and 26μg sublingually) or placebo; at least 7 days apart; at least 1 previous psychedelic experience	Double-blind, placebo-controlled, randomized within-subject design	WM; A & EF; Emotion regulation in social exclusion (SC); Emotion processing (SC); Convergent thinking (C)	Dual N-Back; Digit Symbol Substitution Task; Cyberball Task; Emotional Images Task; Remote Associations Task	LSD microdoses had no significant effects on any of the measures.
Prochazkova et al. (2018)	Healthy participants of a microdosing event (n=38; M=23,	Psilocybin-containing dried truffles (analyzed Psilocybin, Psilocin,	Quasi-experimental design	Convergent & divergent thinking (C); Convergent & divergent thinking (C);	Picture Concept Task (PCT); Alternative Uses Task (AUT);	Psilocybin microdose significantly increased performance on the convergent and divergent thinking tasks (PCT & AUT), but not fluid

	F=15), mean age: 31.1±11.49; Included in the analyses: RPMT (n=38), PCT (n=27), AUT (n=33)	Norbaeocystin, and Baeocystin contents); recommended dosages according to body weight; No prior psychedelic experience (n=2)		Fluid intelligence (GC)	Raven's Progressive Matrices Task (RPMT; short 12-item version); two versions of each test for pre- and post-testing	intelligence (RPMT). Expectation (placebo) effects cannot be excluded due to no control group.
Family et al. (2019)	Healthy older volunteers (n=48; M=27, F=21), mean age: 62.9±5.73; randomly assigned to one of four dose groups (each n=12)	LSD microdose (5µg, 10µg, 20µg) or Placebo; repeated administration of same dose on 6 occasions with 96-hour intervals; no LSD use in past 5 years	Double-blind, placebo-controlled, randomized within-subject design	Reaction time (A); Visual M & L; Visual A; Spatial WM; Balance (O); Proprioception incl. Body position, motion, and equilibrium (O)	Reaction time Test; Paired Associates Test, Rapid visual information processing Test, Spatial working memory Test; BTrackS™; Proprioception protocol by Goble (2010)	None of the LSD dose groups showed significant effects on the cognition tests, balance, or proprioception tests. This suggests that either the dose was insufficient or that these doses do not produce any acute or cumulative effects on cognition in a healthy population.

F Female, *M* Male; *G* Group; *A* Attention & Alertness, *EF* Executive Functions & Cognitive Control, *SC* Social Cognition, *ML* Memory & Learning, *WM* Working Memory, *GC* Global Cognition, *O* Other cognitive functions, *sign.* significantly, ± Standard Deviation, ↑ increase, ↓ decrease

Microdosing Studies

Regarding CP microdoses, the literature screening resulted in five studies that used objective cognitive tests (Hutten et al., 2020; Szigeti et al., 2021; Bershad et al., 2019; Prochazkova et al., 2018; Family et al., 2019). Szigeti et al. (2021) employed the Spatial Span, Paired Associates Learning, Rotations, Odd One Out, Spatial Planning, and Feature Match Tasks in their self-blinded citizen psychedelic microdosing study, and did not find significant accumulative nor acute differences on any of the cognitive measures. Similarly, Family et al. (2019) repeatedly gave randomized LSD microdoses or placebo to healthy older subjects and did not find any significant differences, regardless of dose, on the Cambridge Neuropsychological Test Automated Battery Tests (Reaction Time, Paired Associates Learning, Rapid Visual Information Processing, Spatial Working Memory), the BTrackS™ Test, and the Proprioception protocol. Also, Bershad et al. (2019) employed the Dual-n-back,

Digit Symbol Substitution, Cyberball, Emotional Images, and Remote Associations Tasks on their young adult sample acutely under the influence on repeated, randomized LSD microdoses or placebo, and did not find significant effects on any of the measures. On the other hand, Hutten et al. (2020) found 20mcg of LSD to significantly reduce the speed of information processing on the Digit Symbol Substitution Task without affecting accuracy. In contrast, there was no significant effects on the Cognitive Control Task and neither on reaction times on the Psychomotor Vigilance Test (PVT). On the other hand, they found the number of attentional lapses on the PVT significantly decreased in the 5mcg and 20mcg conditions, but not in the 10mcg condition (Hutten et al., 2020). Prochazkova et al. (2018) did find significant increases in convergent and divergent creative thinking on the Picture Concept Task and the Alternative Uses Task, but no significant difference in fluid intelligence on the Ravens Progressive Matrices Task, from pre-dosing assessment to an assessment during the effects of a Psilocybin microdose.

Extra-Pharmacological Factors

The third research question about the influence of extra-pharmacological factors (EPF) on the cognitive effects of CPs will be reported per EPF (i.e., personality; preparation, expectancies, motivations, and intentions; physical-setting, social-setting, cultural-setting).

Personality

Personality was only implemented into the correlational analysis by Duerler et al. (2020), who found that neuroticism is negatively correlated and fulfilling expectations is positively correlated with LSD-induced changes in social adaptation of one’s opinion from. Hasler et al. (2004) and Quednow et al. (2011) used the personality factors neuroticism and openness as an exclusionary criterion, while Culver & King (1974) matched their groups personalities. Three studies compared the personalities of regular Ayahuasca users with controls and found them to be higher in agreeableness and openness, to have a higher reward dependence and self-transcendence, and to have a lower harm-avoidance and self-directedness (Barbosa et al.,

2016; Bouso et al., 2012; Bouso et al., 2015).

Preparation, Expectancies, Motivations, and Intentions

Regarding the EPF of preparation, informed consent was given by participants in all studies, informing them about the effects of CPs. Furthermore, most of the studies that tested cognition during the acute effects of a CP previously assessed prior CP experiences of their sample (N=21), while eight studies did not assess or mention it in their study. Of the ones that assessed it, seven studies had a sample with prior CP experiences, five studies had an CP-naïve sample, and eight studies had a mixed sample of CP-experienced and CP-naïve participants. Regarding the EPF of expectancies, motivations, and intentions, Uthaug et al. (2018) was the only study that assessed the motivations of Dutch and Colombian Ayahuasca ceremony participants, but did not implement it in their analyses. One of the two studies that investigated CPs' possible therapeutic effects on cognitive impairments related to psychiatric disorders did not inform participants about possible positive effects and additionally implemented a placebo condition.

Physical-, Social-, and Cultural-Setting

The physical-setting is another EPF thought to influence CP effects, and was a laboratory or hospital setting in 26 studies, of which all tested their participant's cognition while under the influence of a CP. Seven of these studies mentioned this setting to be comfortable. Fourteen studies employed computerized tests, and seven studies were implementing magnetic resonance imaging or brain imaging procedures. In contrast, in 16 studies the physical-setting during the CP effects was a naturalistic setting, in which only three studies measured cognition acutely and fourteen studies measured cognition subacutely. Nine of these studies assessed the cognition of populations of regular, long-term CP users, who use Ayahuasca or Peyote (i.e., mescaline) for spiritual purposes in a ritualistic, ceremonial setting and three studies measured the cognition of non-traditional Ayahuasca ceremony participants. Another three studies have subacutely assessed the impact of illicit CP use, which is likely

happening in various naturalistic physical-settings. Szigeti et al. (2021) tested their participants cognition while under the influence of a microdose in their natural environment and Prochazkova et al. (2018) acutely assessed participants of a microdosing event. Regarding the social-setting, fourteen studies included samples of CP-use in a group setting of which ten studies measured after the CP effects were over and four studies measured acutely. Of the latter four studies, two were full-dose Ayahuasca studies and two were microdosing studies. In the 26 studies in a laboratory or hospital setting the CP was individually administering to each participant, and five of these studies mentioned that a supportive researcher, doctor, or nurse was present at all times. Finally, the cultural-setting was traditional in eight studies, meaning the Ayahuasca/Peyote use was embedded into the sample's own culture, while the other 34 studies investigate non-traditional CP use.

Conclusion

Almost all measures of each cognitive dimension that were applied to a person acutely under the influence of a full dose of a CP were showing impairments. This includes acute impairments on tests of attention, executive functions & cognitive control, working memory, and memory & learning. Exceptional cognitive dimensions were social cognition, language, and creativity, on which the results were more variable. Regarding social cognition, most studies found acute CP effects significantly decreased recognition of negative facial expressions and self-referential processing, but significantly increased emotional empathy, the desire to be with others, the behaviour towards positive relative to negative emotional cues, and prosocial behaviour (Dolder et al., 2016; Dos Santos et al., 2021; Kometer et al., 2012; Mendes Rocha et al., 2021; Pokorny et al., 2017; Preller et al., 2018; Smigielski et al., 2020). Furthermore, Duerler et al. (2020) found social adaptation of opinions to be increased, especially if the group's opinion was similar to one's own. These LSD-induced changes in this social adaptation were found to be higher in those higher on neuroticism and those lower in fulfilling expectations, hinting towards an importance of personality in social cognitive

effects of CPs. If the positive effects on emotional empathy and desire to be with others are lasting, they could potentially be helpful in treating disorders of decreased social connectedness, such as depression (Frick et al., 2021). Therefore, it is essential to assess CPs subacute effects on social cognition of clinical populations in the future. As personality seems to be an important factor here, it should be of special focus.

The studies that measured language functions during the acute effects of a CP found mixed results, such as decreased performance on comprehension and word naming tests, while other test results that suggest an increased spread of semantic network activation and increased indirect semantic activation (Goldberger, 1966; Family et al., 2016; Spitzer et al., 1996). The latter two findings suggest an increase in divergent thinking, which is seen as the first phase of creativity. Two studies investigated the acute effects of CPs on divergent thinking and found mixed effects, while convergent thinking, which can be seen as the second phase of the creative process, was decreased in both studies (Kuypers et al., 2016; Mason et al., 2021). As the tests applied for assessing creativity all relied upon language production, it might be that these need to be validated through another sensory modality. Furthermore, making personalized creativity tests to increase its meaningfulness for the individual might decrease attentional impairments and make it more valid (Buchborn et al., 2022). As creativity is a significant common factor among most psychotherapeutic approaches, its assessment should be a focus in future trials of psychedelic-assisted psychotherapy (Holm-Hadulla, 2020).

Memory was measured by just one study during the acute effects of a CP which found it to be decreased (Barrett et al., 2018). The acute CP-induced divided attention deficit might underly this memory decrement, as divided attention was found to impair memory encoding, but not memory retrieval (Craik, Eftekhari & Binns, 2018). In a similar vein, a previous systematic review concluded that CPs acutely decrease semantic and non-autobiographical episodic memory, while often vividly re-eliciting autobiographical memories (Healy, 2021).

This re-eliciting of autobiographical memories might be therapeutically useful, if the reconstructed memory is approached with the right affect, assigned the right meaning, and integrated afterwards (Healy, 2021). If, as Swanson (2018) posited, the unconstrained perception and cognition acutely elicited by CPs are the mechanism of its therapeutic value, the constrains of a neuropsychological testing environment might not be beneficial for pathological populations. In contrast, psychedelic-assisted psychotherapy is often non-directive and supports relaxation and introspection throughout the experience (Denis-Lalonde & Estefan, 2020; Reiff et al., 2020). Therefore, future clinical studies might be more focused on assessing neuropsychological effects after the acute effects of the CP.

Of the sixteen studies that measured cognition subacutely, four asked their participants to remain abstinent from CPs for a certain time (mean = 8.5 days), six had a mean delay of 17 days between CP use and time of measurement, and six did not report the delay between CP use and time of measurement. As the delay might be an important factor, it should be more consistently reported in future studies. Most of these subacute studies of CP users did not find any differences in comparison to non-users. This was on measures of attention, language, memory, and global cognition. Some studies reported better performances of CP users on tests of executive functions (EF), working memory (WM), social cognition, and creativity. Regarding better EF, three studies used samples of regular Ayahuasca users in traditional Ayahuasca churches, while another found better EF performance 24-hours post-Ayahuasca in experienced Ayahuasca users (Bouso et al., 2012; Bouso et al., 2015; Barbosa et al., 2016; Murphy-Beiner & Soar, 2020). Nevertheless, the correlational design of these studies does not allow for a causal inference, as it might be that those who have a higher EF are more open towards Ayahuasca rituals. Also, two studies found a better WM in regular, traditional Ayahuasca users (Bouso et al., 2012; Bouso et al., 2015). Four other studies did not find any differences in a group of traditional Peyote users, a group with Social Anxiety Disorder treated with Ayahuasca, a group of undergraduate LSD-users, and LSD users on another WM

measure, the Digit Span Task (Halpern et al., 2005; Doering-Silveira et al., 2005; Culver & King, 1974; Wright & Hogan, 1972). This test was also applied by Vardy & Kay (1983) to a group of patients with an LSD-induced psychosis, who had significantly better scores than a schizophrenic comparison group. Therefore, it can be concluded that WM is not impaired in CP users, but possibly better in traditional Ayahuasca users. Although, as the traditional Ayahuasca user studies used different WM measures than the Digit Span Task used by the other studies, it might be solely due to differences of the applied tests. After-effects of CPs on measures of creativity were also mixed, as Mason et al. (2021) found increased divergent thinking and decreased convergent thinking 7-days post-Psilocybin, while Uthaug et al. (2018) found no change in divergent and convergent thinking 1-day and 4-week post-Ayahuasca, but a significant increase in convergent thinking at 4-weeks post-Ayahuasca. This difference might be due to a difference in EPFs, as Uthaug et al. (2018) had a mixed sample with Ayahuasca-naïve and Ayahuasca-experienced users, who used the CP in a naturalistic, ceremonial setting, while Mason et al. (2021) applied Psilocybin to a sample with prior CP-experiences in a laboratory setting with acute brain imaging measures. Social cognition was sub-acutely measured by two studies, which found significant increases over time on the Recognition of Facial Expressions Task (Dos Santos et al., 2021; Mason et al., 2021). As they both applied a CP in a comfortable laboratory room with the support of a researcher or nurse, and both measured cognition during its effects, they do not diverge in physical setting. But, Mendes Rocha et al. (2021) found this effect in both Ayahuasca- and placebo-groups, which suggests a learning effect. Dos Santos et al. (2021), on the other hand, had a sample with Social Anxiety Disorder (SAD) and found this effect only in the group who were given Ayahuasca, but not in the Placebo group. Thus, it can be that subjects with SAD benefit from this learning effect only if given a CP, leading to a sub-acute increase in the recognition of facial expressions. To clarify this, these findings need to be replicated in a bigger sample with SAD.

Regarding CP microdoses, three studies did not find significant differences on the neuropsychological measures (Szigeti et al., 2021; Bershad et al., 2019; Family et al., 2019). These three studies used double- or self-blinded, placebo-controlled designs. In contrast, Hutten et al. (2020), who also used a double-blinded, placebo-controlled design, found decreases in speed of information processing on 20µg LSD, and decreases in attentional lapses on 5mcg and 20mcg of LSD, but no significant effect of 10µg LSD on these measures. Prochazkova et al. (2018) found significant increases in creativity, including convergent and divergent thinking, in participants of a microdosing event on which participants used a microdose of Psilocybin-containing truffles without any blinding. As Szigeti et al. (2021) had an almost ten times bigger sample, who self-administered their own self-blinded psychedelic microdoses or placebo, and subsequently did the tests in a naturalistic environment, this can be taken as evidence for an underlying placebo effect. Nevertheless, all five microdosing studies used a healthy sample, restricting extrapolations about cognitively impaired clinical populations, such as those with dementia, mild cognitive impairment, or traumatic brain injury. These neurological disorders might benefit from psychedelics' capability to increase hippocampal neurogenesis and decrease neuroinflammation (Saeger & Olson, 2021; Vann Jones & O'Kelly, 2020; Khan et al., 2021; Kozlowska et al., 2021).

The third research question about the influence of extra-pharmacological factors (EPF) on cognitive effects of CPs is difficult to answer, as only fourteen percent of the acutely measuring studies were conducted in a naturalistic environment, while the others were conducted in a laboratory or hospital room. Furthermore, most EPFs such as personality, motivations, intentions, and expectancies, were assessed by a negligible number of studies and not taken into analyses. These factors need to be investigated in future studies. Nevertheless, the effects of context during the CP experience might influence its after effects, as these were more variable from improved cognition in traditional Ayahuasca users, and individuals with social-anxiety disorder to schizophrenia-like cognitive deficits in those with

an LSD-induced psychosis.

The re-emergence of neuropsychological research with psychedelics since 1990 was focused on improving the understanding of psychosis by using the psychedelic state as a model for the psychotic state (Langlitz, 2006). This model had little contribution for its purpose to improve the understanding of neurobiological substrates of schizophrenia and the development of better antipsychotics, but rather led to an improvement of the understanding of psychedelic psychopharmacology (Langlitz, 2006; Langlitz, 2012, p. 609). This systematic review reflects this paradigm shift by showing the acutely impaired cognition during the effects of CPs and the indifference or improvement of cognition characterizing the subacute effects of CPs. The better cognition of ritualistic Ayahuasca users shown in some studies indicate an importance of social and cultural context. Furthermore, the possible cognitive improvements of socially anxious individuals are further supporting the shift of psychedelic neuropsychological research towards an expansion of investigations on the possibly beneficial subacute CP effects on cognitively impaired clinical populations. Therefore, it might be more valuable to further shift away from the model psychosis paradigm towards a paradigm of psychedelic-assisted psychotherapy.

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Appendix

PubMed Search Query

("cogniti*"[Title/Abstract] OR "neuropsychological tests" [Mesh] OR neuropsych* [tiab]) AND ("hallucinogens"[MeSH Terms] OR "psychotomimetic" [tiab] OR "psychedelic" [tiab] OR hallucinogen* [tiab] OR "Lysergic Acid Diethylamide"[MeSH Terms] OR "Psilocybin"[MeSH Terms] OR "Mescaline"[MeSH Terms] OR Ayahuasca [tiab] OR "Lysergic Acid Diethylamide" [tiab] OR "LSD" [tiab] OR "psilocybin" [tiab] OR "mescaline" [tiab]) NOT ("animals"[MeSH] NOT "humans"[MeSH]) NOT (Review[Publication Type])

PsycInfo Search Query

(DE “neuropsychological assessment” OR TI (neuropsych* OR cogniti*) OR AB (neuropsych* or cogniti*)) AND (DE “hallucinogenic drugs” OR TI (“ayahuasca” OR “dimethyltryptamine” OR “DMT” OR “psychotomimetic” OR hallucinogen* OR “psychedelic”) OR AB (“ayahuasca” OR “dimethyltryptamine” OR “DMT” OR “psychotomimetic” OR hallucinogen* OR “psychedelic”)) NOT (PO Animal NOT PO Human) NOT TI (“review” OR “meta-analysis”)