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Titel: Psykedeliske agenter og deres potentielle fremmende effekt på kreativ præstation-et systematisk review
Titel, engelsk: PSYCHEDELIC AGENTS AND THEIR POTENTIAL ENHANCING EFFECT ON CREATIVITY - A SYSTEMATIC REVIEW
Tro og love-erklæring: Ja
Indeholder besvarelsen fortroligt materiale: Nej
Antal anslag: 134814
Antal normalsider: 56

PSYCHEDELIC AGENTS AND THEIR POTENTIAL ENHANCING EFFECT ON CREATIVITY – A SYSTEMATIC REVIEW

Master's thesis in Medical Biology

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Handed in: 21st December 2018
Character count: 134.814/56 pages

RUC

Resumé (DK)

Fremmelse af kreativ præstation har potentialet til at gøre os I stand til at tænke ud af boksen og finde løsninger på problemer såsom automatisering af jobs. Op mod 50 % af nuværende jobs er estimeret til at blive automatiseret inden 2035 i Danmark og USA. Studerende såvel som erhvervsfolk bruger allerede psykofarmakologiske midler til at øge kognition, og de psykofarmakologiske midler, psykedelika, stiger i popularitet som kreativitetsfremmende midler.

Formålet med dette studie er systematisk at gennemgå den publicerede empiri, der undersøger psykedelikas potentielle effekter på kreativ præstation. Selv-rapporteringer er ikke medtaget. I alt inkluderes 12 studier der møder inklusionskriterierne for den nærværende undersøgelse. Effekten af psykedelika på kreativ præstation er svær at afgøre, da studierne er vanskelige at sammenligne. Dette skyldes 1) den store heterogenitet studierne imellem (fx diversiteten af anvendte metoder, variation af type psykedelika og doseringer), og 2) kvaliteten af de inkluderede studier (fx lille studiepopulation, manglende information samt fravær af randomiserede kontrollerede [RCT] studier). Disse faktorer forvirrer og skævvrider billedet ved forsøg på sammenstilling af de forskellige studier. Nærværende studie finder ikke evidens for at psykedelika fremmer kreativ præstation. Dog finder nærværende studie tendenser, der tyder på, at visse individer med særligt kreative egenskaber (inden for fx tegning eller problemløsning) kan drage fordel af psykedelika til at fremme deres præstationer inden for netop deres kreative felt. Hvorvidt disse potentielle effekter kræver oplevelse af den psykedeliske rus, er endnu uvist. Fundene i dette review er i overensstemmelse med tidligere reviews af den eksisterende litteratur om psykedelikas indflydelse på kreativ præstation. Der er behov for flere resultater fra mere metodisk velfunderede, kontrollerede studier for at bekræfte de observerede tendenser.

Abstract (EN)

Enhancing creative performance has the potential of enabling us to think outside the box and find solutions to problems such as automatization of jobs, as estimates suggest that up to 50% of current jobs will be automated by 2035 in Denmark and the USA. Students as well as businessmen are already using psychopharmacological agents to enhance cognition, and the psychopharmacological agents, psychedelics, are becoming quite popular for enhancing creativity.

The aim of the present study is to systematically review all published empirical publications that investigate the potential effects of psychedelics on creative performance. Self-reports are not included. A total of 12 studies were included the present study. The effect of psychedelics on creative performance is difficult to determine due to issues of incomparability among the studies. These issues arise due to 1) large heterogeneity in the included studies (e.g. diversity of methods used, variation of agents and dosages examined), and 2) quality of the studies (e.g. small sample sizes, lack of information, and lack of randomised controlled trials [RCT]). These factors confound and bias the impression when attempting to compare the different studies. The present study did not find evidence of psychedelics enhancing creative performance. However, tendencies found in the present review suggests that certain individuals with already existing skills within a specific field of creativity (e.g. drawing or engineering problem-solving) could benefit from psychedelics to enhance these same skills. Whether this potential effect requires the presence of the psychedelic experience, is yet to be determined. The findings in the present review are in alignment with previous reports reviewing the literature on the effects of psychedelics on creative performance. More results are needed from more methodologically sound, controlled studies to confirm observed tendencies and correlations.

Foreword

The present report was made as a final project for the master's degree in Medical Biology + Health Promotion and Health Strategies at Roskilde University in 2018.

The base of this project comes from my passion for the human mind and curiosity of cognitive enhancement. With advancing technology and automatization of jobs, a fear of a jobless future spreads throughout our society. Will technology take over our jobs and what will that leave us to do for a living? It is my personal impression that creativity might be one of the single most important skills to keep evolving, to be able to overcome many obstacles, such as a potential jobless future. Agents that might be able to enhance creativity are psychedelics which are becoming popular as cognitive enhancers in both business, education and private life. My first encounter with psychoactive agents as cognitive enhancers was when a fellow student involved me in her considerations on trying out these agents as "smart drugs" or "study drugs", simply to better overcome the challenges of the everyday life as a university-student. I have found this way of applying drugs both fascinating and daunting at the same time. Fear and lack of knowledge of the agents led me to abstain from personal experiences with psychedelic agents. Are these agents as dangerous as they are pictured to be? And what potential do they have? Do they have the potential to help us out of a jobless future?

The present report is aimed at readers with a certain level of knowledge of and interest in neurobiology, neuropsychology and medical biology. The report is primarily aimed at students from Natural Sciences with affiliation to or knowledge within biomedical and neuropsychological subjects within this framework.

Along with the project, special abbreviations and concepts are used. These will be explicated the first time they are mentioned. In addition, the report contains a glossary with the most frequently used abbreviations and terminology which can be used as a reference tool when reading the report. This can be found on the page between *Acknowledgements* and the table of contents. Appendix A contains an overview of the creativity methods/tasks used in the included studies of for the systematic review and Appendix B contains an overview of data extraction from all included studies collected.

Acknowledgements

I would like to thank all those who contributed to the thesis project. I gratefully acknowledge Roskilde University for the encouragement and opportunity to pursue my own research ideas throughout my education.

Special thanks to my supervisor Henrik Berg Rasmussen, Research Manager at Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen University Hospital, for guidance and support throughout the process. Furthermore, I would like to thank the following people for inspiration, general input and feedback: Cand.scient. Erik Christensen and anthropologist Anders Dahl. For editorial assistance I would like to express my special thanks to cand.scient.cons Signe Buccarella Hedegaard. Errors and opinions are my own.

I am deeply grateful for the support and encouragement from my family, especially my mother Susanne and my sister Maria. And most importantly, I would like to thank Gajan, my partner in life, and our daughter Vinaya, for support, endurance and unconditional love.

Roskilde University, 21st December 2018

Mie Lykke Jeppesen

TERMINOLOGY AND ABBREVIATIONS

Terminology

Creative performance	Creative performance or activity resulting in a creative product, expression and/or achievements
Microdose	Non-psychoactive dosages of psychedelics
Phosphenes	The phenomenon of seeing lights without light actually entering the eye
Recreational use (of psychedelics)	Using substances to alter the consciousness
Set & Setting	Concept which refers to the psychological, social, and cultural parameters which shape the response to psychedelic agents
Synaesthesia	The phenomenon of experiencing things through senses in an unusual way, e.g. experiencing a colour as a sound, or a number as a position in space
Trip/psychedelic experience	The phenomenon of experiencing temporary changes in perception, mood, consciousness and behaviour under the influence of psychedelic agents

Common Abbreviations

5-HT$_{2A}$	5-hydroxytryptamine 2A, serotonin	**FC**	Figure Completion
AST	Aesthetic Sensitivity Tests	**LSD**	Lysergic acid diethylamide
BCU	Blank Circle Use	**MAPS**	Multidisciplinary Association for Psychedelic Studies
CT	Convergent thinking	**MDMA**	3,4-methylenedioxy methamphetamine (also known as *ecstasy*)
DAP	Draw a person	**N/A**	Not available
DMT	*N*,*N*-dimethyltryptamine	**n =**	Number of subjects
DT	Divergent thinking	**n.s.**	Not significant
EFT	Embedded Figures Test	**OVT**	Object Visualization Test
PLMT	Pattern/Line Meanings task	**RCT**	Randomised controlled trial
PCT	Picture Concept Task	**TAT**	Thematic Apperception Task
RAT	Remote Association Task	**WAT**	Word Association Test

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1. INTRODUCTION

Cognitive performance enhancers have become quite popular – not only in Silicon Valley but also in Denmark (The New Yorker, 2016; Videnskab.dk, 2017). Young people in the Danish high schools and universities are requesting cognitive enhancers, also known as "study drugs" or "smart drugs", to be able to meet the demands that they feel society makes of them (Videnskab.dk, 2017).

With development of artificial intelligence (AI), concern is rising globally regarding which jobs will be safe from technological automatization and a potential threat of a jobless future. Reports suggest that 50% of jobs will be automated by 2035 in Denmark and the USA (Politiken, 2016; DR, 2018; World Economic Forum, 2018). We need to be creative to find other ways to ensure ourselves economically. Creativity may be one of a few skills which AI technology cannot replace (The Guardian, 2018). Enhancing creativity might be the opportunity for humans to avoid automatization of their jobs. Creative and complex jobs are listed as the most difficult for AI to take over. John Smith, manager of Multimedia and Vision at IBM Research says: "*It's easy for AI to come up with something novel just randomly. But it's very hard to come up with something that is novel and unexpected and useful*." (IBM, 2018).

The desire to "expand" or explore the mind is not a new thing. In fact, psychopharmacological agents have been used in many parts of the world for thousands of years. Especially psychedelics may be the oldest class of psychopharmacological agents, or psychoactive agents, known to man and have been used as such in many parts of the world dating back several thousands of years (Guerra-Doce, 2015; Nichols, 2016). These agents are known to induce spiritual and imaginary hallucinations and feelings of well-being. Particularly well-known is lysergic acid diethylamide (LSD) used by the so-called hippies during the 1960's (Nichols, 2016). In addition, anecdotal reports have also found these psychoactive agents efficient in enhancing creativity. Apple's inventor Steve Jobs (1955-2011) was open to the fact that he had experimented with LSD and that it was a profound experience for him in relation to creating the concept of Apple (Nichols, 2016). Also, the inventor of PCR, the Nobel-prize-winning chemist Dr Kary Mullis, said: "*Would I have invented PCR if I hadn't taken LSD? I seriously doubt it... I could sit on a DNA molecule and watch the polymers go by. I learnt that partly on psychedelic*

drugs." (Nichols, 2016). Additionally, artists of various kinds, such as The Beatles, are believed to have used psychoactive agents to expand their artistic insight and expression (DeRogatis, 2003).

There are many anecdotal reports on the creativity enhancing effects of psychedelics, but where is the evidence? To assess whether these agents can in fact enhance creativity, available studies investigating the topic needs to be examined. From these thoughts, the following problem formulation arises (cf. section 1.1).

1.1. PROBLEMFORMULATION

Can psychedelics enhance creative performance and to what extend?

1.1.1 Demarcation

Results of the present thesis are based on studies that perform creativity assessment methods where the results are evaluated by other persons than the study subject himself/herself. Thus, self-reports on creativity are not included. Furthermore, the thesis is focused on psychoactive agents of the type; psychedelics. These include serotonergic hallucinogens (5-HT [5-hydroxytryptamine] 2A receptor agonists) and entactogens (5-HT releasing agents) (cf. section 2.2.1). Other psychoactive agents such as dissociatives (N-methyl-D-aspartate [NMDA] receptor antagonists) and cannabinoids (CB-1 cannabinoid receptor agonists) will not be investigated in the present report but will shortly be described in the background section 2.2.1. Lastly, only studies investigating creative performance, expression or products that arise from creative activities are included. Thus, studies exclusively investigating traits and characteristics of the creative person as well as environmental influences or contextual factors are excluded.

2. BACKGROUND

The following section contains background information on creativity and psychedelic agents.

2.1 CREATIVITY

Eastern and Western perspectives on creativity differ. However, it is the Western perspective that dominates the research on creativity and the academic psychological literature (Batey and Furnham, 2006). From this perspective, creativity is seen as a trait that is normally distributed, partly genetically determined property of individuals (Batey and Furnham, 2006). This is in contrast with the Eastern perspective which view creativity more as a process of understanding and enlightenment rather than a personal trait (Batey and Furnham, 2006).

The word *create* is derived from the Latin *creatus*, 'to have grown'; defined as a mental process involving the generation of new ideas or concepts or new associations between existing ideas or concepts. The ancient Greeks talked about creativity in the context of poetry 'bringing new life into the world', and the ancient Romans expanded this further to encompass the creativity of art and architecture (Sessa, 2008).

The present report approaches creativity from the Western perspective.

In principle creativity refers to many domains of human activity, including the arts, literature, science, philosophy, and politics (Thys *et al.*, 2014). According to Thys *et al.*, (2014), who have conducted an extensive review of the research on creativity in science, creativity is sometimes narrowed down to the arts, visual arts in particular., In research, on the other hand, it is sometimes operationalised in a way that seems remote from natural human creativity. As a research subject, creativity is studied in disciplines as varied as philosophy, psychology, economy, and the neurosciences.

2.1.1 Defining Creativity

The definition of creativity in academia has not been particularly uniform and researchers have neither reached consensus on a definition nor on assessment methods (Batey and Furnham,

2006). When assessing the literature, it becomes apparent that the term is still being defined as researchers expand their knowledge. The major issue scattering scientific creativity research is the very definition and use of the term *creativity* (Batey and Furnham, 2006). The term is used in such diverse manners that it has "(…)*almost ceased to mean anything*." (Batey and Furnham, 2006).

Creativity is supposedly a syndrome, or a multicomponent construct, in that there are a number of cognitive requirements (e.g., associative tendencies, divergent thinking, fluency, flexibility, originality, and intuition), emotional and motivational influences (e.g., intrinsic interest and determination), personality traits (e.g., openness, wide interests, and autonomy), and contextual factors (e.g., support, resources, benefits, and minimal costs) (Runco, 2009). Additionally, creative ideas are necessary for creativity as suggested by the American professor of psychology Dean K. Simonton (2016):

> "*A creative process or (procedure) generates creative ideas. A creative person uses a creative process (or procedure) to generate those ideas. A creative product provides a vehicle for communicating those ideas to others*".

The origin of a Standard Definition of Creativity is somewhat obscure. Barron (1955), Stein, (1953) and Guilford (1950) have often been credited for the standard definition. According to Runco and Jaeger (2012), however, only the former two should in fact be credited for the standard definition. Their article, which elaborates on and discusses this topic, is a recommendable read. Runco and Jaeger find the first clear standard definition of creativity to be from Stein (1953):

> *"The creative work is a novel work that is accepted as tenable or useful or satisfying by a group in some point in time.... By "novel" I mean that the creative product did not exist previously in precisely the same form".*

Runco and Jaeger (2012) do, however, emphasise that further work is needed to define creativity adequately considering that the current use only points out what criteria must be used, not whom is to judge the criteria or whom is to judge the judges, and the agreement of numbers of criteria (Runco and Jaeger, 2012).

Typically, the literature refers to a two-criteria type of creativity. The standard definition of creativity consists of two criteria; originality and effectiveness (Runco and Jaeger, 2012). Originality implies that something must be *novel*, *unique* or *unusual*. If it is not, it is not original. Something can, however, be original without being creative. For something to be creative, it must be effective as well. Effectiveness can be labelled as *usefulness*, *fit*, *appropriateness* or referred to as *utility.* What is effective or useful is a rather subjective matter (Runco and Jaeger, 2012).

To summarise what creativity is and what is required, it is useful to consult Parkhurst (1999):

> "*The ability or quality displayed when solving hitherto unsolved problems, when developing novel solutions to problems others have solved differently, or when developing original and novel (at least to the originator) products.*".

As such, creativity, is an ability to come up with new solutions, or produce something new which can be utilized. Both criteria seem to depend on subjectivity (Runco and Jaeger, 2012).

2.1.2 Divergent Thinking

Indicators of creativity, depends on the research area of creativity (see 2.1.3). When measuring creativity as a product that result from creative ideas, many researchers seem to rely on assessment methods that are based on *divergent thinking*. See also section 2.1.3.

Divergent Thinking has for a long time been understood as an important part of creative problem solving and is, by Guilford (1950, 1968), tied to the creative potential (Runco, 2011; Runco and Acar, 2012). It is a sign of cognitive flexibility and a term for the more unconventional, numerous, daring or unique generations of ideas, often without preoccupation of what is considered to be the "right" or logical answer (Lezak *et al.*, 2012). The principle factors of divergent thinking are associational fluency, ideational fluency, spontaneous flexibility, and originality.

Convergent Thinking is a term for the process of the tendency to give "correct", conventional and obvious responses (Lezak *et al.*, 2012). For example; responding "brick" to a question on how to build a wall.

2.1.3 Assessing Creativity

When investigating creativity, research can be divided into four research areas (Batey and Furnham, 2006); (1) the person who creates, (2) the cognitive process involved in the creation of ideas, (3) the environment in which creativity occurs or environmental influences, and (4) the product that results from creative activities.

All these research areas are useful in assessing creativity, as it, as mentioned earlier, is supposedly a syndrome (cf. section 2.1.1). However, when investigating the creative product, one would assess the product resulting from creative activities (4).

Many assessment tools are based on Guilford's assertion that creativity is based on divergent thinking (section 2.1.3). A popular creativity test battery based on divergent thinking is the Torrance Tests of Creative Thinking (TTCT) which is verbal and non-verbal tests of divergent thinking, assessing fluency, flexibility, originality, and elaboration (Torrance, 1966). According to Runco and Acar (2012), most tests of divergent thinking now exclusively evaluate fluency, originality, flexibility, and elaboration, in spite of Guilford's other factors. Often the only factor included is fluency which is defined in terms of productivity. A fluent individual contributes with a large number of ideas. Originality is usually defined in terms of novelty. Flexibility leads to diverse ideas that use a variety of categories. The least common factor, elaboration, is suggested when the individual follows an associative pathway for some distance (Runco and Acar, 2012). Fluency can be viewed as a constituent of creativity, but also of intelligence (Thys *et al.*, 2014). And research have been tying creativity and intelligence together (e.g. Batey and Furnham, 2006). To address this, Carroll (1993) performed a comprehensive investigation of psychometric creativity and found that: "*Creativity is linearly independent of many of the factors in other domains, or more generally, of what is regarded as intelligence as measure by standard tests*". Furthermore, Batey and Furnham (2006) conclude that a high IQ is a necessary but an

insufficient trait for success in science and engineering, and it is less likely to be important for achievement in the arts.

Some researchers propose that divergent htinking is inadequate as a measure of creativity, because it merely measures *the potential* of creativity**.** Runco and Acar (2012, p. 66) writes:

> *"Divergent thinking is not the same as creative thinking. Divergent thinking often leads to originality, and originality is the central feature of creativity, but someone can do well on a test of divergent thinking and never actually perform in a creative fashion."*

To make divergent thinking tests more reliable Runco and Acar (2012, p. 67) points out; that "(…)*judges can be objective and give reliable ratings*" and the natural following question on; "(…)how to select the best judges".

2. 2 PSYCHEDELIC AGENTS

2.2.1 Definitions

Psychopharmaceuticals, or psychoactive agents, are agents that acts primarily on the central nervous system (CNS) where it alters brain function, resulting in temporary changes in perception, mood, consciousness and behaviour. These agents may be used recreationally (e.i. to alter the consciousness) or therapeutically as medication (Koob *et al.*, 2010). Some types of psychoactive agents are *hallucinogens* and *psychedelics*. Hallucinogens are psychoactive agents that induce hallucinations. The term hallucinogen is often used broadly to cover all psychoactive agents such as cannabinoids, 3,4-Methylenedioxymethamphetamine (MDMA, also known as ecstasy), entactogens (also known as empathogens) and dissociative agents (which distort perceptions of sight and sound). For an overview of hallucinogens, turn to table 1. Psychedelics is yet another term which is used broadly, however, according to one of the most prominent researchers in the field, the American pharmacologist and medicinal chemist David Earl Nichols, psychedelics are serotonergic hallucinogens. That is, psychoactive agents that has 5-hydroxytryptamine (5-HT) 2A agonist (or partial agonist) properties (Nichols, 2016). Table 1 presents an overview of agents categorised as psychedelics along with some selected hallucinogens. The name "psychedelic," essentially means "mind manifesting", and on this basis

Dunlap and colleagues (2018) proposes that entactogens become a subdivision of psychedelics together with the "classical hallucinogens" (e.g. LSD, psilocybin, mescaline). The term psychedelics was coined in 1957 by psychiatrist Humphry F. Osmond (1917-2004) (Nichols, 2016). Jaffe's (1990) definition of psychedelics: "…*the feature that distinguishes the psychedelic agents from other classes of drug is their capacity reliably to induce states of altered perception, thought, and feeling that are not experienced otherwise except in dreams or at times of religious exaltation*.". A psychedelic experience or "trip" is when experiencing these beforementioned features under the influence of psychedelics.

Table 1: Classification of hallucinogens, examples of agents and receptor binding.

Abbreviations: LSD, lysergic acid diethylamide; NMDA, N-methyl-D-aspartate; THC, tetrahydrocannabinol; 5-HT$_{2A}$ (5-hydroxytryptamine 2A)

Class of hallucinogen	Subdivision	Classic examples of psychoactive agents	Receptor binding
Cannabinoids	-	THC	CB-1 cannabinoid receptor agonists
Dissociatives	-	Ketamine, salvinorin A (a specific opioid κ agonist)	NMDA receptor antagonists
Psychedelics	Entactogens (serotonin releasers)	MDMA	5-HT$_{2A}$
	Serotonergic hallucinogens	Ayahuasca, psilocybin, mescaline and LSD	5-HT$_{2A}$ receptor agonist (or partial agonist)

Serotonergic hallucinogens can be classified based on their chemical structure as phenethylamines and tryptamines. Within the tryptamines, there are the simple tryptamines including the classic natural hallucinogens psilocybin, DMT and mescaline, and the ergolines including mainly LSD (Liechti, 2017).

The term "entactogen," was coined in 1986 the American pharmacologist and medicinal chemist David E. Nichols. It translates from Greek to mean that which "produces a touching within" (*en* = within, *tactus* = touch, *gen* = to produce) (Nichols, 1986).

2.2.2 Psychedelics, Creativity and the 5-HT$_{2A}$ receptor

This section gives a short introduction to the link between psychedelics, creativity, and the 5-HT$_{2A}$ receptor. For in-depth information on signalling pathways and additional neurotransmitters and their receptors related to psychedelics, I recommend the recent review by Nichols *et al.* (2016).

Creativity is related to both cognition and emotion, which are the two major mental processes interacting with each other to form psychological processes (Gu *et al.*, 2018). Psychedelics are also known to be related to these mental processes. There is a scientific consensus that the link between psychedelics and the mental processes is mediated by especially the 5-HT$_{2A}$ receptor (Nichols, 2016). In addition, serotonin is presumably linked to altered connectivity in the brain, which is observed in both creativity and under the influence of psychedelic drugs (Robin L. Carhart-Harris *et al.*, 2016; Gu *et al.*, 2018). Serotonin is a key neurotransmitter and neuromodulator that regulates a variety of behaviours and mental processes (Cameron and Olson, 2018). The molecular structure is depicted in section 2.2.3.

Psychedelics have in common that they interact with the 5-HT$_{2A}$ receptor which is thought to have a crucial role in the psychedelic experiences induced by these psychoactive agents (e.g. Geiger *et al.*, 2018). The first evidence from human studies is provided by (Vollenweider *et al.*, 1998). They show that effects mediated by psilocybin are blocked by ketanserin, a 5-HT$_{2A}$ receptor–selective antagonist, or the atypical antipsychotic Risperidone but were enhanced by the dopamine antagonist and typical antipsychotic Haloperidol. Several more studies have been carried out by the same and other researchers (Nichols, 2016).

The 5-HT_{2A} is expressed throughout the brain and found in high concentrations in areas that are responsible for sensory processing and cognition. Among these areas are; the neocortex, thalamus, locus coeruleus (LC), and ventral tegmental area (VTA) (Nichols, 2016).

2.2.3 Ayahuasca and DMT

One of the psychedelics which use has expanded the most in recent years is ayahuasca. It is a plant-derived preparation that contains *N,N*-dimethyltryptamine (DMT), also known as the "spirit molecule" (Strassman, 2000). DMT is a classical (serotonergic) psychedelic with 5-HT_{2A} agonist properties and according to a recent review by Cameron and Olson (2018) it is "*archetype for all indole-containing serotonergic psychedelics*" as its structure is embedded in other classic psychedelic molecules e.g. LSD and psilocybin (cf. figure 1). Also, the structures of these compounds are similar to that of serotonin (cf. figure 1). Furthermore, the molecule is one of the few psychedelic compounds produced endogenously by mammals, and its biological function in the human physiology remains a mystery. Isoforms of the molecule have been synthesised by chemists (Cameron and Olson, 2018).

Figure 1: Structural relationship between DMT and other brain function modulating compounds. Overlapping features of DMT and these compounds are highlighted in red. Modulated from Cameron and Olson (2018)*. Abbreviations: DMT, N,N-dimethyltryptamine; LSD, lysergic acid diethylamide.*

Ayahuasca, also known as yagé or hoasca, has a long history of use by natives in the Amazon valley of South America (Nichols, 2016; Cameron and Olson, 2018). In the native American language Quechua ayahuasca "vine of the soul" *ayahuasca*meaning soul, ancestors or dead persons, and *wasca* (huasca) meaning vine or rope (Luna, 2011). Ayahuasca is a preparation of two plants: the pounded bark from *Banisteriopsis caapi* vines and leaves from *Psychotria viridis*.

The latter containing DMT. Although DMT is not orally active, *B. caapi* contains β-carboline alkaloids that inhibit the liver monoamine oxidase (MAO) that normally breaks down DMT; thus, ayahuasca is taken orally as a "tea" or brew (Cameron and Olson, 2018).

Dosage and effects

The preferred route of administration differs from ayahuasca to DMT. Ayahuasca are usually ingested orally in the form of a brew while DMT is usually smoked by recreational users (i.e. non-religious users) (Cakic *et al.*, 2010). DMT, when smoked, has a rapid onset (a few minutes) and short duration of action (less than an hour) which led DMT to be known in the 1960s as a "businessman's lunch" (Cameron and Olson, 2018).

A small clinical trial with encapsulated and freeze-dried ayahuasca showed psychological effects 30–60 minutes after ingesting one of three doses (0.5, 0.75, and 1.0 mg/kg), peaked between 60–120 minutes, and after 240 minutes (4 hours) all of the psychological effects resolved (Riba *et al.*, 2001). These stages are depicted in figure 2. For reported effects, turn to table 2. The authors concluded that the stimulatory and visual psychoactive effects were of longer duration and milder intensity than those previously reported for intravenously administered DMT.

Table 2: Selected reported effects of ayahuasca ingestion. Selected from Riba et al. (2001).

Visual effects	Enhancement in object's brightness and sharpness
Cognitive effects	Enhanced rate of thinking which was generally focused on personal psychological content, and enhanced feeling of closeness to others

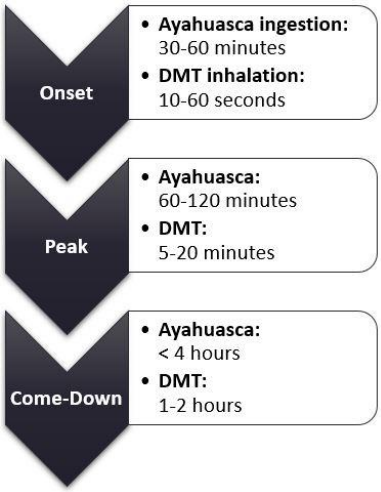

Figure 2: Stages of ayahuasca/DMT from onset to after-effect. Data from The Third Wave (2018c). *Abbreviations: DMT,* N,N-*dimethyltryptamine.*

2.2.4 LSD

It was the Swiss Dr. Albert Hofmann, the natural products chemist who accidently discovered the effects of LSD in 1943 while working at the Sandoz Laboratories in Basel, Switzerland, wrote an autobiographical account of his discovery entitled LSD: My Problem Child (Hofmann, 1979). He synthesised LSD for the first time in 1938 (Nichols, 2018). The structure of the molecule can be seen in figure 1 in section 2.2.3 along with its resemblance to serotonin. LSD is a classical (serotonergic) psychedelic with 5-HT_{2A} partial agonist properties (Nichols, 2016; PubChem, 2018). In neuroscience and drug development LSD has been an important tool (Nichols, 2018) and has influenced the arts and society. By recreational users LSD is also known as *Acid* (The Third Wave, 2018c). Recreational use of this agent was widely popular in America and Europe throughout the 1970s, 80s, and 90s and it is estimated to have been used by about 10% of Americans and Europeans (The Third Wave, 2018c).

Unlike the other classic serotonergic hallucinogens LSD binds adrenergic and dopaminergic receptors at sub-micromolar concentrations (Rickli et al, 2016). LSD has been found to increase functional connectivity between various brain regions at the whole-brain level compared to placebo (Müller *et al.*, 2017).

Dosage and effects

Liechti (2017) have reviewed all of the clinical studies that employed LSD in the last 25 years. He reports that a full LSD reaction is expected at doses of 100–200 µg and low-moderate doses to be around 40–80 µg intravenously or 100 µg orally (Liechti, 2017). Suggested stages of LSD are depicted in figure 3 and some selected reported effects of LSD are depicted in table 3.

Table 3: Selected reported effects of LSD. Selected from Liechti (2017).	
Visual effects	Enhanced eyes-closed imagery
Cognitive effects	Attributed meaning to previously meaningless stimuli (music) and increased empathy and feeling of closeness to others
Multisensory effects	Synaesthesia

Figure 3: Stages of LSD from onset to after-effect. Data from The Third Wave (2018c).

2.2.5 Mescaline

Mescaline is a widespread cactus alkaloid and present in high concentrations in few species, notably the North American peyote (*Lophophora williamsii*) and the South American wachuma (*Trichocereus pachanoi, T. peruvianus*, and *T. bridgesii*). It is also in these regions, United States, Mexico, and Peru, that archaeological findings suggest that mescaline has been used for more than 6000 years (Cassels and Sáez-Briones, 2018). Like many other hallucinogens, scientists have found a way to isolate and synthesise mescaline. The structure of mescaline is depicted in figure 7 in section 2.2.7.

It was on basis of mescaline, together with LSD, that the term "psychedelic" was originally coined by Osmond as mentioned in section 2.2.1. As it is a psychedelic, as defined in section 2.2.1, it interacts with 5-HT_{2A} receptors. This psychedelic has agonist properties (Cassels and Sáez-Briones, 2018).

Dosage and effects

Dosage varies slightly depending on how the compound is extracted; hydrochloride (HCl), sulphate or freebase (Erowid, 2018a). For a "full-blown" hallucinogenic experience oral doses of about 300 mg freebase are required. As such, mescaline has a low psychedelic potency (Cassels and Sáez-Briones, 2018). A common range for mescaline HCl is 200-300 mg. 300-500 mg is considered strong and 500-700 mg is considered "heavy" (Erowid, 2018d). The duration of a mescaline trip is 4-8 hours. Suggested stages for mescaline are depicted in figure 4 and some selected reports are depicted in table 4.

Table 4: Selected reported effects of mescaline. Selected from The Third Wave (2018c).

Visual effects	Intensification of colour patterns, and spatial distortion
Cognitive effects	Ego loss, and increased empathy
Physiological	Motor dysfunction
Multisensory effects	Synaesthesia

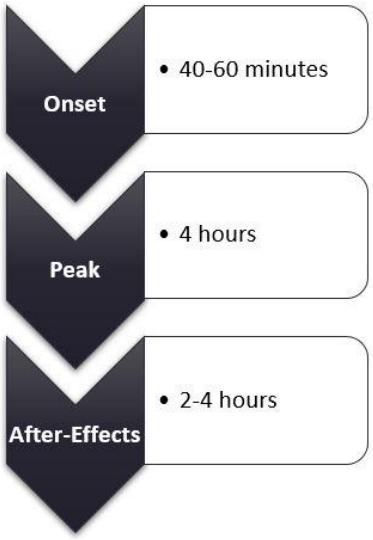

Figure 4: Stages of mescaline from onset to after-effect. Data from Erowid (2018d).

2.2.6 Psilocybin

Psilocybin is a naturally psychoactive compound especially found in *Psilocybe* mushrooms. In vivo, psilocybin is metabolised quickly into another psychoactive compound psilocin (cf. figure

5) which is the primary psychoactive agents of the two (Geiger *et al.*, 2018). In figure 1 (cf. section 2.2.3) the structural resemblance of psilocybin and serotonin is depicted. The mushrooms go by different names such as 'magic mushrooms', 'sacred mushrooms', psilocybin' or simply 'shrooms' (Geiger *et al.*, 2018). The Aztec people used psilocybin to provide deep spiritual insight and inspiration. They gave the mushrooms the name *Teonanácatl* which has been translated to 'God's flesh' (Metzner, 2005)

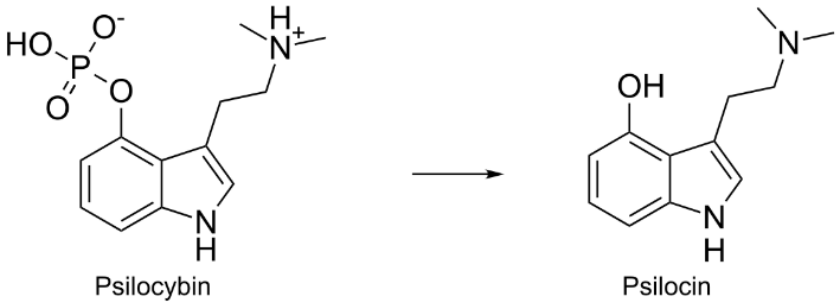

Figure 5: Molecular structure of Psilocybin and its metabolite Psilocin. Modfied from (Geiger *et al.*, 2018)

Both psilocybin and psilocin can be produced synthetically. Initially, the synthesising process was developed by Albert Hofmann and colleagues (Geiger *et al.*, 2018). Mushroom containing psilocybin can be found in the wild as well as they can be cultivated. There is however a risk of misidentification which can lead to mild cases of discomfort and in more serious cases they can be fatal.

The most ancient record of humans using psychoactive mushrooms are presumably from Africa in the form of murals, in Egyptians tombs in the form of cultivation evidence and a mural in Spain in prehistoric times (Froese *et al.*, 2016). In more modern times, the study of psilocybin began with ethnomycologist Robert Gordon Wasson (1889-1986) in the late 1950s. The research field continued during the 1960s and in the early 1970s with famed researchers such as Timothy Leary, Ralph Metzner, and Ram Dass at Harvard University, Albert Hofmann at Sandoz Laboratories, and Terrence McKenna, and Jonathan Ott (Geiger *et al.*, 2018). According to Tylš *et al.*, (2014) research in this period was often with the synthesised version of psilocyn; Indocybin. Today, psilocybin is one of the most commonly used psychedelics in human studies.

This is due to its relative safety, moderately long active duration, and good absorption in subjects (Geiger *et al.*, 2018).

In most developed countries psilocybin has been classified as illegal. The major exception is the Netherlands. In Denmark psilocybin has, as the only psychedelic investigated in the present review, been accepted for use in medical or research purposes (Retsinformation.dk, 2008). And clinical trials with psilocybin on healthy subjects are currently ongoing in Denmark (NRU, 2018). Additionally, at the Imperial College London a psychedelic research group has an upcoming trial on psilocybin for major depression. The research group which includes the Danish neuroscientist David Erritzøe, among other prominent researchers, is led by the famous psychedelic researcher Dr Robin Carhart-Harris (Imperial College London, 2018).

Dosage and effects

Hasler *et al.*, (2004) found significant differences in high and low doses of psilocybin. While low doses are mildly sedating with enhanced visual acuity, higher doses are more stimulating with significant visual distortion. The general effects may include physiologic, visual, auditory, cognitive effects, transpersonal, and multisensory effects (i.e., synaesthesia). Geiger *et al.*, (2018) reviewed some of the reported effects of psilocybin (cf. table 5) and visualised the stages of a traditional psilocybin experience from onset of ingestion to after effects (cf. figure 6). Dosage vary individually and from mushroom to mushroom. A "manageable dose" of psilocybin/psilocin have been reported to be 0.25 milligrams per kilogram of body weight (mg/kg). A high dose is 0.5 mg/kg and a low dose is suggested to be around 0.125 mg/kg. This translates to low dose to high dose range of 10 mg-40 mg for an 80 kg adult (Erowid, 2016). An effectual dose for feeling the effects of psilocybin is suggested to be between 0.2-0.5g and for to produce a trip lasting 3-6 hours a dose in 1-2.5g range (The Third Wave, 2018a).

Figure 6: Stages of psilocybin ingestion from onset to after-effects (Geiger *et al.*, 2018).

Table 5: Selected reported effects of psilocybin. Modified from Geiger et al. (2018)	
Visual effects	Enhancement in colour saturation, pattern recognition and visual acuity
Cognitive effects	Enhanced objective and statistical analysis, ego loss, and increased empathy
Multisensory effects	Synaesthesia

2.2.7 MDMA

MDMA, the active ingredient in Ecstasy, is a synthetic compound, synthesised in 1912. The effect of MDMA on humans was not tested until the American biochemist and pharmacologist Alexander Theodore Shulgin (also known as Sasha Shulgin, 1925-2014) tried MDMA on himself in 1976 (Benzenhöfer and Passie, 2010). He is also the co-author of the book *PiHKAL: A Chemical Love Story*, which contains Shulgin's personal experiences with phenethylamines (Erowid, 2018e)

Unlike the other psychedelics elaborated in the present report, which are serotonergic hallucinogens, MDMA is an entactogen, also known as an empathogen. The function of MDMA is different from that of the serotonergic hallucinogens, which primarily works by having agonist, or partial agonist, properties on the 5-HT receptor (see table 1 in section 2.2.1). Besides working on the 5-HT receptor, MDMA, and other entactogens function as "serotonin releasers" (see table 1 in section 2.2.1). Additionally, MDMA are by some called a 'psychedelic amphetamine' (Erowid, 2018b). This is due to its structural similarities to compounds like amphetamine, methamphetamine and mescaline (cf. figure 7), while at the same time exhibiting effects like that of psychedelics. However, the subjective effects are unlike any of the classical psychoactive agents and is reported to be one in few agents known to reliably produce a prosocial state (Dunlap *et al.*, 2018).

Figure 7: Structural relationship between MDMA, mescaline and other psychoactive agents. The common phenethylamine core is highlighted in red. Compounds are classified as psychostimulants, hallucinogens, or entactogens based on subjective effects in humans. Modified from Dunlap *et al.* (2018). *Abbreviations: MDMA, 3,4-Methylenedioxymethamphetamine.*

Liechti and Vollenweider (2001) performed and summarised studies investigating which neuroreceptors are mediating the subjective effects of MDMA. They found that the overall psychological effects were dependent on release of 5-HT, "stimulant-like euphoric mood effects" appeared to be partly related to dopamine D_2 receptor stimulation, and the "mild hallucinogenic-like perceptual effects" appeared to be due to 5-HT_2 receptor stimulation.

Dosage and effects

A recent review by (Dunlap *et al.*, 2018) suggests that 75–150 mg MDMA produces effects that lasts for hours. The threshold for effects are reported to be 30 mg. A low dose is about 40-75 mg and a strong dose is above 150 mg (Erowid, 2018c). Turn to figure 8 for a depiction of the stages of MDMA and table 6 for a depiction of some reported effects. In contrast to the other elaborated psychoactive agents in the present report, MDMA produces only little hallucinations if at all (Liechti *et al.*, 2000). There are however clinical evidence that suggests MDMA to induce more vividness in colours, along with inducing memory difficulties and accelerated thinking (Liechti and Vollenweider, 2001).

Table 6: Selected reported effects of MDMA. Selected from Dunlap et al. (2018) and Liechti and Vollenweider (2001).	
Visual effects	More vivid colours
Cognitive effects	Enhances trust, openness and empathy Induce short-term memory difficulties, accelerated thinking
Other	Impaired balance

Figure 8: Stages of MDMA from onset to after-effects. Data from Erowid (2018b).

2.2.8 Safety of Psychedelics

Many are probably familiar with a story or anecdote about the dangers of psychedelic drugs. However, none of the included studies in the present thesis report on any serious adverse effects. In fact, very few serious incidents are reported in the literature on psychedelics. Furthermore, the literature contains no reported cases of fatalities directly related to psychedelics used in medical or research purposes. The fatalities reported have occurred after use of newer synthetic phenethylamine compounds and are without relation to ingestion of psilocybin, LSD, mescaline or DMT (Nichols, 2016). MDMA (a synthetic phenethylamine

compound) have just been approved for phase III clinical trials in the US to treat posttraumatic stress disorder (PTSD) and has been granted "Breakthrough Therapy" status by the FDA (Feduccia *et al.*, 2018). Likewise, is psilocybin approved for medical and research purposes (cf. section 2.2.6).

All psychedelics have potential adverse effects such as diarrhea, nausea, and vomiting among others. In addition, some of the psychedelics can cause short-term emotional distress and, although very rare, cases of long-lasting psychosis are known. The latter tends to be in individuals who abuse other drugs, have or are at risk of mental illness, and not in settings where participants are carefully screened for factors that could predispose them to long-term adverse psychological effects (dos Santos *et al.*, 2017). However, the common belief that classic psychedelics (i.e., psilocybin, DMT, LSD and mescaline) increase the risk of psychiatric illnesses does not seem to be true (Geiger *et al.*, 2018). In fact, according to a study by Carhart-Harris *et al.* (2016) LSD improves psychological well-being after the experiment, in spite of acute psychosis-like symptoms.

However, individuals who might want to enhance their creativity, might not seek out a clinical or therapeutic setting (which does not, to my knowledge, exist yet for psychedelics in Denmark or the US). Instead these individuals are likely to try out these agents on their own and get the drugs from the black market, as they are not (yet) legal. This is exactly what is happening with prescription stimulant medications such as Ritalin or Adderall (i.e. amphetamine); they are used as study drugs and bought with false prescriptions and taken by individuals without the consult of doctors or other qualified professionals (Arria and DuPont, 2010).

Moreover, the classic psychedelics do not cause addiction. It is unclear whether this applies to MDMA since the existing literature on the topic offers conflicting notions(Nichols, 2016; Dunlap *et al.*, 2018).

There are potential synergistic or cocktail effects, such as drug-drug, drug-food or drug-disease interactions with psychedelics and this issue is ever-present in the limited data available (Geiger *et al.*, 2018). According to The Third Wave, a psychedelic informative organisation, LSD, DMT, and psilocybin share the same risk profile when combining agents. The organisation recommends avoiding medications or drugs such as Tramadol and amphetamines when using

psychedelics. It also assesses that alcohol and benzodiazepines combination yields a low risk profile, but that the psychedelic effect is likely to decrease. The Third Wave also evaluates that combining any of the mentioned psychedelics with MDMA has a low risk profile and a potential to yield a synergistic effects (The Third Wave, 2018b).

3. METHODOLOGY

3.1 SEARCH METHOD AND SEARCH TERMS

The literature search was performed in 2018 in the period from 25th of July until 12th of October via the Royal Danish Library's search engine REX and PubMed/MEDLINE. Following search terms were used and Medical Subject Headings (MeSH) was used in PubMed/MEDLINE:

"Creativity", OR *"Creativity/drug effects"[Mesh]* OR *"Creativity/physiology"[Mesh]* OR *"Creativity/psychology"[Mesh]* OR *"divergent thinking"* OR *"convergent thinking"* OR *"flexible thinking"* OR *"fluency"* OR *"elaboration"* OR *"spontaneous thinking"* OR *"crystallized knowledge"* OR *"fluid knowledge"* OR *"appropriateness"* OR *"originality"* OR *"novelty"* OR *"Open thinking"* OR *"associative thinking"* OR *"improvisation"* OR *"inventiveness"* OR *"Idea production"*

AND

"Hallucinogens"[Mesh] OR *"Hallucinogens" [Pharmacological Action]* OR *"Receptor, Serotonin, 5-HT2A"[Mesh]* OR *"Methoxydimethyltryptamines*"[Mesh]

Additionally, a manual search was performed.

The searches were limited to results published in English and Danish and include reviews articles and original articles used in the background section. Original articles and clinical studies are used in the qualitative systematic review.

Initially, I wanted to perform a meta-analysis with statistical analysis and examination of results from different clinical studies with quantitative outcomes. However, due to the limited number of published studies with sufficient comparable results, this has not been possible. Likewise, it has not been possible to pool these results. For this reason, instead of performing static analysis, I have chosen to perform a qualitative systematic review and describe the studies and their results. In addition, meta-analyses have some limitations due to the requirement that the studies should have the same measurable outcomes and be statistically comparable. Thus, a meta-analysis would probably have required narrowing the field of study to possibly just one hallucinogenic agents to fulfil the requirement for low heterogeneity among

the studies. Meta-analyses are thus very specific, which also speaks for the high quality and validity associated with this type of study.

A systematic review examines and summarises the available knowledge to qualitatively address the problem (Liberati *et al.*, 2009). To avoid systematic errors in the assessment of hallucinogenic agents as potential creativity enhancers, a systematic review approach is used to minimise bias strengthening the credibility of the conclusion as much as possible. In my preparation of the present systematic review, I have therefore chosen to use the PRISMA method where the main points of a good systematic review are based on; (a) a clearly defined set of goals with an explicit and reproducible method, (b) a systematic search that attempts to identify all studies that meet the criteria for inclusion, (c) an assessment of the validity of the results of the relevant studies, including the assessment of any bias, and (d) a systematic presentation of study characteristics and results (Liberati *et al.*, 2009).

The available studies have guided the direction for which hallucinogenic agents are thought to have the greatest possible enhancing effect on creativity. Naturally, the present review is affected by the facts that not all hallucinogenic agents have been tested in relation to creativity and not all agents have been tested under the same creativity assessment methods. Although investigating the possible creativity enhancing effect, I have not restricted myself in my literature search regarding *creativity* as a search term.

A flow chart based on the criteria has been prepared alongside the included and excluded studies as well as the selection process that has been made along the way in meeting the represented criteria. For the qualitative systematic review, a total of 189 articles were chosen on the basis of title, abstract and/or keywords. Finally, 12 studies were included for the present review.

3.2 INCLUSION- AND EXCLUSION CRITERIA

Inclusion criteria: (i) the studies should include only human participants, (ii) the studies should use a creativity assessment method or task alongside administering a hallucinogenic agent, (iii) patients under the age of 18 are excluded at baseline and (iv) hallucinogenic agents

should be either serotonergic psychedelics (5-HT_{2A} receptor agonists), or entactogens (5-HT) releasing agents, and not dissociatives (NMDA receptor antagonists) or cannabinoids (CB-1 cannabinoid receptor agonists), and (v) creativity measures should measure an aspect of creativity performance, or expression or products that arise from creative activities.

Other hallucinogens such as dissociatives (NMDA receptor antagonists) and Cannabinoids (CB-1 cannabinoid receptor agonists) are not investigated in the present report. Brief descriptions of them are included in the background section on psychedelic agents (cf. section 2.2). Additionally, results on creative personal traits, characteristics of the creative person, environmental influences or contextual factors in relation to creativity will not be included.

Exclusion criteria: (i) reviews, and (ii) self-reports. Thus, studies containing both self-reports and results that are non-self-reports can be included. In these cases, however, only results of non-self-reports are included while self-reported results are disregarded.

3.3 QUALITY ASSESSMENT

The quality of the included studies is evaluated individually based on type of study; randomised controlled trial (RCT), case-control, cohort or preliminary study.

3.4 DATA EXTRACTION

Data extractions from the included studies are as follows: (i) name of the first author, (ii) publication year (iii) study design, (iv) type of psychoactive agent(s), dosage(s) and duration, (v) number of subjects, (vi) gender, (vii) age, (viii) ethnicity, (ix) method, (x) statistical method (xi) main results. If the studies include statistical analysis, only results that are statistically significant at the $p \leq 0.5$ level, will be included.

3.5 DATA PROCESSING

Data extracts are plotted in tables in Microsoft Office and distributed according to psychedelic agent; ayahuasca/DMT, LSD, MDMA, Mescaline, and Psilocybin. No statistical data processing of the study results has been performed.

4. RESULTS AND ASSESSMENT

The following section is divided into subsections according to psychedelic agent to give a clear overview of results from the data extraction as well as assessment of these results and the studies. First, a general overview of the included studies is provided along a flowchart to visualise the search and selection process (cf. figure 9). Each subsection provides an overview of the provided and extracted informations from the included studies. That is, study characteristics, dosages, length of study, history of drug use, history of pathology among participants, educational and/or professional background of study participants, creativity method or task, and results.

Together, this data constitutes the foundation of the discussion in the next section 5. Appendix A contains an overview of the creativity methods/tasks used in the included studies of for the systematic review and Appendix B contains an overview of data extraction from all included studies collected. As the study by Berlin *et al.*, (1955) studies both LSD and Mescaline the study appears in two sections; 4.2. and 4.3.

Based on a total of 189 potentially relevant studies, 12 were included in the present systematic review on psychedelic agents for creativity enhancement. The flowchart (cf. figure 9) was prepared along with the selection process. As shown in the figure, 160 studies were initially excluded due to irrelevance, while the remaining 29 studies qualified for a more thorough reading and 17 of these studies were excluded on the basis of the exclusion criteria (cf. section 3). Of these, 12 studies met the inclusion criteria. The qualified studies are all published in the period from 1955-2016 and divided into subgroups according to the type of psychedelic agent; ayahuasca/DMT, LSD, MDMA, Mescaline and Psilocybin. This was done to distinguish between the different types of psychedelic agents and their possible effects on creative performance.

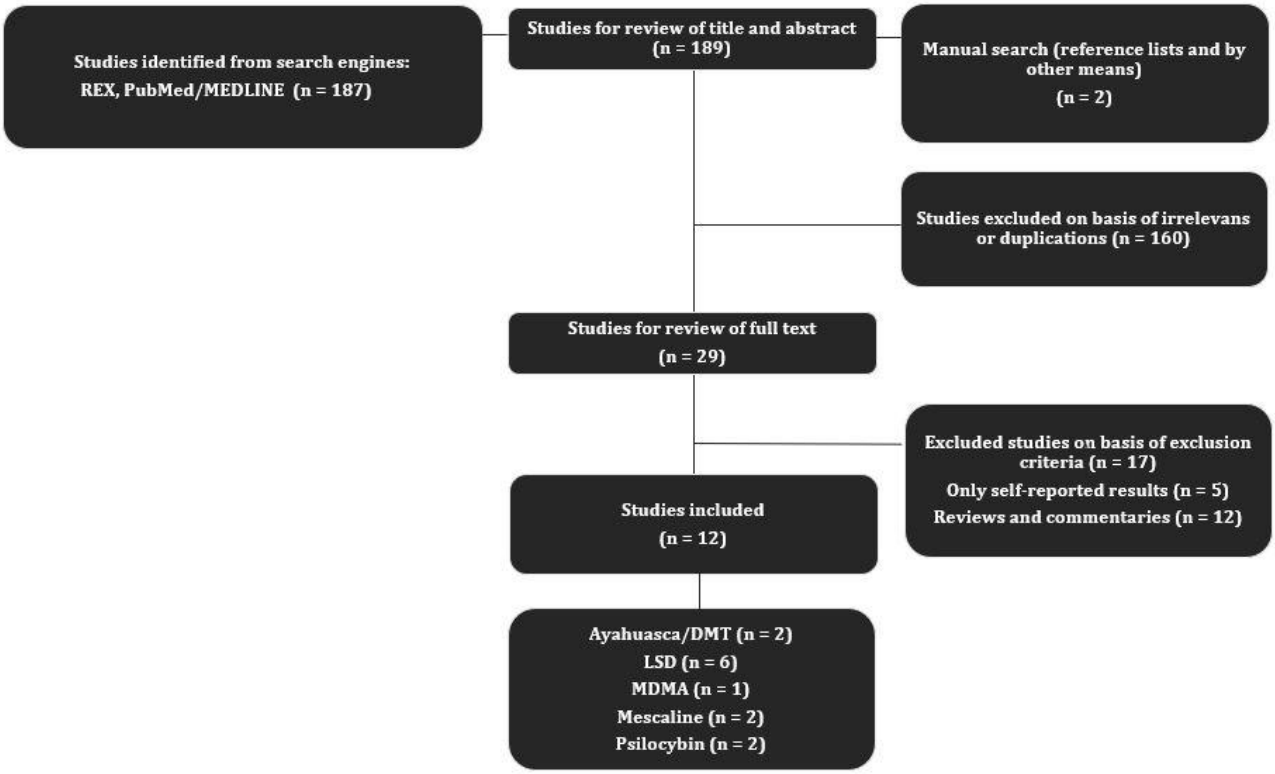

Figure 9: Flow diagram for the present systematic review. n =: number of studies. One study examined two psychoactive agents, which is why the total number of studies are 13, and not 12, in the last box with the overview of psychoactive agents. Abbreviations: DMT, N,N-dimethyltryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylendioxy-N-methylamfetamin.

The included 12 studies are: Berlin (1955), Fischer and Scheib (1971), Frecska *et al.* (2012), Harman *et al.* (1966), Janiger *et al.* (1989), Kuypers *et al.* (2016), Landon and Fischer (1970), Marrone *et al.* (2010), McGlothlin *et al.* (1964), McGlothlin *et al.* (1967), Weintraub *et al.* (1959) and Zegans *et al.* (1967).

The studies are published between 1955 and 2016. All studies, but one, were conducted in the USA. The one study conducted outside of the USA is from Hungary (Frecska *et al.*, 2012) and was conducted in Brazil and Hungary.

All studies analysed the effect of a psychoactive agent on altered states of consciousness.

Drugs administered in the 12 studies can be divided in four types of drugs; lysergamides (LSD; n = 5), tryptamines (ayahuasca/DMT; n = 2, and psilocybin; n = 2), phenethylamines (Mescaline; n = 2), and empathogens (MDMA; n = 1). One study also includes methamphetamine (Marrone *et al.*, 2010) and another includes 20 mg amphetamine (McGlothlin *et al.*, 1967). Results from

these agents (amphetamine and methamphetamine) will not be elucidated or discussed in this report as they are psychostimulants and not psychedelics (cf. section 2.2.1)

Overall, the 12 studies vary greatly in both study characteristics, type of agent and dosage, number and characteristics of participants (gender, age, history of drug use, history of pathology and educational/professional background), creativity measure or task, and study results. In the sections below are the details of the studies according to the before-mentioned categories emphasising their differences. The studies are however grouped by type of psychedelic agent.

4.1 AYAHUASCA/DMT

Two studies investigate the effect of ayahuasca: Frecska *et al.* (2012) and Kuypers *et al.* (2016). Table 7 gives an overview of the two studies. The details of the table and the two studies are elaborated in the following subsections and depicted in table 7 (next page).

The administered amount of ayahuasca was between 44.5 ± 15.6 ml and 116.7 ± 17.1 ml (Kuypers *et al.*, 2016) and 583 ± 315.8 ml (Frecska *et al.*, 2012), where the latter was the total amount ingested by the participants on 4-5 occasions during a period of two weeks. Kuypers *et al.*, (2016) was the only of the studies which estimated the amount of DMT; 42.8 ± 14.9 mg and 75.5 ± 11.1 mg depending on the group.

Table 7: Overview of data extraction from studies investigating ayahuasca/DMT on creativity measures.

Abbreviations: Aya, ayahuasca; BCU, Blank Circle Use; CT, convergent thinking; DMT, N,N-dimethyltryptamine; DT, divergent thinking; FC, Figure Completion; Gr1/2, group1/2; PCT, Picture Concept Task; PLMT, Pattern/Line Meanings task; SD, standard deviation

Study	Study design	Psychoactive agent, dose, duration	n, gender, age, ethnicity	Method/task	Statistical method	Main results
Frecska et al., 2012	Controlled. Partly blinded. Pre- vs. post-drug.	Aya. Dosage: N/A. 4-5 Aya-sessions, 2 weeks	Total n = 61 Aya group: n = 40, 23 females, age (mean ± SD): 30,9 ± 7.7. Control group: n = 21, 11 females, age (mean ± SD): 27,1 ±8.6. Caucasians	TTCT – BCU & FC (& phosphenes)	+	Baseline creativity – control vs Aya: → <u>Control and ayahuasca– Test 2 vs Test 1:</u> **Fluency & relative originality:** BCU & FC: → **Relative flexibility:** BCU: → **Highly original solutions:** BCU & FC: ↑ <u>Phosphenes – Test 2 vs Test 1:</u> Control: ↓ Aya: ↑
Kuypers et al., 2016	Controlled: Within participant.	ayahuasca/DMT Gr1: 75.5 ± 11.1 mg DMT Gr2: 42.8 ± 14.9 mg DMT	Total n = 26 Gr1: Low experience w. Aya: n = 15, 10 females, mean age 37.4 ± 5.8. Gr2: High experience w. Aya: n = 11, 7 females/mean age 52. Caucasians	PLMT & PCT	+	PLMT: → <u>PCT:</u> CT: ↓ DT: ↑

4.1.1 Frecska et al., 2012

The study was a controlled study comparing effects of ayahuasca on psychometric creativity measures in a group of participants and a control group not receiving anything.

The inclusion criteria for the study were prior experience with psychedelics on at least three occasions, and prior experience with ayahuasca. However, participants were excluded if they had experienced a lack of or a mild degree of ayahuasca experience during the sessions (resulting in less than four moderate or strong experiences during the two-week study period based on five-point Lickert scale ratings). The authors reported no use of psychotropic for non-psychiatric conditions among the participants. There were no reports of lifetime history of substance dependence.

The participants had no history of psychiatric or neurological disorders and/or use of psychotropic for non-psychiatric conditions. No history of head injury leading to

unconsciousness for more than 5 minutes. No illicit drug-use or alcohol use in the past two weeks. They all had a BMI within <18.5 and >30. No history of cardiac or endocrine illness.

Participants from the control group consisted of students from a The Swedish School of Economy located in Helsinki, Finland and students from Károli Gáspár University in Budapest respectively. Information regarding ethnicity of the participants is not made available in the studies.

Method and tasks for assessing Creativity. Frecska *et al.* used the TTCT in two test periods; pre- and post-ceremonial period. The specific tasks of the TTCT were the standardised BCU and FC. The authors also included a measure of phosphenes, which is usually not considered a creative response. Additionally, they used Phosphenic Responses as a task where the participants were to draw any perceived phosphenes. Phosphenes is the phenomenon of seeing lights without light actually entering the eye. It can show as flickering light, glowing dots, pulsating waves, and simple geometric figures (Frecska *et al.*, 2012). These are well-known as a phenomenon to be associated with the use of hallucinogens. The authors include this measure in the TTCT as phosphenes can appear in a picture itself or as part of a complex figure, but do note that phosphenes is not considered a creative response *per se*. They selected the six most common forms. Participants gave responses, and any response belonging to any of the six categories was then evaluated by two independent raters and given a score point and then summed.

Their results showed an increase in original solutions, a subscale of DT, but no significant changes on other subscales of divergent thinking (fluency, relative originality and relative flexibility). They found no significant difference in baseline measures of creativity between ayahuasca group and control group. Their results show that when ingesting ayahuasca repeatedly in a ceremonial setting, it had a positive effect on originality as well as positive effects on phosphenic activity. This means that participants made significantly more highly original solutions to the standardized tasks they were given (BCU and FC).

Post-ayahuasca, that is, two weeks after the ayahuasca ceremonies, showed no effect on the creativity measures fluency, relative flexibility and relative originality in either Blank Circle Use

and/or Figure Completion. Similarly Test 2 for the control group showed no effect on these measures.

High originality was significantly increased ($p < 0.0001$) in both Blank Circle Use and Figure Completion in the ayahuasca group post-ayahuasca compared to pre-ayahuasca, but not in the comparison group. BCU (mean ± SD) showed 1.7 ± 1.04 compared to pre-ayahuasca 0.7 ± 1.01. Figure Completion (mean ± SD) showed 2.9 ± 1.88 compared to pre-ayahuasca 1.1 ± 1.06.

Phosphenes in BCU was significantly increased in post-ayahuasca compared to pre-ayahuasca. Phosphene measures was significantly decreased in the comparison group in Test 2 at the $p < 0.0001$ level with (mean ± SD) showing 0.8 ± 1.12 compared to Test 1, 1.6 ± 2.16.

4.1.2 Kuypers et al., 2016

The Kuypers study compares pre- and post-effects of ayahuasca on creative thinking in two separate spiritual ayahuasca-using groups divided by ayahuasca experience (low-experience and high-experience).

All their participants had prior experience with ayahuasca and had to abstain from psychoactive drugs, alcohol and medications two days prior to the experiment. Participants were categorised according to their experience with ayahuasca. Participants with a low experience with ayahuasca (27.5 ± 33.4 occasions) were assigned to group 1 (Gr1), while participants whom had a high experience with ayahuasca (103.6 ± 152.9 occasions) were assigned to group 2 (Gr2).

The authors do not explicitly state whether their assessment of potential pathologies is based on examination of the participants or information provided by them. Years of education between the two groups (Gr1 and Gr2) were found to be significantly different ($t21.43 = -3.04$; $p = .006$). Gr1 had a mean of 15.5 years of education and Gr2 a mean of 18.4 years of education. Participants in group 2 had on average 2.9 years more education compared to group 2.

Method and tasks for assessing Creativity. The authors used the PLMT and PCT in two assessment periods; pre-ayahuasca (3 hours before) ayahuasca session and post-ayahuasca (1,5-2 hours after) initial dose.

Results for the PLMT task show that no significant differences were found in either group for either measures; fluency or originality. For the PCT task, the authors found a significant effect on the group regarding fluency, originality, and ratio (originality/fluency). Scores of fluency and originality were higher in Gr1 compared to Gr2. At the same time, ratio was higher in the Gr2 compared to the Gr1. The statistical analysis shows differences between the groups when comparing pre- and post-drug effect on fluency. The data indicate that fluency in the low-dose group decreased post-ayahuasca, while it increased in the high-dose group post-ayahuasca.

In addition, they found that *Fluency* decreased in Gr1 post-ayahuasca compared to pre-ayahuasca, and that ayahuasca had no effect on PLMT post vs. pre-drug. However, on the PCT, which measures both divergent thinking and CT, they found that ayahuasca decreased convergent thinking and increased divergent thinking compared to pre-drug testings. All in all, the authors conclude that the participants performed better on divergent thinking tests post-drug administration.

4.1.3 Summarised Results and Assessment

Both studies investigating the effect of ayahuasca used figural creativity tests that assesses divergent thinking. But use different tasks. The comparability between the studies is therefore difficult.

Results from Frecska *et al.,* showed an increase in original solutions, a subscale of DT, but no significant changes on other subscales of divergent thinking (fluency, relative originality and relative flexibility). Their results show that when ingesting ayahuasca repeatedly in a ceremonial setting, it has a positive effect on originality as well as positive effects on phosphenic activity. This means that participants made significantly more highly original solutions to the standardised tasks they were given (BCU and FC). Their results are however not robust, as their control group did not participate in the ceremonial events; they were university students in from another country. The conclusions made from these comparisons do not seem valid. Furthermore, as the agent was not a pure isolated agent, but a mixture-compound it is difficult to say with certainty what compounds made these effects. The DMT's effect on the 5-HT_{2A} receptors could be affected by another ingredient in ayahuasca; tetrahydroamine, which is a

serotonin reuptake inhibitor. As such, the effect of DMT could be modulated, which might be why ayahuasca works in the first place; due to potential synergistically, effects of the different compounds in the ayahuasca brew.

Kuypers *et al.* showed that psilocybin had no effect on PLMT post vs. pre-drug. On the PCT, however, which measures both divergent thinking and CT, they found that psilocybin decreased convergent thinking and increased divergent thinking compared to pre-drug testings. Participants performed better on divergent thinking tests post-drug administration, a test, that is known to be used as a measure of creativity. However, as the authors note themselves, divergent thinking can only indicate the *potential* of creativity and does not reflect creativity itself.

Together these study results point to a possibility that ayahuasca can enhance some aspects of figural divergent thinking, especially originality, while at the same time decreasing convergent thinking. It could be interesting to see ayahuasca enhances the minds ability to switch between the two states more efficiently, and tap into a divergent set of thinking, or perhaps more correctly, tap out of more convergent mindset. In addition, it could be interesting to test whether ayahuasca can enhance verbal creativity and/or divergent thinking.

4.2 MESCALINE

The two studies administered mescaline: Berlin *et al.* (1955) and Harman *et al.* (1966). Dosages of mescaline were between 200-700 mcg. The study by Berlin *et al.* also investigated the effect of LSD in a dose of 50 µg as well as placebo. Table 8 gives an overview of the two studies.

The following subsections elaborates on the details from table 8 (next page) and the two studies.

Table 8: Overview of data extraction from studies investigating mescaline on creativity measures.

Abbreviations: DAP, Draw a person; EFT, Embedded Figures Test; LSD, Lysergic acid diethylamide, N/A, not available

Study	Study design	Psychoactive agent, dose, duration	n, gender, age, ethnicity	Method/task	Statistical method	Main results
Berlin et al., 1955	Placebo. Controlled: within-participant. Pre- vs post-drug effect.	400-700 mg mescaline or 50 µg LSD – and placebo	Total n = 5 USA. Age & gender: N/A. Ethnicity: not specified	DAP & Bender-Gestalt figures	None	Aesthetically value (n = 4): Mescaline and/or LSD vs pre-drug: ↑
Harman et al., 1966	Pre- vs acute-drug testing.	200 mg mescaline	Total n = 27, 8 females Age: N/A. Ethnicity: not specified	Purdue Creativity Test, OVT & EFT	+	Purdue Creativity Test (n = 18): fluency of ideas: ↑ Flexibility: → Miller OVT (n = 27, 8 females 19 males): Improvement in performance: ↑ Witkin EFT (n = 14, 4 females, 10 males): Performance enhancement: ↑

4.2.1 Berlin et al. 1955

The study includes graphic artists and one playwright who ingested mescaline and LSD. The results of the playwright are elaborated in section 4.3.1 because these results are related to the influence of LSD and not mescaline. The participants were to create work that, by the fellow artists, was of greater aesthetic value post-drug effect compared to pre-drug effect, that is, the work performed under the influence of the agent was compared to the artists' usual work. The authors report that participants had no prior experience with psychoactive agents.

Method and tasks for assessing Creativity. The four graphic artist were to conduct the DAP and the one playwright was to write scenes/passages and review earlier and current work. Their results were evaluated by fellow artists. Besides the DAP, there was also a Bender-Gestalt test of figures.

Results. The panel of fellow artists evaluated the created works of greater aesthetic value than the usual work. The authors only elaborate on the work of one artist who was under the influence of mescaline. The authors do not report how many participants were under the influence of mescaline, LSD or placebo, nor do they explicitly state how many participants were

subjected to more than one agent. Interestingly, it was found to decrease the literary creativity (cf. Berlin *et al.*, 1955) post-drug vs. pre-drug. Considering that this observation is based on a single participant, it is interesting but of very limited scientific value.

4.2.2 Harman et al., 1966

The study by Harman *et al.* is based on the Purdue Creativity Test, Object Visualization Test (OVT) & EFT to evaluate creative problem-solving abilities of the pre-drug effect (several days prior to the drug administration) and acute-drug effect in 27 male professionals from local industries and academic institutions. All participants had an occupation which, according to the authors, normally requires creative problem-solving abilities.

The participants in the study were psychologically normal with stable life circumstances as determined by psychiatric interview-examination. And participants were expected to be adequately motivated to discover, verify and apply problem-solutions within his/her industrial or academic work capacity. This was not elaborated any further in the study.

Method and tasks for assessing Creativity. The participants were divided into seven small groups (n = 3 or 4). Creativity was assessed using the Purdue Creativity Test, the Miller OVT and the Witkin EFT. To avoid unnecessary bad hallucinogenic experiences, and to support the psychedelics experience, the researchers provided comfortable settings for their participants. Furthermore, the researchers advised their participants to "turn off" their analytical faculties and to stop using their cognitive and perceptual processes in the "familiar way" and to heighten the likelihood of discovering "new ways".

Results. For the Purdue Creativity Test they found a significant increase in *fluency of ideas* in the acute-phase compared to the pre-session testing ($\chi^2 = 5.88$, df = 12, $p < 0.02$). The second subscale of the Purdue Creativity Tests, *flexibility*, did, however, not show any significant change. The Miller OVT and the Witkin EFT showed significant increase acute-phase compared to the pre-session testing in *improvement of performance* ($\chi^2 = 6.00$, df = 26, $p < 0.02$) and *performance enhancement* ($\chi^2 = 8.64$, df = 13, $p < 0.01$), respectively.

4.2.3 Summarised Results and Assessment

Mescaline (and/or LSD) was found to enhance fluency of ideas (Purdue CT, Harman *et al.*), improve performance on MOV and W EFT (Harman *et al.*) as well as enhance aesthetic value (DAP, Berlin *et al.*). Mescaline did not enhance or worsen flexibility (Purdue CT, Harman *et al.*). The effects seen in the study by Berlin *et al.* are impossible to assign to a specific agent due to the lack of information provided by the study. However, the study does find enhancement of aesthetic value when administering a psychedelic agent, although it is not clear whether the effects were of LSD or mescaline.

It is difficult to draw any conclusions from the results from The Berlin study as their findings and methods are poorly elaborated, if at all. The study does not include any statistics and results rely solely on the evaluation of fellow artists. Whether these artists are the same as the artists from the experiment is not clear nor is the number of evaluating artists. As such, it is also difficult to appraise the evaluations as we know nearly nothing of these "fellow artists" as evaluators. Furthermore, the number of participants in this study is very small and diverse in terms of field of creativity. One participant's field of creativity is literature and the other four's field is visual art. As such, their results are difficult to compare, but could be useful in showing a potential tendency towards enhancement of being able to artistically express oneself with bolder colour and freer lines, which according to the evaluating artists, resulted in more work with greater aesthetic value. Likewise, the authors do not state how the work of the playwright is evaluated. This study does however provide some potential valuable subjective reports and self-reports on the effects of mescaline and LSD, although it is on a small number of participants. This is however beyond the scope of this article. Furthermore, very little information is available on the participants as neither gender, age, ethnicity, years of education or psychological profile are provided.

Harman *et al.* (1966) guides their participants in a specific direction, which can skew or bias the results. The results obtained from the two subscales of the Purdue test, showed that mescaline provided a significant positive change in fluency. That is, there was more fluency of ideas post-drug than pre-drug. This could be due to the fact that the participants were encouraged to discuss with one another after drug administration but prior to the main

problem-solving period. From this they found that of the 44 problems brought by the participants, 20 had new ideas for further investigation after the experimental sessions.

So, overall, psychedelics was found useful in figural creativity tasks as well as useful in producing ideas, although not in a greater range of solutions than under normal conditions (pre-drug) and only under conditions that support the psychedelic experience and in participants that seemingly already work in jobs that require creative skills.

The results on mescaline as enhancing aesthetically value, are mere showing a tendency, as they firstly are not supported by statistical significance and as they are only obtained from the results from four participants.

4.3 LSD

Six studies investigate the effect of LSD: Berlin *et al.* (1955), Janiger *et al.* (1989), McGlothlin *et al.* (1964), McGlothlin *et al.* (1967), Weintraub *et al.* (1959) and Zegans *et al.* (1967). Table 9 gives an overview of the six studies. Dosages of LSD in the studies varied between single dosages between 50-200 µg to 0.5-2.5 µg/kg. Two studies used placebo (Berlin *et al.* and Zegans *et al.*).

Half of the studies do not explicitly state the participants' history with psychoactive agents (Janiger & Dobkin De Rio, Weintraub *et al.* and Zegans *et al.*). The other half report that their participants have no experience with psychoactive agents: (i) Berlin *et al.* (1955), (ii) McGlothlin *et al.* (1964); this is only explained for the experimental group. There are no available data for the comparison group. And, (iii) McGlothlin *et al.* (1967); previous experience with LSD or peyote was an exclusion criterion. Some participants had experience with marijuana. Three studies report no pathologies among their participants: (i) McGlothlin *et al.* (1967), (ii) Weintraub; screened for "serious psychopathology" by means of psychiatric interviews and psychological tests, and (iii) Zegans *et al.*'s candidates were rejected if they displayed psychological or physical contraindications (not specified) to their participation. The other half of the studies did not state whether they investigated participants for potential pathologies or not (Berlin *et al.*, Janiger *et al.* and McGlothlin *et al.*).

The following subsections elaborate on the details from table 9 (next page) and the six studies.

Table 9: Overview of data extraction from studies investigating LSD on creativity measures. *Abbreviations: CT, convergent thinking; DAP, Draw a person; DT, divergent thinking; EFT, Embedded Figures Test; LSD, Lysergic acid diethylamide, N/A, not available, RAT, Remote Association Task; TAT, Thematic Apperception Task, WAT, Word Association Test*

Study	Study design	Psychoactive agent, dose, duration	n, gender, age, ethnicity	Method/task	Statistical method	Main results
Berlin et al., 1955	Placebo. Controlled: within-participant. Pre- vs post-drug effect.	400-700 mg mescaline or 50 µg LSD – and placebo	Total n = 5 USA. Age & gender: N/A. Ethnicity: not specified	DAP, Bender-Gestalt figures & literary creativity	None	Aesthetically value (n = 4): Mescaline and/or LSD vs pre-drug: ↑ Literary creativity (n = 1): LSD vs usual consciousness: ↓
***Janiger et al.,* 1989**	Controlled: Within participant. Pre- vs. post-drug effect.	LSD 2.5 µg/kg	Total n = 20 Professional artists Age and gender: N/A. Ethnicity: not specified	Draw and paint Kachina doll	None	Creative production: Post-drug vs pre-drug: →
***McGlothlin et al.,* 1964**	Controlled: comparison group. Pre- vs. post-drug effect.	LSD 200 µg	Total n = 29 Experimental: n = 15 experimental, 5 females, mean age 36. Comparison: n = 14, 5 females, mean age 34. 25 were professional research personnel. USA.	DT & CT tests and WAT	+	DT/CT tests: Associational fluency, ideational fluency, Alternate uses, alternate signs, consequences & remote associations: → WAT (n = 24): Popular associations, mean number of deviant associations, exact reproductions and deviant association corrections: →
***McGlothlin et al.,* 1967**	Controlled. Pre- vs. post-drug effect.	LSD 200 µg 6-month follow-up	Total n = 70 Experimental (LSD 200 µg): n = 24 Control groups: Amphetamine: n = 23 LSD 25 ug: n = 23 US-born males. Age: N/A	DT, DAP & TAT	+	6 months vs 2 weeks: **Creativity test results:** Associational fluency, Alternate uses, Plot tiles, Hidden figures, Remote associations, Originality (TAT) & Imaginativeness (DAP, here; imaginative rating): →
***Weintraub et al.,* 1959**	Controlled + randomised.	LSD 2.0 µg/kg	Total n = 50 Experimental: n = 25 Controls: n = 25 Normal male volunteers. Age: N/A. USA.	WAT	+	Popular Reaction-words: LSD vs control: ↓ Traumatic and Nontraumatic Stimuli: Association Disturbances & Reaction Times: ↑ Serious Deviations: ↑ Minor Deviations: → Close reactions: ↑ Distant reactions: → Serious and minor Reproduction disturbances: ↑
***Zegans et al.,* 1967**	Controlled, placebo, randomised.	LSD 0.5 µg/kg in distilled water, or placebo Post-test 2 hours post treatment	Total n = 30 Experimental group: n = 19 Controls (placebo): n = 11 Male volunteers > 21 years of age. USA.	RAT, WAT, EFT, Tachistoscope & Mosaic design	+	RAT Correct & Time, WAT fast, intermediate, slow, EFT correct & time, Tachistoscope & Mosaic design: → WAT unique: ↑

4.3.1 Berlin et al., 1955

The study includes graphic artists and one playwright who ingested mescaline and LSD. The results of the playwright are elaborated in section 4.3.1 because these results are related to the influence of LSD and not mescaline. The participants were to create work that, by the fellow artists, was of greater aesthetic value post-drug effect compared to pre-drug effect, that is, the work performed under the influence of the agent was compared to the artists' usual work. The authors report that participants had no prior experience with psychoactive agents.

Method and tasks for assessing Creativity. The four graphic artist were to conduct the DAP and the one playwright was to write scenes/passages and review earlier and current work. Their results were evaluated by fellow artists. Besides the DAP, there was also a Bender-Gestalt test of figures.

Results. The panel of fellow artists evaluated the created works of greater aesthetic value than the usual work. The authors only elaborate the results of one artist whom is under the influence of mescaline. The authors do not report how many participants are under the influence of mescaline, LSD or placebo, and do not explicit how many participants are subjected to more than one agent. The one clear result on the effect of LSD is of the playwright whom received LSD. From this participant results, they found a decrease in the literary creativity (Berlin *et al.*, 1955) post-drug vs. pre-drug.

4.3.2 Janiger et al., 1989

The study investigates the effect of 2.5 µg/kg LSD on drawings and painting in normal and altered conscious states (i.e. pre- and post-administration of LSD). The study includes the work of 20 professional artists.

The authors do not report whether participants had no prior experience with psychoactive agents.

Method and tasks for assessing Creativity. A stylistic assessment of the drawings/painting of Kachina dolls was used as the assessment of creativity. The work was evaluated by an art professor and classified according to eight categories: 1) dominant style, 2) compositional

characteristics, 3) linear characteristics, 4) stroke characteristics, 5) textual characteristics, 6) colour characteristics, 7) value characteristics, and 8) dimensional characteristics.

Results. According to the study, the most predominant changes were in the categories 1) dominant style, 6) colour, 3) line, and 5)/ texture characteristics. Overall, the authors conclude that LSD did not result in artistic productions inferior to those performed pre-drug administration (i.e. not aesthetically superior). They do, however, note a "certain increase" in articulateness (confidence) which was noted to be caused by the LSD experience, but only in those artists who showed a deficiency in technical proficiency. Due to the heterogeneity of the participants combined with the aesthetic nature of analysing the results, it is not possible to make any objective statements about how LSD effected the artists' creativity. However, it would appear that the agent enhanced certain aspects of the artists' work; a tendency towards more expressionistic work, a sharpening of colour, a greater freedom from prejudiced mindset, an increased syntactical organisation, a deeper accessibility of past impressions, and a heightened sense of emotional excitement.

4.3.3 McGlothlin et al., 1964

The study investigates the short-term effects of 200 µg LSD on divergent thinking performance in 29 participants. The experimental group had no previous experience with LSD or similar agents. Details are not given for the comparison group. All but four of the experimental participants were professional research personnel (n = 11). No further details are provided on the matter. All participants from the comparison group were employees from the RAND cooperation, which was a global non-profit think tank. The experimental group consisted of 15 participants and the comparison group of 14 participants.

Method and tasks for assessing Creativity. The performance tests, or divergent thinking and convergent thinking tests, were as follows: Associational fluency, ideational fluency, Alternate uses, alternate signs, consequences & remote associations. First test, pre-drug exposure, was conducted one day prior to drug exposure. Second test conducted one week post-drug exposure. According to the authors, the comparison group should not be considered a control group, but merely a group to "*measure the practice effect of the test-retest situation*" and not to

"*determin[e] the specific drug effects, independent of suggestion, expectation or other variables*" (McGlothlin *et al.*, 1964, p. 266). Additionally, an alternate form of the WAT test battery was used on 24 of the participants (experimental n = 10, comparison n = 14). Their test builds on the Rapaport word association list (Rapaport, 1958; McGlothlin *et al.*, 1964) (cf. section 4.3.5). The researchers tested the participants in both a pre- and post-drug setting, which they in relation to the WAT termed the association portion of the test and the reproduction portion of the test, respectively. The groups were given test 1 one day prior to pre-drug administration and test 2 one week following post-drug administration. This was also the case for the comparison group. They scored answers by *Popular associations* (as objectively defined by Rapaport), *mean number of deviant associations*, *exact reproductions*, and *deviant association corrections.*

Results. The study finds no significant differences between the experimental group and the comparison group for any of the performance tests and neither for the WAT. The authors themselves assign their inconclusive results to the heterogeneity between the two groups of participants.

4.3.4 McGlothlin et al., 1967

The study investigated long-term effects of 200 µg LSD pre- and post-drug on art performance; 2 weeks and 6 months follow-up. A total of 70 participants were included and divided into an experimental group receiving 200 µg LSD (n = 24) and two control groups, one receiving amphetamine (n = 23) and the other receiving a lower dosage (25 ug) of LSD (n = 23).

The authors excluded participants having prior experience with LSD or peyote, previous familial history of psychosis or previous treatment with psychotherapy. Some were excluded on basis of interview (not further elaborated) and on "doubtful" MMPI profiles (seemingly referring to an assessment of their reliability – but would that have an impact on creative performance?). Some had experience with marijuana (*n* not specified). All potential participants were told that the experiment included drugs and that they might or might not receive LSD. The educational or professional backgrounds of the participants are not specified.

Method and tasks for assessing Creativity. To assess art performance the following tests were used: Associational fluency, Alternate uses, Plot tiles, Hidden figures, TAT & remote associations. All four creativity tests (the former four), were all based on Guilfords' divergent thinking battery, and contained the following measures; fluency, flexibility and originality. 1) Associational Fluency, 2) Alternate Uses, 3) Hidden Figures and 4) Plot Tiles. Mednick's Remote Associations was also included. These tests were given in alternate forms at the three test sessions. From the two latter, TAT and remote associations, also called projective tests, two additional measures were obtained: TAT stories, which were rated on originality, and DAP drawings rated on imaginativeness.

Results. All 72 completed the two-week follow-up, but two from each of the control groups, did not complete the six-month testing. No significant differences were found between pre- and post-drug in either the two-week follow-up or the six-month testing for any of the creativity measures or standardised art tests. Using a one-tailed test the spontaneous flexibility (Alternate Uses) did show an increase for the experimental group at the 0.05 significance level, both for the two-week follow-up and the six months testing. The authors do however note that, since their pilot study (McGlothlin *et al.*, 1964) does not support a prediction of increase in the Alternate Uses test, they found it better to rely on the results from a two-tailed test, which did not provide evidence of increase of creativity for the experimental group.

4.3.5 Weintraub et al., 1959

The study investigates the effect of LSD 2.0 µg/kg on associative processes in a total of 50 normal male volunteers. The participants were randomly divided into an experimental and a control group of equal size. The authors do not provide any information on age nor educational or professional background. The participants were screened for "serious psychopathology" by means of psychiatric interviews and psychological tests.

Method and tasks for assessing Creativity. Like McGlothlin *et al.* (1964), this study used the WAT based on Rapaport's word association list of 60 words. The list is made up of traumatic ("suicide", "masturbate") and non-traumatic ("dog", "chair") words. Weintraub *et al.* investigated traumatic and non-traumatic, serious and minor deviations, and close and distant

reactions as stimuli in the WAT. The authors divided the participants into two groups and assigned them randomly. One group served as the control, although usually when using the WAT, participants serve as their own controls (pre- and post-testings). The authors note that each test record consisted of scores given by two judges and that the scoring agreements were above the scoring needed for the scoring to be objective.

Results. The authors found a significant decrease in *Popular Responses-words* for the LSD participants compared to controls ($p < 0.01$, $t = 3.35$). For the *Assosciation Disturbances* and *Reaction Time Disturbances* on Traumatic and Non-traumatic stimuli they found a difference between the experimental and the control group, significant at the 0.001 level. In both cases the significant difference can be attributed to the mean reaction times to non-traumatic words as they are significant in contrast to the mean reaction times for traumatic words. They also found significant increase in Serious Deviations and Close reactions, in contrast to Minor Deviations and Distant reactions for the experimental group. Lastly, the authors found a significant increase in Serious and minor Reproduction disturbances for the experimental group. Furthermore, there were more close reactions and serious deviations in the experimental group than in the control group. Lastly, the experimental group did not differentiate between traumatic and non-traumatic word stimuli compared to the control group. In short; the authors found several significant changes in association tests. These results are, however, difficult to compare directly with the other studies which are discussed in section 5.

4.3.6 Zegans study et al., 1967

The study investigated the effect of 0.5 µg/kg LSD on creativity performance in 30 male volunteers pre- and post-drug administration. The participants were randomly assigned to receive either LSD ($n = 19$) or placebo ($n = 11$).

The authors do not provide information on the participants' history with psychoactive agents. Candidates were rejected if they displayed psychological or physical contraindications (not specified) to their participation. Prior to volunteering, the potential participants did not know that the experiment included psychoactive drugs. All participants were paid for participation and the amount was the same whether they received LSD or placebo. Participants should

restrain from eating two hours prior to experiment to minimize differences in drug absorption. Information on the educational and professional backgrounds of the participants is not given in the study.

Method and tasks for assessing Creativity. The study performed several tests to the effect on creativity. The following tasks were: WAT, EFT, RAT, FAT, Tachistoscopic and Mosaic design. The participants were to perform a 15-minute period free association. The authors state that this was done to be able to assess the participants' pre- and post-drug reactions (s. 742).

The experimental tasks were divided into two parts divided by a pause. During the pause, after the first half of the test, the participants were given a glass of distilled water, and in the water of those randomly selected to receive LSD, LSD was added. All participants were escorted to a lounge where they could "read or relax" in the two hours leading up to the retest.

In **RAT** the participants were presented with two times 15 items, one pre-drug/placebo and one post-drug/placebo. The items consisted of three stimulus words, without immediate relationship. All three could, however, be associated with a fourth word. The measures were number correct and mean time to correct answer (maximum of 2 minutes).

WAT was used to determine if LSD could enhance one's ability to make more "creative, less stereotypical responses". Positive responses were considered to be originality and uniqueness. The test consisted of two parts; one pre-drug and one post-drug. The 60 items included were divided into two equally sized groups (30 each) pre- and post-drug. Responses were scored for latency of response and originality. Latency was categorised accordingly to Rapaport (fast, intermediate, and slow). Most common responses were considered stereotypes and responses divergent of these were considered originals.

The **Mosaic Design Test** was designed for this particular experiment, although the authors note its similarity with other tests "*presently in use*". The test was used to test the participants' abilities to conceive interesting patterns and capacities to execute their conceptions. The participants were given two minutes to examine the materials and then 15 minutes to use the tiles to create a pattern. The designs were rated by two judges on a 5-point scale from 1 (highly disorganised, with minimal imaginative use of materials) through 5 (highly original design of superior organisation and aesthetic appeal).

The **FAT** were used by the authors to indicate the capacity of creativity by the participants as the authors felt that "(…)*the ability of an individual to give free reign to associations emerging from his preconscious is intimately related to the imaginative exercise involved in creativity*" (s. 743). The test setting was that each subject lay alone on a comfortable bed in a room with dimed light. The participants were instructed to explicitly repeat any thoughts coming to awareness during the 15-minute period of the test. The explicit thoughts were scored on disorganisation and originality in content.

The **EFT**, examines the participants' ability to perceive figures hidden in the general gestalt of a complicated line drawing. The authors felt the test could be useful in determining if LSD can assist an individual in 1) widening the participants' perceptual scope, and 2) perceiving relationships hitherto obliterated by his dependence upon conventional, preconceived figural expectations.

A **Tachistoscopic Stimulation** was used to determine if LSD made participants' latency time in recognising a word or an object shorter compared to the participants given placebo. A standard tachistoscope was used to project word and figure stimuli on a screen. The number of correct responses was registered.

Results. When analysing their data, the authors divide the participants from both the experimental group and control group into two groups: improve group and not-improve group and compare these results as well. When pooling the mean changes, they found that experimental participants proved significantly better than placebo subjects at producing unique responses to the WAT ($p < 0.05$, $t = 1.66$). For the remaining tests they found no significant results. They did however perform a two-tailed test on the Mosaic Design test, as the results initially contradicted their prediction, that is, the results showed that control subjects performed better than experimental subjects on the Mosaic Design test. They found a tendency, but not any significant results in this matter. They concluded that LSD did not lead to a general enhancement.

4.3.7 Summarised Results and Assessment

The heterogeneity of the studies of the potential creativity enhancement of LSD makes it difficult to compare the results. Making an overall assessment is thus a challenging task. Additionally, the results of McGlothlin *et al.* (1967) are not directly comparable with the rest of the LSD studies, because their study investigates the long-lasting effects, in contrast to the other studies which focus on acute effects.

Three of the studies do use the WAT (McGlothlin *et al.* [1964], Weintraub *et al.* and Zegans *et al.*) but they do so in two different ways. Therefore, the results are difficult to compare in a meaningful manner. McGlothlin *et al.* (1964) found no effect although they administer the highest concentration of LSD of the three studies. Weintraub *et al.* found a significant increase in many of the aspects of the WAT, and, interestingly, they found that LSD participants showed no differentiating between the two stimuli; traumatic and non-traumatic words. Zegans *et al.* also found a significant increase in aspects of the WAT but used the test differently than Weintraub *et al.* and Zegans *et al.* found that LSD participants increased unique responses compared to controls. The results from Zegans *et al.* only appear meaningful in relation to creativity, as they relate to the criteria of creativity (se background), and there is no apparent relation between traumatic or non-traumatic words and creativity. However, the WAT itself is a measure of association and as such could give some insight into divergent or convergent thinking.

In sum, it cannot be confirmed that LSD has enhancing properties on general creativity. However, these results show a tendency of LSD enhancing semantic association (such as the WAT), in contrast to visual tasks. Of the included studies, the ones yielding positive results are the ones administering the lowest amounts (Berlin et. al, Weintraub *et al.*, and Zegans *et al.*) with dosages of 50 µg, 0.5 µg and 2.0 µg/kg. The results from Berlin *et al.* are, however, impossible to assign to a specific agent due to the lack of information in the study. Their results do, however, show that psychedelics can enhance the aesthetic value of visual artwork.

4.4. MDMA

Only one of the included studies investigates the effect of MDMA in a total of 11 recreational users of amphetamines. Table 10 gives an overview of the study.

Table 10: Overview of data extraction from study investigating MDMA on creativity measures.
Abbreviations: MA, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine.

Study	Study design	Psychoactive agent, dose, duration	n, gender, age, ethnicity	Method/task	Statistical method	Main results
Marrone et al., 2010	Inpatient, within-participant, double-blind study, placebo, controlled.	MDMA (100 mg), placebo and MA (20, 40 mg) on separate days 13 days	Total n = 11, 2 females, mean age 29.3±5.0 years. Ethnicity: not specified. Recreational users of amphetamines	Movie describing (verbal fluency)	+	Disfluency: MDMA & 20MA vs control: → 40 MA vs control: ↓ MDMA vs 40MA: ↑ Coherence: MDMA & 20MA vs control: → 40MA vs control: ↑ MDMA vs 40MA: →

4.4.1 Marrone et al., 2010

Participants were administered MDMA (100 mg), placebo and methamphetamine (20, 40 mg) on separate days to do an inpatient, within-participant study. The study is double-blind.

All participants were recreational users of MDMA or methamphetamine, and among current usage of drugs the reports were: Six participants used methamphetamine 4.2±4.7 days per month; 10 reported current MDMA use 2.1±1.8 days per month. Four participants also reported current cocaine use (one to four times per month), nine reported marijuana use (4.2±2.3 days per week), nine reported alcohol use (one to three times per week), and two reported ketamine use (once per month). All were patients at the New York State Psychiatric Institute, and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria other than methamphetamine abuse. None were reported to have any pathology. The participants had an average of 14.1 years of formal education.

Method and tasks for assessing Creativity. The authors measured verbal fluency pre- and post-drug in recreational users of methamphetamine. Participants were to describe a movie they had seen the night before the experiment and were rated on verbal fluency (disfluency and coherence). The aim of the study is to assess the effect of methamphetamine and MDMA on

speech. The authors describe that they found that MDMA adversely affected fluency, and they note that their results here were in agreement with anecdotal reports.

Results. Disfluency was significantly higher in the participants administered MDMA, placebo and 20MA compared to participants administered 40MA ($p < 0.05$). No significant differences were found between MDMA and placebo, and MDMA and 20MA. However, 40MA showed significant lower score compared to control/placebo. The authors describe that they found that MDMA adversely affected fluency, and they note that their results here were in agreement with anecdotal reports (abstract). However, their data suggest only adverse effects of MDMA on speech compared to 40 MA, not compared to control (cf. table 10). No significant differences were found for MDMA compared to placebo or MA for Listener ratings of speaker's coherence. However, 40MA showed significant higher score compared to control/placebo ($p < 0.05$). Methamphetamine improved verbal fluency and MDMA adversely affected fluency. The authors find for MDMA that Syllables and Talkative were correlated.

4.4.2 Summarised Results and Assessment

It is important to outline that their data suggests only adverse effects of MDMA on speech compared to 40 MA, not compared to control (cf. table 10). As such, MDMA does not seem to affect creativity in the form of verbal fluency in recreational users. it could be interesting to see if there is a baseline difference in creativity between recreational users and naïve drug users, to see if a potential creative enhancing effect is acute or chronically conditioned.

The study results from this study, could be influenced by the use of especially marijuana, which has been reported as potentially creativity enhancing (Jones *et al.*, 2009).

When investigating the effect of a specific agent, potential confounders should be considered. In the study by Marrone there are several confounders as their participants all are recreational users of another type of drug, methamphetamine. This agent is also a hallucinogen, although it work its primary effect on dopamine receptors and is structurally similar to dopamine itself (NIDA, 2013). The methamphetamine in their study was, in contrast to usual recreational usage, administered orally and could have a different effect than participants were used to. The fact that Marrone and colleagues do not explicit whether their participants were to abstain from

drugs prior to the experiment, is a weakness, as the other drugs explicated used by the recreational users, could interfere with the study results and function as confounders.

4.5 PSILOCYBIN

Two studies administered psilocybin: Fischer & Scheib, 1971 and Landon & Fischer, 1970. Dosages of psilocybin were between 80-160 µg/kg. Table 11 gives an overview of the two studies.

Table 11: Overview of data extraction from studies investigating psilocybin on creativity measures.
Abbreviations: DAP, Draw a person. Note: FR and WL are study subjects and WW represents a poetic writer.

Study	Study design	Psychoactive agent, dose, duration	n, gender, age, ethnicity	Method/ task	Statistical method	Main results
Fischer & Scheib, 1971	Single-blinded. Controlled. Pre- vs peak-drug effect.	Psilocybin 160 µg/kg	Total n = 6, 3 females, mean age 23. Ethnicity: not specified. College-age volunteers w. prior psilocybin experience	DAP	Descriptive	DAP: →
***Landon & Fischer,* 1970**	Controlled: within-participant. Control refers to non-aroused states of daily activity.	Psilocybin 80 µg/kg (test passage) 160 µg/kg (recall)	Total n = 2, male (FR & WL), 28 years of age, university instructors in literature Ethnicity: not specified.	Linguistic writings	None	<u>Semantic orientation:</u> **Control:** FR & WL vs WW: → **Test:** FR vs WW: ↓ WL vs WW: ↑ <u>Syntactic structure:</u> Closure strength & T-unit length – WL & FR vs WW: → T-unit length WW – control vs test: ↓ Sentence length - WL & FR vs WW: ↓ Embedded syntactic units pr. sentence – WL & FR vs WW: → Coordinated syntactic units pr. sentence: WL & FR vs WW: → WL & WW – test vs control: ↑ Rhetorical structure: ↑

Both studies investigating psilocybin share one author: Roland Fischer.

The studies investigate psilocybin but on different creative productions. One on DAP, a test that can assess artistic ability in the form of drawings. The other study investigated linguistic skills on a semantic, syntactic, and rhetoric level.

4.5.1 Fischer & Scheib, 1971

The study investigates the effect of psilocybin on artistic drawings from a total of six participants.

Participants had prior experience with psilocybin and were "above average scholastic performing" college-age volunteers. All participants were tested for degree of "brain-damage" with a perceptual test (Minnesota Percepto-Diagnostic Test) prior to, at peak of, and post psychoactive agent administration.

Method and tasks for assessing Creativity. The study analyses drawings (DAP) from six participants and evaluates them on a sophistication-of-body-concept scale and grades according to the recommendation of Dr E. A. Witkins (s. 178). The drawings are also evaluated in terms of aesthetic pleasingness by two independent adjudicators; a professional artist, Trudy Fischer, and a psychiatrist Leo Navratil. Participants are also rated on a MacKinnon creativity performance score which is based on the Myers Briggs Type Indicator (MBTI) as the sum of *intuition* (N) plus *perceiving* (P) personality trait scores $\sum$(N+P). The authors state that they measured creativity at three times, T1, T2 and T3 (i.e. pre-drug, at drug-peak, and post-drug administration).

Results. The authors find that the participants categorised with a lower mean MacKinnon score ($\bar{x}$ = 66.0) score higher on the Witkin score pre-drug than the participants categorised with a higher MacKinnon score ($\bar{x}$ = 88.6). They also find that the lower MacKinnon score category participants peak-drug produced "unrateable" drawings, as scored by the Witkin score, although these participants' drawings were rated as more aesthetically pleasing than the high mean MacKinnon group.

Essentially the authors categorised their participants in three types of creative experiencers and performers: 1) uncreative individuals, 2) sensitive, creative experiencers performing creatively without psychedelics, although unable to produce aesthetically pleasing art in a drug-induced state or low-scoring on creativity without drugs but performing creatively in a drug-induced state, and (3) a minority with creative hallucinatory experiences which are creative performers.

The authors found that psilocybin enhances the creative performance but only in participants who are already being creative. However, not all participants that are creative experience a rise in creativity under the influence of psilocybin. Although the authors state that they measure creativity at three times, it is not apparent from their results which only offer T1 and T2, pre-drug and peak-drug administration. It is worth noting that the authors also found creative participants, so-called creative performers, who did not benefit from the psilocybin, in terms of enhancing creativity. Thus, it is not certain that all creative individuals will get more creative under the influence of psilocybin.

Summing up the reported findings; psilocybin enhances the creative performance but only in participants already being creative.

4.5.2 Landon & Fischer, 1970

The study compared the effect of psilocybin on poetic writing with effects of religious conversion experiences (i.e. altered state of consciousness) in two male volunteers. Both participants were university instructors in literature and chosen for literary comparability with Walt Whitman (WW) a nineteenth-century American poet (1819-1892). WW work represented "peak experience" in this study and was used as a benchmark. The study does not report on potential pathologies or prior drug history in the two participants.

Method and tasks for assessing Creativity. The authors analysed texts on a semantic, syntactic, and rhetoric level. Control passages were passages taken from previous written literature during "non-aroused states of daily routine". Test passages were written under the influence of ingested psilocybin and the participants were asked to to recall and describe a previous more intense hallucinogenic experience induced by 160 microgram/kg psilocybin. Prior to experimental test passage, they repeatedly administered 160 µg/kg (at approx. 3 weeks interval) to the two participants. Then at the test passage, the participants were administered 80 µg/kg and were asked to recall a more intense experience from the episodes with 160 µg/kg.

Results. The authors found differences in texts when administering psilocybin compared to texts written during more natural states of mind. They state that some of their results are significant, but do not provide the statistics to prove this (s. 126-127). In addition, they found

that the more altered the state of consciousness was, the more concrete the semantic orientation was. Specifically, this was observed as shortened and simplified syntactical units and modified rhetorical structure. The authors do not assess whether creative performance is enhanced.

4.5.3 Summarised Results and Assessment

The results from Fischer & Scheib offer us the aesthetically taste of two individuals, only one of whom is a professional artist herself, and as such might be able to take a more objectively, or more technically, view of the aesthetically pleasingness. It is however interesting that they find large differences between participants, which do point to a notion that the effects of psilocybin as being quite individual.

Landon found differences in texts when administering psilocybin compared to texts written during more natural states of mind. They do not themselves conclude whether or not creative performance is enhanced or not. An alteration in product, to something new and useful meet the criteria for something to be creative (cf. section 2.1.1). As such, psilocybin shows a tendency to be able to change creative linguistic performance, that is the quality of the artistic product. This is also suggested by the Janiger *et al.* study. More studies on a larger number of participants are needed to prove this tendency, as the tendency is only based on two participants whom are artists.

It is difficult to compare the two studies as they 1) measure two different kinds of creative performances and 2) differ greatly in the number of participants. Especially the Landon & Fischer study, is difficult to draw conclusions from either of the studies as their results are based on 2-6 participants. The two studies on psilocybin together point to the possibility that psilocybin potentially can enhance both creative written linguistic and drawing performances, although it might be in individuals whom are already familiar with the psychedelic experience/agents.

5. DISCUSSION

This section includes general discussion of the results from the systematic review and more reflective discussions. Some perspectives are found in section 6 and concluding remarks are given in section 7.

5.1 ASSESSMENT OF THE INCLUDED STUDIES

Overall it is difficult to draw any conclusions from the collected results from the included studies. This is mainly due to the heterogeneity of the objectives, methodology, samples, applied measures, and psychedelics examined among the small number of studies. An elaborate discussion regarding the applied measures and assessments of creativity is found in section 5.2.

5.1.1 Placebo or Not

The issue of using placebo or not when wanting to investigate the effect of a specific intervention, is worth noting. If the study does not use placebo, what can really be said of the potential effects the study might find? When investigating agents that induce noticeable psychological responses, which are not expected of the placebo [inactive placebo], the participants, as well as the researchers, with or without prior experience to psychoactive agents, will easily be able to tell what agent was administered to whom, as for example only hallucinogens induces hallucinations. Using an active placebo could overcome this challenge as is would be less obvious which participants receives placebo. Nevertheless, the issue remains even when using active placebo in the form of other psychoactive agents such as amphetamines, which, like an inactive placebo, does not induce hallucinations. This renders so-called blinded studies of psychoactive agents questionable. Furthermore, there is the well-known issue of the "placebo effect" which is worth taking into consideration when researchers evaluate their empirical data. This effect could have an impact on the study results including placebo [Berlin *et al.* (1955) (cf. sections 4.2.1 and 4.3.1.), Zegans *et al.* (1967)(cf. section 4.3.6) and Marrone *et al.* (2010)(cf. section 4.4.1)] in such a way that participants could expect an improvement on the experimental tasks. This is especially an issue for the studies informing their participants

that they might receive a psychedelic agent (e.g. McGlothlin *et al.* (1967). Additionally, the clinical setting might also impact and skew the results by influencing the participants psychologically. The included studies performed partly in naturalistic settings (e.g. Frecska *et al.*, [2012] and Kuypers *et al.*, [2016]) could have been influenced by for example the hypnotic chants of the medicine man leading the ayahuasca ceremony. Collectively the mind-set and the setting can be called the context, however in psychedelic research these are usually referred to as *set and setting*[1] (Carhart-Harris *et al.*, 2018).

5.1.2 Agents and Dosages

It is well-known that there are biological and psychological gender differences, especially regarding the brain. Therefore, it is a pity that not all included studies explicit the gender of their participants. Whether the gender differences are noticeable in the field of psychedelics, has, to my knowledge, yet to be uncovered. On creativity, Baer and Kaufman (2006) review concludes that there are tendencies showing small gender differences.

Comparing not only the psychedelics but also the dosages from these included studies, is a difficult task because the study populations differ considerably in their experiences with psychedelics. In some of the studies the participants are drug-naïve, in others the participants have low or high experience and lastly, and in some the participants are in therapy for drug abuse (cf. Marrone *et al.*, [2010]). Potential drug tolerance among experienced users might have an impact on their performance regarding creativity tasks. Another issue making it difficult to compare the studies, is that most of the studies do not explicitly state the time of drug administration and experimental testing. As described in section 2, the psychedelics all exert their effect at different times, which again depend on the route of administration (on which only a few of the included studies provide information). One would expect that the researchers have

[1] Set and setting: The set and setting hypothesis basically holds that the effects of psychedelic agents are dependent first and foremost upon set (personality, preparation, expectation, and intention of the person having the experience) and setting (the physical, social, and cultural environment in which the experience takes place).

taken these things into consideration, although it is not made clear to the rest of us. Additionally, this issue makes it difficult to replicate the studies.

Regarding LSD dosages, it is interesting to note that the studies administering the lowest amounts, among the included studies, appear to be the ones yielding positive results (e.i. Berlin *et al.*, [1955], Weintraub *et al.*, [1959] and Zegans *et al.*, [1967]) with dosages of 50 µg, 0.5 µg and 2.0 µg/kg. This might suggest a dose-response relationship worth looking further into when researching the effects of LSD on creativity. Anecdotes report varying effects depending on dosage. Another explanation could be the time of testing. The studies do not report when the drugs were administered or when the tests were performed. This makes it impossible to assess the relationship between time of ingestion and time of testing. Further research into the pharmacokinetics of these agents in relation to creativity is needed to elucidate these thoughts.

Agents. Psilocybin and ayahuasca both contain a wide range of other compounds than LSD, MDMA, and Mescaline do since the former are naturally occurring agents and can be ingested as such, while the latter are pure, synthetically manufactured drugs. Thus, effects related to the *natural* psychedelics could be due to synergistic effect. In fact, this has been suggested in relation to ayahuasca (cf. section 2.2.3). This might also be the case for psilocybin, especially when used recreationally, as it is often ingested as mushrooms where the concentration of the active compound can differ (Pellegrini *et al.*, 2013)], compared to the more clinical setting, where the active compounds are being dosed in more exact amounts. Culture method or geographical collection location along with preparation and route of administration determine the concentration of the psychoactive compounds in both psilocybin and ayahuasca. One of the included ayahuasca studies do, however, estimate the concentration of DMT in the ayahuasca brew ingested. However, according to Tylš, Páleníček and Horáček (2014) research on psilocybin in the 50s-70s were often of the synthesized form of psilocybin: Indocybin, as mentioned in background section 2.2.6 on psilocybin.

5.2 DISCUSSION OF CREATIVITY METHODS

Besides the differences in the chosen psychedelics, the issue of heterogeneity of the assessment measures (e.g. standardised vs. subjective judgement), makes it next to impossible to compare the studies and their results. Although this diversity is a good thing (e.g. elucidation of several aspects of creativity) it also lowers the comparability, the generalisability and consequently the value of the research. Some of the assessments are hampered by weaknesses. Some appear to be too subjective [expert judgement by a single person (cf. Janiger *et al.*, 1989) or evaluated by undergraduates (cf. Marrone *et al.*, 2010)], and several are not validated [e.g., Mosaic Design, Tachistoscope image identification (cf. Zegans *et al.*, 1967), phosphenes (cf. Frecska *et al.*, 2012)]. Additionally, the validity of some of the standardised methods have been questioned (RAT and TTCT) (Folley, 2006). And as many creativity methods rely on aspects of TTCT (cf. section 2.1.3), this consequently leads to questionable results. It is particularly difficult to compare results that rely on subjective evaluations (e.g. aesthetic value of drawings) with more objective and quantifiable measures (e.g. the TTCT). The question of aesthetically pleasingness hits a soft spot in relation to creative performance assessments; who is to judge what one individual finds useful or not? Considering that this discussion is peripheral to the scope of the present report, I will simply note the suggestion from Thys *et al.* (2014) who propose to use "meaningful" instead of "useful" as criteria for artistic creativity. They write: "*Although music can be very useful, it is essentially meaningful*". I do appreciate both as criteria (*useful* and *meaningful*), essentially an expert or professional of arts must know more than I on evaluating artistic drawings. My intention is therefore not to dispute their evaluations, but simply to shed light on the possibility that another qualified evaluator or expert potentially could evaluate the same drawings differently. As is the case for all subjective evaluations, the validity of the evaluation is heightened when it is performed by two or more specialists. Besides these thoughts on one of the aspects of the definition of creativity, I reckon that other criteria, in terms of creativity (as defined in section 2.2.1) are met in all the included studies.

Although all included methods arguably assess creative performance, it seems intuitive that linguistic tasks (e.g. poetic writing) measures different brain functions than tasks drawing abilities (e.g. DAP). This notion is supported by Thys *et al.* (2014). Included studies that do make

use of the same of similar assessments such as DAP and the Drawing Kachina Doll tasks are difficult to compare due to the discrepancies. This also applies to the included studies that use the TTCT or aspects of it to assess creativity. However, the fact that several studies only used parts of the TTCT (e.g., only "unusual uses") makes it difficult to compare them directly and make a combined assessment.

Lastly, even though the assessments from the included studies measure different aspects of creativity and are methodologically diverse, there are, however, some overlaps. Several tests rely on divergent thinking or aspects of divergent thinking (e.g. PLMT, PCT, BCU, FC, Guilford's tests, RAT, TAT, WAT). There seem to be an issue with some of the included studies' way of judging or evaluators, whose qualification and/or number is not clear. As for the studies that make use of the verbal section of TTCT (e.g. Marrone *et al.*, [2010]) or *fluency* (McGlothlin *et al.* [1964 and 1967], Harman *et al.* [1966], Frecska *et al.* [2004] and Kuypers *et al.* [2016]), it should be noted that this confounds by IQ as fluency is a constituent of not only creativity but also of intelligence (cf. section 2.1).

5.3 CREATIVITY ENHANCED OR CREATED BY PSYCHEDELICS?

Fischer & Scheib (1971) suggest that psychedelics only enhance already existing creative characteristics in individuals already being creative performers. It would appear reasonable to expect positive results on creativity tests from individuals who have creative characteristics. But are we right in doing so? The results from the studies explicitly including individuals with potential creative characteristics (e.g. Berlin *et al.*, 1955) are likely to elucidate the matter.

Berlin *et al.* (1955) test their participants on drawing skills, which makes perfect sense considering that they are graphic artists. The results indicate that graphic artists on psychedelics benefit from psychedelics. However, the study does not specify whether the administered psychedelics are LSD or mescaline. Similarly, Janiger *et al.* (1989) tests professional artists on drawing skills, but do not get positive results. Berlin *et al.* (1955) and Landon and Fischer (1970) test the linguistic skills of their participants. Both studies find that the participants do not benefit from the psychedelics tested.

In the Harman *et al.* (1966) study the participants creative problem-solving skills are tested. This approach makes perfect sense considering that the participants all work in fields requiring this specific skill. According to the results, the participants benefit from taking mescaline.

The rest of the studies do make no mention of potential creativity abilities or skills of their participants. Baring this in mind, one would expect less positive results when testing for example graphical artists' ability to produce linguistic writings or their (potentially lacking) engineering problem-solving skills. To quote Albert Einstein (1879-1955): "*Everyone is a genius. But if you judge a fish by its ability to climb a tree, it will live its whole life believing that it is stupid*". In the context of creativity, one could rephrase this quote to something like: Everybody is creative - but if you judge a musician by his ability to solve engineering problems, he will believe he is not creative. Thus, when assessing whether psychedelics enhance creativity, it is crucial to take the characteristics and abilities of the individuals into consideration. Otherwise, there is a risk of comparing apples and oranges. That is, unless one has in mind to find out whether psychedelics can promote *new* creative abilities which the individual does not yet possess or only does so to a very limited degree.

Supposedly, the psychedelic experience generates new ideas which can be transformed into the *expression* of creativity. It seems contra-intuitive that psychedelics could induce new abilities, e.g. make an individual able to play a melody on a guitar, without previous experience of playing a guitar. Yet, the world is filled with wonders and anecdotes of people waking up from comas with new skills and abilities they did not exhibit before – could the same be true for psychedelics? Can individuals without any prior experience, or ability, within a specific field of creative performance develop a new ability using psychedelics? If so, could it be driven by the psychedelic experience as suggested by researchers such as Fisher and Scheib (1979) or something else entirely? These are interesting theories whose assessment requires additional practical studies to investigate.

Thus, although psychedelics might not provide a person with a new specific set of skills or ability to perform in such a way that a given product turns out novel, original, and effective (i.e. creative), the psychedelic experience might facilitate creativity by opening the mind to more creative thinking (e.g. new ideas) and provide a more free state of mind which is not disturbed by negative contextual factors (as described in section 2.1.1) (e.g. potential negative judgement

of peers). This could allow for more playfulness in the form of 'toying' with ideas. A recent preliminary study, however, speaks against the notion of the psychedelic experience as necessary for creative performance. The study, which was published in Psychopharmacology in December 2018 by Prochazkova, Lippelt and colleagues, shows that microdosing psychedelic mushrooms (truffles) enhanced creativity factors in the participants. Microdosing should not induce a psychedelic experience, as it is taken in microdosages which are about a tenth of recreational dosages inducing a *trip* (i.e. psychedelic experience) (Prochazkova *et al.*, 2018; Scientific American, 2018). Prochazkova, Lippelt and colleagues report on significant improvement in both convergent and divergent thinking performance (PCT & AUT) post-microdosing compared to pre-microdosing, although not in fluid intelligence[2]. The study did not use a control group, and as such their results could be influenced by other factors (Prochazkova *et al.*, 2018). The study is, however, in line with findings by Harman *et al.* (1966), Zegans *et al.* (1967) and Kuypers *et al.* (2016), which show positive changes in creative performance tasks.

Together these findings suggest that psychedelics themselves are not sufficient in developing new creative abilities in individuals but might be able to enhance already existing creative abilities. The results further suggest that individuals already exhibiting creative abilities benefit from psychedelics in terms of enhancing these specific abilities. Further studies are needed to elucidate whether it is the psychedelic experience or simply the psychedelic agents that potentially enhance creativity.

5.4 LIMITATIONS OF SYSTEMATIC REVIEW

The purpose of the present systematic review is to investigate the potential enhancing effects of psychedelics on creative performance. To my knowledge, the present review is the largest of

[2] Fluid intelligence: The ability of understanding relationships among the components of an abstract problem and using such relationships to solve the problem. In contrast to crystallized intelligence, which refers to the knowledge accumulated through experiences (Oxford Bibliographies, 2018).

its kind. Although the review is systematic, it has its limitations. Firstly, as easy it is to criticize the assessments of creativity, as difficult it is to conclude on the findings from these assessments. Secondly, the lack of a golden standard for the definition of creativity yields potentially different outcomes of the search in the databases, because the search terms could differ. This constitutes a fundamental problem in this type of research. Due to the supposed nature of creativity, as a syndrome, there are numerous potential confounding factors and alternate explanations for the results. when trying to isolate a specific creativity phenomenon (performance), other important aspects are potentially neglected (see section 2.1.1 for additional aspects and factors of creativity). Throughout my discussion, I have attempted to include some thoughts on some of these aspects and factors, since some of them intuitively form part of the validation of the research within these fields.

As mentioned in section 3, the included psychoactive agents were chosen based on their potential for enhancing creative performance. Other psychoactive agents such as ibogaine or 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine) needs to be investigated to elucidate their potential in enhancing creativity. A review including other types of hallucinogens or other psychopharmacological agents, such as psychostimulants (e.g. amphetamines) would probably yield different results, since their mechanisms of action are different and might not "spark" the creative idea.

In my criteria for data extraction (cf. section 3.4) I have only selected results with statistical significance, when statistical analysis was performed. There might have been additional information showing tendencies to collect if these results had been included. Furthermore, I excluded self-report results. This was primary done to limit the scope of the review, rather than a lack of value assigned to self-reports. In fact, when investigating an obscure phenomenon such as creativity, self-reports would have proven useful in evaluating the results from the creativity assessments – especially when considering the subjective nature of artistic performance evaluations (e.g. aesthetic value). In addition, even though objective measures yield results, which could be evaluated as negative, participants could find themselves benefitting from their experiences. This was apparent in the included studies that included self-reports, such as Janiger *et al.* (1989). These studies found no overall effect but note that the artists themselves reported their work to be of more interest and aesthetically superior to their usual work.

6. PERSPECTIVES

Is it realistic that we will use psychedelics to enhance creativity to avoid a jobless future, as mentioned in the introduction? Are people willing to try out psychedelics to get more creative? Do people *want* to get more creative? And do specific psychedelics work better on specific fields of creativity? And how could we collectively in our societies benefit from creativity enhancers? Obviously, additional research is needed to fully answer these questions.

It would be interesting to investigate whether different psychedelics enhance, or facilitate, creativity in different creative areas, such as art, music, science, and engineering. It is not possible to draw any conclusions in this matter based on the minimal number of studies available on the subject. Nevertheless, psychedelic agents to exhibit different effects (cf. section 2.2) and one could thus speculate that the different psychedelics foster different areas of creativity - or different factors supporting creativity, such as working specifically well on *suppressing* factors that might inhibit creativity, or by *enhance* factors that might promote creativity.

Some individuals use psychedelics recreationally. Other potential users might consider using psychedelics to meet the perceived pressure, competition and need for perfectionism (Petersen *et al.,* 2018). In the latter situation, could it be that the potential positive effects of the psychedelics are more psychological than creative production enhancing? There are several reports on the mental benefits of psychedelics as they promote relaxation and social trust. Thus, individuals using psychedelics could become less competition-oriented for example. Trust and relaxation could also have an impact on creativity performance, since they might constitute other aspects of the creativity syndrome (cf. section 2.1.1). Thus, psychedelics might enable some users to tap out of aspects (e.g. ego) that could suppress the creative-thinking mind. Further research is needed to assess these theories. Additionally, in relation to promoting relaxation and social trust, psychedelics could prove useful in promoting mental health. Lastly, in an ideal world, promoting creativity could enable us to find solutions to wicked problems such as ending poverty and war worldwide, securing clean water and sanitation or other of the 17 Global Goals (The Global Goals, 2015) for a better world, for all of us.

In addressing these issues, psychopharmaceuticals, as those investigated in the present review or those mentioned in section 5.4., could provide inspiration in research and development of novel psychopharmaceuticals with minimal adverse effects.

7. CONCLUDING REMARKS

The present study did not find evidence of psychedelics enhancing creative performance. The results point to the possibility of psychedelics enhancing aspects of creativity in certain individuals. Due to the scattered empirical data, poor study quality, incomparable designs, small study populations, and the general heterogeneity among the participants, it is not possible to determine which individuals would benefit the most from psychedelics and from what type of psychedelic agent – if at all. The results overall merely show tendencies and are disturbed by a wide range of confounders and bias.

Additionally, further studies are needed to elucidate whether it is the psychedelic experience or simply the psychedelic agents that potentially enhance creativity. Furthermore, a consensus among psychedelic researchers on creativity and creativity assessments would prove most useful. More results are needed from more methodologically sound, thorough, controlled studies to confirm these tendencies and correlations.

The findings in the present review are in alignment with previous reports reviewing the literature on psychedelics and creativity (Krippner, 1985; Baggott, 2015).

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