

Bachelor Degree Project



PSYCHEDELIC AGENTS: CHANGES INDUCED IN SUBJECTIVE EXPERIENCE AND BRAIN ACTIVITY

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Abstract

This thesis combines phenomenological and neuroscientific research to elucidate the effects of psychedelic agents on the human brain, mind and psychological well-being. Psychoactive plants have been used for thousands of years for ceremonial and ritual purposes. Psychedelics are psychoactive substances that affect cognitive processes and alter perception, thoughts, and mood. Illegalization of psychedelics in the 1960s rendered them impossible to study empirically but in the last couple of decades, relaxed legal restrictions regarding research purposes, renewed interest in the effects of psychedelic drugs and new brain imaging techniques have started to reveal the possibilities of these mind-altering substances.

Psychedelics mainly affect the serotonin receptor 5-HT_{2A} which in turn affects the functioning of largescale cortical areas by changing cerebral blood flow, alpha oscillations and functional connectivity. These cortical changes not only induce immediate alterations in perception and cognition but have been shown to have positive effects in therapeutic interventions for depression, anxiety, and addiction, and also positively affect well-being in general. Although the pharmacology and neurobiology of psychedelics are still poorly understood, the potential benefits justify empirical research on psychedelics in humans.

Keywords: psychedelic, hallucinogen, subjective experience, phenomenology, brain imaging, electroencephalogram, magnetic resonance imaging, positron emission tomography

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Introduction

The term “psychedelic” was coined by Humphrey Osmond in 1957 to characterize substances capable of liberating human perception from cultural conditioning. Osmond claimed that psychedelics, such as lysergic acid diethylamide (LSD), could induce insightful experiences and enable people to better understand themselves and their relationship to the world. Another commonly used term for psychedelics is “hallucinogens”, however, this term is viewed as controversial since it implies that psychedelic substances cause hallucinations, which they rarely do. Mostly psychedelics produce visual alterations of perceived objects that are understood to be illusionary in character (Brandt & Passie, 2012).

Psychedelics may be the oldest psychopharmacological agents known, and psychoactive plants have been consumed for thousands of years (Nichols & Barker, 2016). There is a huge amount of archaeological evidence and historical documentation proposing that hallucinogenic drugs have been used across the ages for ceremonial and ritual purposes around the world. In the Indian Vedas there is the sacred *Soma* drink made most likely of somalata (*Sarcostemma acidum*). Mayan and Aztec cultures describe *Teonanácatl* (meaning “sacred mushroom” or “God’s flesh”). In Meso-American cultures they consumed morning glory seeds. The enigmatic *Kykeon* drink was used by the ancient Greek Eleusinian mysteries and most likely contained ergot fungus. Siberian shamans used the fly agaric mushroom (*Amanita muscaria*), and so on (Metzner, 2005; Schultes & Hofmann, 1979). A common root of many ancient Paleolithic religions and animistic beliefs is hypothesized to be based on hallucinogen-induced visions and shamanic practice (La Barre, 1979).

In the early Twentieth Century in Western psychology, self-experimenting with drugs to research consciousness has been documented. Philosopher and psychologist William James used nitrous oxide i.e., “laughing gas” and psychologist Heinrich Klüver experimented with mescaline, as did the writer Aldous Huxley who in 1954 wrote his famous book *The Doors of*

Perception about his experience (Móró, Simon, Bárd, & Rácz, 2011). Dr. Albert Hofmann first synthesized lysergic acid diethylamide (LSD) in 1938 at Sandoz Laboratories in Switzerland. He was looking for a circulatory stimulant (analeptic compound) but preliminary animal studies did not prove significant and scientists lost interest. It was not until 1943 when Dr. Hofmann accidentally absorbed a small dose of LSD through his fingertip that the extraordinary psychological properties became evident. This kickstarted an intense period of scientific investigation on therapeutic potential and mechanism of action of psychedelics (Lee & Shlain, 1985).

From the late 1940s, psychedelic substances became popular in scientific research. They were used extensively as an adjunct in psychotherapy since they reportedly enhanced emotionality (Kaelen et al., 2015), and many psychiatrists expressed great enthusiasm about their potential. There were several serious attempts to use LSD in the treatment of alcoholism and other addictions (Crocket, Sandison, & Walk, 1963; Grof, 1980) and in various kinds of therapies, such as in treatment for depression, anxiety, schizophrenia and even autism (Nichols & Barker, 2016). It was also used in treatment with issues related to dying and death (Grof, Goodman, Richards, & Kurland, 1973). However, the political situation during the late 1960s had major consequences for continued research (Lee & Shlain, 1985). Nichols and Barker (2016) claim that the rejection of social norms and the anti-war attitude of adolescents often were perceived to be a consequence of drug use. Hence psychedelics were believed to be “perverting” the mind of the youth, and they were placed in Schedule 1, the most restrictive category of drugs. This classification made it impossible to use psychedelics in research.

Even though the legal status of psychedelics differs from country to country, psychedelics research found new ground at the beginning of the millennium. Relaxed legal standards regarding legitimate research and new methods and brain imaging techniques have

enabled studies of the direct effects of psychedelics on brain activity. Interest in the benefits of psychedelics in psychotherapeutic treatment has been rekindled in the past twenty years.

The research questions this thesis intend to answer are: What are the phenomenological features of psychedelic states and their neural correlates? Are psychedelics efficient treatment options in specific therapeutic settings? I expect to find that the neural correlates of psychedelic altered experiences can explain the altered phenomenological features of experiences under psychedelics and that these changes in brain activity may be beneficial in certain therapeutic settings.

In the following sections, I will address what psychedelic agents are, what are their main mechanisms of action, what kinds of effects they have on subjective experiences, and how the ingestion of different psychedelic agents alters brain activity. I will especially discuss how the alterations in brain activity might relate to alterations in subjective experiences. I will also address whether there is evidence for beneficial effects of psychedelic agents that would justify their use in a therapeutic setting. In the conclusion I will try to answer my research questions. In sum, the aim of this thesis is to combine phenomenological and neuroscientific research to elucidate the effects of psychedelic agents on the human brain, mind and psychological well-being.

Method

For this literature review articles were collected from databases such as Web of Science, Scopus, and PsycINFO with search terms such as “psychedelics”, “hallucinogens”, “brain imaging”, “subjective experience”, and “treatment” in different constellations. The focus was limited to studies on human subjects made with psilocybin or LSD. From several hundred articles, the best suited articles concerning subjective experience, brain imaging and therapy were selected.

What are Psychedelics?

Hollister (1964) defined hallucinogens as agents that produce changes in perception, mood, and thoughts without producing addiction, memory or intellectual impairment, and that have minimal autonomic effects. Yet, it has been difficult to develop a formal classification of hallucinogens since other drug classes may produce overlapping effects (Halberstadt, 2015) and because different hallucinogens have several action mechanisms. In fact, although the terms hallucinogen and psychedelic are often used interchangeably, hallucinogens can be considered to cover a broader set of agents than psychedelics, and also include deliriants and dissociative drugs (see Table 1 for one possible classification).

Table 1. Classification of Hallucinogens

Hallucinogens	Deliriants	Jimson weed, angel's trumpet, henbane, etc.
	Dissociative	Ketamine Nitrous oxide (N ₂ O) PCP <i>Salvia divinorum</i>
	Psychedelics	Minor Marijuana, hashish New synthetic drugs (2C-B, 5-MeO-DMT etc.) Ibogaine
		Major LSD <i>Psilocybe</i> mushroom Mescaline cacti DMT (ayahuasca, yopo, etc.) LSA (morning glory, HBWR, etc.)

Note. PCP = phencyclidine; 2C-B = 2,5-dimethoxy-4-bromophenethylamine; 5-MeO-DMT = 5-methoxy-dimethyltryptamine; LSD = lysergic acid diethylamide; DMT = N,N-dimethyltryptamine; LSA = d-lysergic acid amide (Modified from: Móró et al., 2011, p.11 Reprinted with permission from the first author).

Plants from the hallucination-inducing *Solanaceae* family are considered to be deliriant and not psychedelics because of their sleepwalking-like effects. Dissociative drugs such as ketamine, nitrous oxide (“laughing gas”) and phencyclidine (PCP), all of which are mainly NMDA receptor antagonists, and *Salvia divinorum*, which contains salvinorin A and is a potent κ -opioid receptor agonist, can be classified as dissociative hallucinogens.

Psychedelic (i.e., “mind-manifesting” or “mind-revealing”) agents are a powerful class of hallucinogens that affect cognitive processes and alter perception, thoughts, and mood in ways that have been compared to dream experiences or religious exaltation (Nichols & Barker, 2016). In 1996, Glennon suggested that classic hallucinogens, or *major psychedelics*, are agents whose primary site of action is serotonin 5-HT_{2A} receptors. From a neuropharmacological point of view, psychedelics include serotonergic psychoactive phenethylamines and tryptamines (Móró & Noreika, 2011). The major psychedelics are lysergic acid diethylamide (LSD), psilocybin from mushrooms belonging to *Psilocybe* family (“Magic mushrooms”), mescaline from e.g. *peyote* cacti, DMT (N,N-dimethyltryptamine) contained in many species of plants (used e.g., in the brew ayahuasca), and d-lysergic acid amide (LSA) which is found in the Hawaiian baby woodrose and in the seeds of morning glory (Halpern & Sewell, 2005; Nichols & Barker, 2016) (Table 1). Sometimes the listings of psychedelics also contain MDMA (3,4-methylenedioxy-methamphetamine, also known as ecstasy) and 2C-B (2,5-dimethoxy-4-bromophenethylamine, or “Nexus”). Occasionally, even potent forms of cannabis have been reported to induce hallucinations, and thus cannabis is sometimes classified as a minor psychedelic (Blackmore, 2013).

Given the complexity in the classification of psychedelics and the use of the term “hallucinogen” to refer to psychedelics and other substances inducing delirium or dissociative states, henceforth the terms *classical hallucinogen* and (*major*) *psychedelic* will be used interchangeably in this thesis to refer to LSD, psilocybin, mescaline, DMT and LSA. Yet, the

focus of the thesis is mainly on LSD and psilocybin, as these agents have been most studied in the past few decades.

Results from different studies with classical hallucinogens consistently show that classical hallucinogens do not cause physical withdrawal symptoms nor compulsive drug-seeking behavior (Johnson, Richards, & Griffiths, 2008; Studerus, Kometer, Hasler, & Vollenweider, 2011). They have a low abuse potential and are considered rather safe. Tolerance rapidly develops after just three or four daily doses, and eventually there is practically a complete loss of response. Regular use is therefore unlikely (Halberstadt, 2015; Studerus et al., 2011). Even though so little is known about the mechanisms leading to tolerance to hallucinogens, the development of tolerance is understood to be due to downregulation of serotonin receptors (Buckholtz, Zhou, Freedman, & Potter, 1990). DMT seems to be the only major psychedelic that is an exception to the rule and does not produce tolerance in humans (Strassman, Qualls, & Berg, 1996). However, generally classical hallucinogens are considered rather risk-free and practically impossible to cause an overdose with because of their relatively low acute toxicity (Nichols & Barker, 2016).

While natural psychoactive tryptamines are found in mushrooms, plants, and toads (Rickli, Moning, Hoener, & Liechti, 2016), many tryptamines derivatives are synthesized. Novel synthesized psychoactive substances constantly appear on the illegal drug market and are used not only because of their potency but also due to legal loopholes (Araújo, Carvalho, de Lourdes Bastos, De Pinho, & Carvalho, 2015). Small changes in the molecular structure can change the pharmacology of these substances and consequently, their receptor interaction and toxicity become unknown (Rickli et al., 2016). Even though major psychedelics are considered safe, information regarding the safety of new psychedelics is very limited. As a consequence, reports of intoxication and deaths have appeared over the last years in relation to the use of these novel psychedelics (Araújo et al., 2015).

Why Psychedelics are Ingested

Psychedelics seem to be deeply embedded in human culture, as sacramental (the psychedelic drug is a part of a religious rite) and spiritual (the psychedelic experience of transcendence is of main importance rather than the drug itself) tools (Móró & Noreika, 2011). In religious and spiritual settings, psychedelic drugs are used as aids to “becoming divine within”. In spiritual settings, psychedelics have been given the name *entheogens* meaning just that: “becoming divine within” (Ruck, Bigwood, Staples, Ott, & Wasson, 1979). Even nowadays, psilocybin mushrooms are ritually ingested by several indigenous Mexican tribes (Guzmán, 2008), and mescaline is consumed in rituals of the peyotist Native American Church (Lawson & Scholes, 1986).

However, most non-addictive drug use in Western societies is primarily nonreligious (Müller & Schumann, 2011). Instead, the purpose of the hallucinatory experience is often to increase self-discovery and self-understanding (autognosis) (Móró et al., 2011). In the study by Móró et al. autognostic use accounted for 36% of all occasions of psychedelic drug use. Móró and Noreika (2011) have proposed an explanation for how psychedelic agents could be helpful in increasing self-knowledge. This hypothesis resembles the Threat Stimulation Theory (Revonsuo, 2000) of the biological function of dreaming. It suggests that similarly to dreams, psychedelics can offer a virtual training function that may increase self-knowledge and help develop coping strategies that one can use later in life, psychedelic drug use creates a training situation where exceptional experiences are triggered to rehearse coping strategies and gain self-knowledge that promotes self-enhancement (Móró & Noreika, 2011).

There are many other motivations in addition to increasing self-knowledge. Psychedelics can be used to shake up or shape one’s fundamental worldview, or to enhance mood, avoid boredom and hopelessness, increase social contact, increase sensation and pleasure, stimulate artistic creativity or performance, express an alternative lifestyle, draw attention, express membership in a group, and reveal curiosity (Móró et al., 2011).

Action Mechanisms of Major Psychedelics

Serotonin or 5-hydroxytryptamine (5-HT) is the simplest of all known tryptamines.

Stimulation of 5-HT_{2A} receptors depolarizes the cell, which makes it more prone to firing. 5-HT receptors are important for perception, attention and affect regulation (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004). Overstimulation of 5-HT_{2A} receptors causes a reduction of attentional abilities and may cause a lack of motivation to perform (Hasler et al., 2004).

5-HT receptors are responsible for mediating hallucinogenic effects in human subjects (Halberstadt, 2015). All major psychedelic drugs are agonists at the serotonin receptor 5-HT_{2A}, which are expressed in the layer 5 (excitatory) pyramidal neurons. These neurons are the main source of output from cortical regions that send information to hierarchically lower cortical areas (e.g., from visual association regions to the primary visual cortex) (Bastos et al., 2012).

Serotonin shares its chemical structure with the core structure of tryptamines such as psilocybin and LSD, shown in Figure 1. Although LSD and other psychedelics show high similarity with 5-HT, it appears that adrenergic and dopaminergic receptors play an additional role in facilitating some aspects of the effects mediated by these compounds (Halberstadt & Geyer, 2011).

5-HT_{2A} is mainly expressed in the cortex and hippocampus with the densest distribution in posterior cingulate cortex and other high-level association regions. The lowest distribution of 5-HT_{2A} is found in the primary motor cortex (Carhart-Harris et al., 2012a). As the effects on the 5-HT_{2A} receptors are crucial for hallucinogenic action, this may be one explanation why psychedelics affect perception and cognition so distinctly while motor actions generally are not affected (Carhart-Harris et al., 2014a). Studies have found that blocking of the 5HT_{2A} receptors with the agonist ketanserin weakens the hallucinogenic effect (Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). (Ketanserin is a serotonin

receptor-blocking drug used, for example, to lower blood pressure in patients with chronic or acute hypertension; Karolinska Institutet, 2019.)

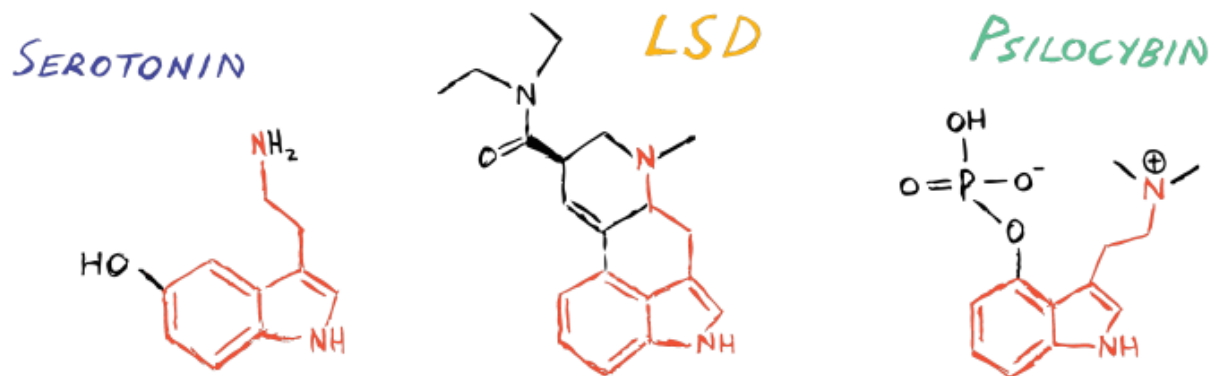


Figure 1. Chemical structures of serotonin, LSD & psilocybin. (Author's own illustration, based on information from The Third Wave, 2019)

The Effects of Psychedelic Agents on Subjective Experiences.

Daniel X. Freedman, one of the pioneers of LSD research, noted (1968) that LSD-induced state of consciousness might be described as “portentousness”, with feelings of miracle, wonder, and awe. It is a way to experience boundlessness, from the banal to the profound, for the mind to experience and see more than it can explicate. The effects of psychedelic agents on subjective experience are uniquely individual and difficult to measure objectively. Next, I describe how expectations and environment effect the psychedelic experience, then present the typical acute effects of psychedelics on subjective experience, and finally I briefly discuss what kinds of long-term effects psychedelics may have.

The Effect of Expectations and Environment on Psychedelic Experiences

The effects produced by psychedelics are highly dependent on a person's mindset (what expectations she might have) and the environment. These are often summarized as *set* and *setting*. If the environment makes the person feel safe and is designed to facilitate mystical experiences, the probability of a positive outcome is greater (Nichols & Barker, 2016). When psychedelics are ingested in a party or any unstructured setting, the probability of negative outcome is somewhat greater compared to the safer setting. Behaviors and feelings at the start

of the process may be positively or negatively reinforced by the drugs effects (Müller & Schumann, 2011).

The effect of the state of mind prior to ingestion on subjective experience was nicely illustrated in a study by Griffiths, Richards, McCann, and Jesse (2006) who conducted an experiment using psilocybin. Of 36 volunteers, 11 reported mild or moderate anticipatory anxiety before the experiment. Any negative experiences in post-session ratings were only among these 11 participants.

More recently, Studerus, Gamma, Kometer, and Vollenweider (2012) investigated multiple predictor variables on response to psilocybin. They found that having a high score on the personality trait *absorption* (when a person becomes absorbed in their mental imagery, particularly fantasy), being emotionally excited and happy right before psilocybin intake, and having experienced only few psychological problems lately were all strongly associated with mystical and pleasant experiences. Extraverted subjects (who are high on sociability) seemed to enjoy the psychedelic experience slightly more than introverted subjects (Studerus et al., 2012). In contrast, youth, emotional excitability and experimental settings involving positron emission tomography (PET) were strongly associated with anxious or unpleasant reaction to psilocybin (Studerus et al., 2012).

When drug-induced effects are emotionally highly unpleasant or negative, this is often called a “bad trip” or “horror trip”. Such negative experience is not common in experimental settings. In an experiment by Hasler et al. (2004) on acute effects of psilocybin, they gave a high dose of psilocybin to 315 participants. Only one participant reported a fearful experience, with pronounced anxiety, marked by fear of losing control, and depressed mood. The anxiety gradually subsided and the dysphoric reaction disappeared six hours after drug ingestion. None of the participants who received a medium dose ($n = 215$) or low dose ($n = 115$) reported adverse effects. When Studerus et al. (2011) pooled raw data from eight

experimental studies, with altogether 110 subjects, only one subject reported experiencing symptoms of anxiety, depression or emotional instability several weeks after the experiment; yet, the symptoms were severe enough for him to seek professional help.

It is not completely clear to what extent different state and trait factors, such as expectations or personality, influence the experience. On different occasions, the same individual may experience different responses (Halberstadt, 2015). As discussed later, the psychedelic experience is also highly dose-dependent.

Psychedelic-Induced Subjective Experiences

Although each drug experience is unique, the general effects of classical hallucinogens are remarkably similar. It can be concluded from consumer reports that psychedelics may not provide new sensory stimulus but rather change an individual's mental state and present stimuli and memories in a new way, including self-perception (Müller & Schumann, 2011). The most common features of the psychedelic experience are shown in Figure 2 and will be covered in more detail below.

Perception. In the psychedelic state, cognition is less fussy and accurate, and perception of the external world is easily biased by internal states and emotions: for example, anxieties and wishes (Carhart-Harris et al., 2014a). In a psilocybin study conducted by Hasler et al. (2004) with a large sample of participants (N=690), they investigated dose-dependent (very low dose - low dose - medium dose - high dose) induced changes in sensory perception (e.g., visual illusion and synesthesia) and mood states as well as alterations in the perception of self, time and space. They found that psilocybin dose-dependently and profoundly affected psychedelic experience in all areas: that is, with increasing dose, alterations in the experiences also increased (e.g., stronger visual alterations when the dose was higher).

One common subjective effect of psychedelics is strongly altered time perception. A few minutes may be perceived as hours or the other way around (Nichols & Barker, 2016),

and sometimes sensations of timelessness occur (Halberstadt, 2015). Wittmann et al. (2007) tested working memory and conscious experience related to time perception. They found that psilocybin affected individuals' ability to accurately reproduce interval length or synchronize a motor response by tapping a finger to regular auditory beats longer than two to three seconds. There was also significant correlation between subjective measures of altered time sense and working memory impairment. Wittmann et al. suggest that instead of alteration of the internal timing mechanism, the disturbed timing could reflect impairments of decision-making, attention or memory mechanisms.

Top 10 rated items

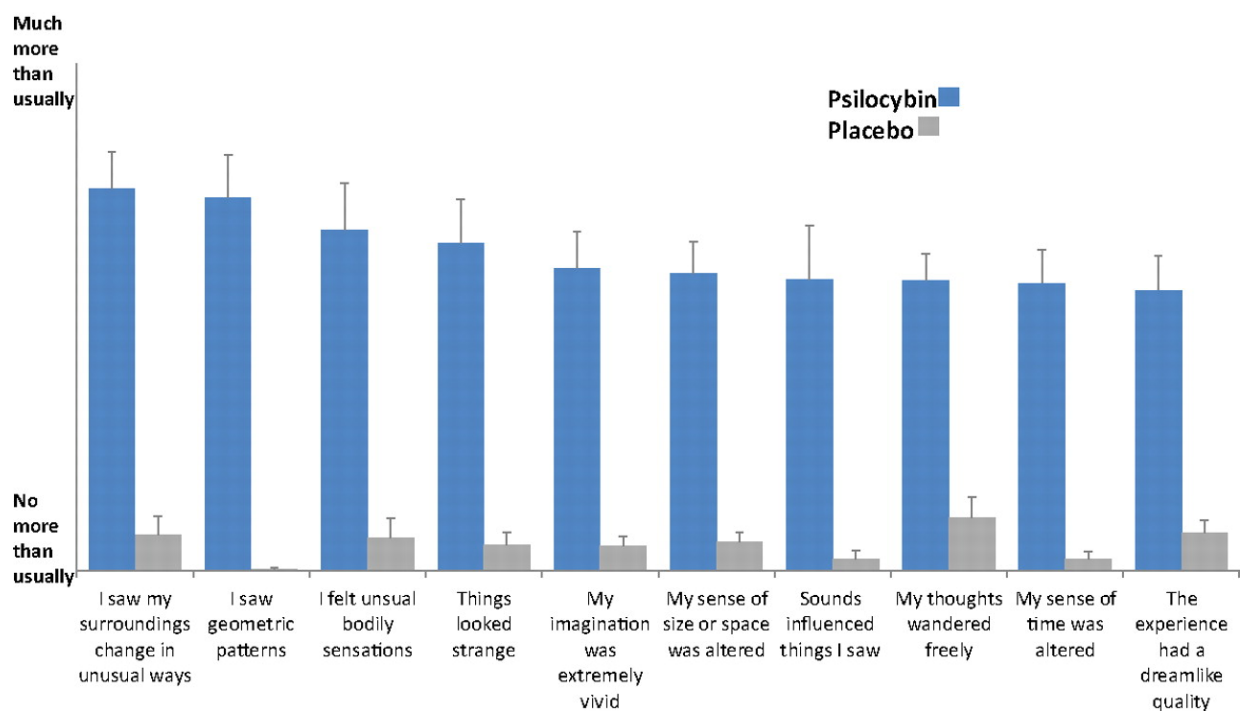


Figure 2. Subjective ratings of psychedelic experiences after psilocybin and placebo. Mean values for subjective ratings (n=30). “No more than usually” refers to normal state of consciousness. All 10 items were rated significantly higher in the psilocybin condition than in the placebo condition. (Adapted from: Carhart-Harris et al., 2012a, p. 2139. Reprinted with permission from the first author.)

Affect. Schmid et al. (2015) investigated subjective and autonomic effects of LSD and found that, in addition to visual hallucinations, depersonalization, and synesthesia, LSD increased closeness to others, trust, openness, happiness and subjective well-being. Moderate

to small increases in heart rate, blood pressure, pupil size, and body temperature were measured, as well as increase in prolactin, plasma cortisol (both are markers of serotonergic activity), epinephrine (also known as adrenaline), and oxytocin levels. Oxytocin has been shown to contribute to prosocial behavior and empathogenic effects; that is emotional closeness and openness such as empathy or sympathy, as well as relatedness and closeness to others (Ramos et al., 2013).

Kaelen et al. (2015) tested the hypothesis that LSD enhances the emotional response produced by music. They asked the question: How emotionally affected were you by the music? Participants rated that they were significantly more strongly affected under the influence of LSD than in the placebo condition. The enhanced or intensified feelings towards music under the influence of LSD were described as “tenderness”, “power”, “wonder”, and “transcendence” (Kaelen et al., 2015).

Hallucinations. Hallucinations are sensations that may seem real but are created by the mind. They are considered one of the most prominent features of psychedelic-induced ASC with changes in, for example, closed eyes imagery, synesthesia (when senses are intertwined; e.g., tasting color or seeing sounds), optical illusions (when an object is perceived in a way that differs from reality) and elementary hallucinations (the simplest form of auditory hallucinations, e.g., an extended tone or whistling). True auditory or visual hallucinations rarely happen, such as hearing voices or seeing things that are not there. In the Hasler et al. (2004) study on psilocybin, no auditory hallucinations were reported with any dose, and their sample size was impressive, with 690 participants.

Instead of true hallucinations, alterations in perception concern changes in and intensification of preexisting sounds and images. Even at relatively low doses, subjects report optical phenomena such as “curtains waving”, “walls breathing”, undulating carpets, and so forth (Nichols & Barker, 2016). The hallucinogenic experience is almost always recognized

as illusory and should more accurately be described as a pseudo-hallucination (Studerus et al., 2011).

Even though the hallucinogenic experience mostly is rated as pleasurable and highly valued, occasionally subjects are confronted with unpleasant and sometimes frightening memories, thoughts and emotions. Furthermore, most subjects describe the effects as tiring. The “coming down” from the hallucinogenic effects, even if the experience was positive, is generally welcomed, and the subjects appreciate returning to their normal state of consciousness (Studerus et al., 2011).

Magical Thinking. Magical thinking is a phenomenon that is possible under the influence of psychedelics. In magical thinking, mystical interpretations of sensations and experiences are made. Especially if there is a lack of evidence or certainty about a situation, there is a greater chance of dreaming up explanations or coming up with incredible explanations (Friston, 2010). Increased introversion, inactivation and dreaminess are usually seen in subjects, and dreaminess is still reported 24 h after administration of psilocybin (Hasler et al., 2004).

According to Carhart-Harris et al. (2014a), magical thinking promotes creative and imaginative thinking, which is associated with positive affect. Carhart-Harris et al. also state that wishful thinking or beliefs are a byproduct of “positive” magical thinking when the individual interprets the world as they wish it would be. The opposite would be paranoia when the individual jumps to negative conclusions. Paranoia involves intense thoughts and feelings of fear and anxiety.

Ego Dissolution. The self is a fundamental part of the normal human waking consciousness. This “I”, “me” and “mine” speech in everyday language invites the assumption that the self is a permanent feature of consciousness (Lebedev et al., 2015). Carhart-Harris and Friston (2010) argue that the self is better viewed as an “umbrella”

construct that includes a variety of mental phenomena such as self-monitoring, self-recognition, self-awareness, self-control, self-identity, theory-of-mind, reality testing, goal-directed cognition, and so forth.

Ego-disturbance manifests as the feeling of one's "ego", "self" or "I" is disintegrating (Lebedev et al., 2015). In psychedelic experience, this kind of ego-dissolution where the border between the external world and oneself is dissolving is a notable feature (Carhart-Harris et al., 2014a). According to Hasler et al. (2004) the loosening between self and environment is usually experienced as touching or unifying with a higher reality. In this state individuals can perceive environmental stimuli in a new way, reported to heighten one's perceptual world, meaning that the person feels, sees and perceives more than usual, often leading to some kind of insight (Müller & Schumann, 2011).

Because psychedelics affected the sense of self, it was speculated that the psychedelic effect also could enhance suggestibility and cooperation in humans. In the 1950s the United States government wanted to investigate whether psychedelics could be used in a military setting. The pressure to find new enhanced interrogation and behavioral control methods, as well as means to incapacitate the enemy, was motivated by the Cold War. The US government authorized a research program named "MK-ULTRA". The purpose was to investigate the possibilities of using LSD to facilitate behavioral and mind control. However, the drug's efficacy for this purpose was never revealed (Lee & Shlain, 1985). Nevertheless, a couple of studies reported that LSD increased suggestibility (e.g. Middlefell, 1967; Sjöberg & Hollister, 1965). Sjöberg and Hollister also tested suggestibility induced by psilocybin but found no such results.

A more recent study by Carhart-Harris et al. (2015) further investigated LSD induced suggestibility. Using the creative imagination scale (an alternative to standard hypnotic suggestibility tests), the experimenter read ten descriptions regarding altered subjective

experiences to the participant. Every description was 200-250 words long. Participants were asked to keep their eyes closed and “think along” with the description. Descriptions included suggestions such as feeling time slowing down or sunrays heating their hands. Carhart-Harris et al. found that LSD indeed enhanced responsiveness to suggestions.

It has been hypothesized that increased suggestibility may be due to increased neural network flexibility and decreased network integrity in the brain that makes the individual feel less assured about her own beliefs, resulting in higher sensitivity to external influences (Carhart-Harris et al., 2014a; Muthukumaraswamy et al., 2013). LSD might enhance suggestibility by temporarily interrupting the drive to keep control over one’s environment and mind, and effect of LSD in increasing suggestibility seems to positively correlate with the personality trait conscientiousness (Carhart-Harris et al., 2015).

Mystical Experience. Ego dissolution is a prominent feature of a mystical or spiritual type of experience (Lebedev et al., 2015). Mystical experience is a rather broad term that also covers spiritual experiences. According to Blackmore (2013), mystical experience is probably impossible to define in a manner that does the experience justice. The best we may be able to do is to list some common features.

There are four markers commonly described in conjunction with mystical experience, the first is *ineffability*, which means that the experience cannot be explained in words or otherwise imparted to others. The second is *noetic* quality: that is, a sense of illumination, knowledge or insight. The third marker is *transiency*, which means that the experience cannot be clearly remembered afterward but is easily recognized when it recurs, which allows continued internal development. The fourth is *passivity*; although there are ways to make the mystical experience more likely, it cannot be induced by order, and, once the experience begins, the experiencer feels as if her own will is in abeyance (Blackmore, 2013).

It appears that all major psychedelics have the property to elicit mystical experiences but not “psychedelic-like” compounds such as cannabis and MDMA (Carhart-Harris & Nutt, 2010). The mystical experience can be described as diminished subjectivity or increased objectivity and diminished temporal and spatial awareness, with a sense of divinity, profound peace and joy and a sense of unity with the world (Carhart-Harris et al., 2014a). This kind of experience is difficult to express in words. In 1901, the Canadian psychiatrist Richard Maurice Bucke tried to explain mystical experience which he called “cosmic consciousness”. He described it as a third form of consciousness: above human self-consciousness and above the simple consciousness that humans share with other animals. Its primary characteristic is “a consciousness of the cosmos, that is, of the life and order of the universe” (Bucke, 1901, p. 3). According to Blackmore (2013), the mystical consciousness has been described as revealing the “depth beyond depth of truth”, which disappears when the drug wears off - in many cases leaving mainly nonsense words behind, while the sense of insight and meaning remains.

The Long-Term Effects of Psychedelics

Although most studies have focused on the acute effects of psychedelics, several investigations address the longer-term effects. Studerus et al. (2011) investigated both short-term (24h) and long-term effects (8-16 months) after administered psilocybin. Short-term, only headaches, tiredness and exhaustion were reported, in relatively mild forms. This suggests that normal functioning is almost restored 24h after drug administration. As to long-term effects (8-16 months after), the reserachers found that most subjects were still positively impressed by the psychedelic experience. Interestingly, even if the subject had experienced significant distress during the psychedelic experience she still rated it as very enriching and sometimes even influential.

Similar results were found by Griffiths, Richards, Johnson, McCann, and Jesse (2008) in a follow-up conducted 14 months after psilocybin ingestion. Over 50% of participants rated

the experience as among the five most spiritually significant or personally meaningful experiences of their lives. This correlated significantly with having a mystical experience on the drug administration day. Over 60% of participants rated increased life-satisfaction and well-being; none rated the experience as having decreased life-satisfaction or well-being (Griffiths et al., 2008).

The most often reported subjective changes in personality and attitude after psychedelic use is reduced aggressive, materialistic and egocentric orientation and increased appreciation of nature, art, and music (Studerus et al., 2011). The subjective evaluations were supported by behavioral changes such as time spent in museums, number of musical events attended and number of music album bought. However, the positive changes in personality were connected to the psychedelic experience only if the subject had a previous interest in hallucinogenic drugs but not if the drug intake was initiated by their therapist (McGlothlin & Arnold, 1971, as cited in Studerus et al., 2011).

Bouso, dos Santos, Alcázar-Córcoles, and Hallak (2018) conducted a systematic review to assess personality changes in regards to psychedelics. They found that the transitory effects of psychedelics may be due to functional synaptic changes modulated by 5-HT_{2A} receptors, while more persistent and long-term effects may be due to changes in gene expression. It is suggested that personality is modulated by interaction between environment and genes, where changes in gene expression could be caused by toxicological (e.g., drugs) or psychological (e.g., distress) factors - implying that personality is not as stable over time as previously thought (Svrakic & Cloninger, 2010). Personality changes observed after administration of psychedelics included increased openness and self-transcendence; these were predicted by the increased connectivity induced in the brain by the psychedelic state. Results suggest that these effects are persistent, enduring from days to several weeks and even months after (Bouso et al., 2018).

In a correlational study Lerner and Lyvers (2006) compared possible life-changing experiences between users of nonpsychedelic drugs (e.g., amphetamines and marijuana), users of psychedelic drugs (e.g., LSD and psilocybin), and social drinkers. Psychedelic users scored significantly higher on concern for others and empathy, mystical beliefs (e.g., being one with the universe or God) and life values of spirituality. Irrespective of cultural origin or income, psychedelic users scored lower on financial prosperity than the other two groups.

Microdosing Psychedelics

Microdosing means that a very small quantity of a psychedelic substance is ingested: small enough to not give any or only minimal acute effects but believed by some to generate positive long-term effects in well-being and general health (Polito & Stevenson, 2019). Legal issues make the investigation of microdosing of psychedelics very difficult to study experimentally, and there have been no published empirical studies so far. However, as interest in psychedelic research is growing, so does interest in psychedelics in the general population. Numerous online communities and blogs that report and discuss anecdotal outcomes of psychedelic use (e.g., www.reddit.com/microdosing/wiki, www.thethirdwave.co, and www.microdosing.com). From these websites, Polito and Stevenson (2019) tracked participants for an exploratory research project aiming to investigate peoples' experiences of microdosing for six weeks (on any day or days they wanted). Participants filled in daily ratings of psychological functioning (i.e., connectedness, happiness, creativity, well-being, focus, productiveness, and contemplation) and additional pre- and post- psychometric measures (tapping e.g. attention, creativity, mystical experience and mood).

As could be expected, the participants were expecting large and widespread benefits from microdosing. It is not clear to what degree these expectations influenced their subjective reports and interpretation of their experiences. Nevertheless, Polito and Stevenson (2019) found an increase on dosing days across all psychological functioning measures compared to

baseline scores. In the days following the dosing day, only the ability to focus and productivity remained slightly increased. However, their questionnaire revealed several variables that changed over the six-week microdosing period: variables that broadly can be interpreted as improvements in mental health, such as decreased depression and anxiety; and processes linked to attention, such as decreased mind wandering and increased absorption. Contradictorily, participants also reported an increase in the trait *neuroticism* during the microdosing period; however, this may reflect their overall increase in intensity of emotions, both positive and negative. The long-term changes were unrelated to the number of doses over the period, suggesting that microdosing, whether frequent or a single dose, can have an effect on mental health and attention (Polito & Stevenson, 2019). As mentioned before, the research on microdosing is lacking, it is possible that microdosing psychedelics may involve unknown risks. Note that larger doses of psychedelics are generally taken infrequently, even by enthusiasts.

Neural Correlates of Psychedelic Experiences

The primary site of action for major psychedelics is the 5-HT_{2A} receptors, which are mainly found in the cortex. The prefrontal cortex (PFC) is the executive area of the brain where output from the limbic areas and input from sensory organs converges. This area heavily expresses 5-HT_{2A} receptors and is therefore highly affected by psychedelics (Nichols & Barker, 2016).

Some scientists argue that psychedelics make it possible to study how the mind arises from brain activity, because of their ability to target processes that seem to be important to maintaining normal waking consciousness (Carhart-Harris et al., 2014a; Halpern & Sewell, 2005). In this section, I will review studies that have investigated the neurophysiological (blood-flow) changes in the brain induced by psychedelics, as measured by

electroencephalography (EEG), magnetoencephalography (MEG) and brain imaging methods, such as functional magnetic resonance imaging (fMRI).

EEG

Research on the effects of LSD on brain activity back in the '50s and '60s was limited to EEG studies, many of which were animal studies. There were some investigations with human subjects. A study made by Gastaute, Ferrer, Castells, Lesevre, and Luschnat in 1953 found that in nine out of ten subjects, LSD caused an increase of alpha frequency (as cited in Evarts, 1957). Forrer and Goldner (1951) examined changes in EEG in a group of psychotic subjects when they received LSD, but found no changes.

In the early days of neurophysiological research, conclusions about the relationship between psychological and electrophysiological effects of psychedelic agents were made with caution, since such evaluation would necessarily have included a substantial amount of speculation, impossible to support by experimental observations. Mostly, the psychological effects in human subjects were explained based on the neurophysiological effects measured from the brains of animals (Evarts, 1957). Evarts did, however, guess that disturbance of visual perception resulted from disturbance of cortical connections under the influence of LSD, even though this could not be empirically verified at that time. He also speculated that visual hallucinations could be the result of a wide variety of chemical, anatomical and psychological changes in the nervous system. At that time, LSD had been shown to trigger “arousal” or “alerting” responses in EEG, but so had many other agents that were not psychedelics. The problem with establishing a causal relationship between psychological and electrophysiological events was one reason many scientists avoided studying the action of psychedelics (Evarts, 1957) before that became illegal.

Nowadays, techniques to measure brain activity are more advanced, and using EEG together with, for example, fMRI makes predictions more legitimate. Carhart-Harris et al.

(2014a) found a highly significant positive correlation between subjective feelings of the disintegration of the ego and a decrease in magnitude of alpha power under psilocybin in the posterior cingulate cortex (PCC).

In an LSD study conducted in 2016, Carhart-Harris et al. found a significant relationship between ego-dissolution and decreased alpha and delta power, and between decreased alpha power and simple hallucinations. These decreases in alpha and delta power were widespread all over the brain, and affected PCC, precuneus and other higher-level cortical regions. Tagliazucchi, Carhart-Harris, Leech, Nutt, and Chialvo (2014) also noticed that psilocybin decreased low-frequency power localized to higher-level cortical regions. This implies that the primary action of psilocybin and other major psychedelics is to cause desynchrony through a loss of oscillatory power in higher-level cortical regions, possibly through the 5-HT_{2A} receptor.

It has been hypothesized that cortical alpha serve as a filter to keep irrelevant stimuli away from consciousness (Jensen & Mazaheri, 2010). Decreases in alpha oscillations have been described to reflect increased cortical excitability (Preller et al., 2019). The reduced alpha power under psychedelics could facilitate the release of chaotic patterns of excitation that appear spontaneously and create visual hallucinations (Carhart-Harris et al., 2016).

Brain Imaging

To give the reader some background, I will introduce some central concepts, such as resting-state functional connectivity and the default mode network, that are essential for understanding the results of brain-imaging studies on psychedelics.

Resting-state functional connectivity (RSFC) refers to the connectivity between brain regions in a task-free condition. It has been recognized that resting-state fluctuations in brain activity have functional and neurophysiological relevance. These spontaneous patterns self-organize into coherent patterns of activity that reflect the neural systems when a person is

resting or not engaging in any activity - called *intrinsic* or *resting state networks* (RSN) (Fox et al., 2005).

The default mode network (DMN) was identified in 2001 by Raichle et al. Although originally believed to be a non-task resting-state network activated when the brain is at wakeful rest, it was later discovered that DMN participates in a multitude of goal-oriented tasks that focus on self- and other-related information. DMN is not a single structure in the brain but composed of multiple functionally interconnected anatomical units (Buckner, Andrews-Hanna, & Schacter, 2008). Areas generally included in DMN are the medial prefrontal cortex, posterior cingulate cortex, and the inferior parietal lobule, but many other structures, such as the lateral temporal cortex, retrosplenial cortex, hippocampal formation, and the precuneus are often considered part of the network. Many of these areas are densely packed with 5-HT_{2A} receptors, and thus likely heavily affected by major psychedelics.

The DMN is involved in higher-level, metacognitive (thoughts about thoughts) operations, such as theory of mind (Sepulcre, Sabuncu, Yeo, Liu, & Johnson, 2012), mental time travel (Buckner & Carroll, 2007) and self-reflective and introspective functions (Qin & Northoff, 2011). DMN activity is especially associated with self-reflection, self-referential processing, and selfhood more generally (Buckner et al., 2008); the DMN resting-state connectivity positively correlates with internal awareness (Vanhaudenhuyse et al., 2011).

The highest number of cortical connections are found between the nodes of the DMN. DMN regions consume more energy and receive about 40% more blood flow than any other brain regions (Raichle et al., 2001). Even during goal-directed cognition, when the DMN is relatively deactivated, it receives more blood flow than the rest of the brain (Carhart-Harris et al., 2014a). DMN regions also host the highest number of cortical connections to other brain networks. When coupling within the DMN increases or decreases, so does the coupling between the DMN and other brain networks. Other brain networks do not share the function

of the DMN (de Pasquale et al., 2012), suggesting that the DMN is working at the highest level of the functional hierarchy, as a conductor of global brain function (Carhart-Harris & Friston, 2010).

In one of the first brain-imaging studies on psychedelics, Carhart-Harris et al. (2012a) conducted an experiment using functional magnetic resonance imaging (fMRI) and arterial spin labeling (ASL). They measured changes in cerebral blood flow (CBF) in a resting state scan before and after administration of psilocybin and placebo. The results showed a decrease in CBF after psilocybin, localized in cortical and subcortical structures such as the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and thalamus. In some subjects, psilocybin decreased blood flow up to 20%. The PCC is associated with awareness and arousal, as well as control of the balance between externally and internally directed thoughts (Leech & Sharp, 2013). Normally, the mPFC and PCC are highly coupled; however, under psilocybin, there is a decrease in resting-state functional connectivity between them. The magnitude of the decrease predicts the intensity of the subjective experience (Carhart-Harris et al., 2012a).

These results were replicated by Mathukumaraswamy et al. (2013) using the classic Blood-oxygen-level-dependent (BOLD) signal of fMRI. Decreases in resting-state network activity were only observed after drug infusion. The decreases were consistent with the CBF decreases in the previous study: in the cortical nodes of the DMN in mPFC and PCC. Mathukumaraswamy et al. also used magnetoencephalography (MEG) and found that psilocybin reduced oscillatory power in the posterior and frontal association cortices, including central parts of the DMN, for instance PCC. They suggest that PCC desynchronization can be explained by increased excitability of deep-layer pyramidal neurons, known to be rich in 5-HT_{2A} receptors. Decreases in alpha power in PCC were related to subjectively experienced disintegration of self or ego and the experience having a

supernatural quality. Mathukumaraswamy et al. conclude that the subjective effects of psychedelics result from a desynchronization of ongoing oscillatory rhythms in the cortex, triggered by 5-HT_{2A} receptor-mediated excitation.

In a review article, Carhart-Harris et al. (2014a) summarize the results of the previous studies. They note that, when resting-state functional connectivity was used to measure changes in brain network integrity, decreased connectivity was observed within the mPFC and hippocampus, as shown in Figure 3. A significant increase in variance, however, was located in the bilateral hippocampi and parahippocampal gyri, and also in high-level association networks. This kind of variance was not apparent in motor- or sensory-specific networks. Carhart-Harris et al. reports that, under the influence of psychedelics, both activity and connectivity are decreased in the DMN, which is linked to ego dissolution or ego disintegration.

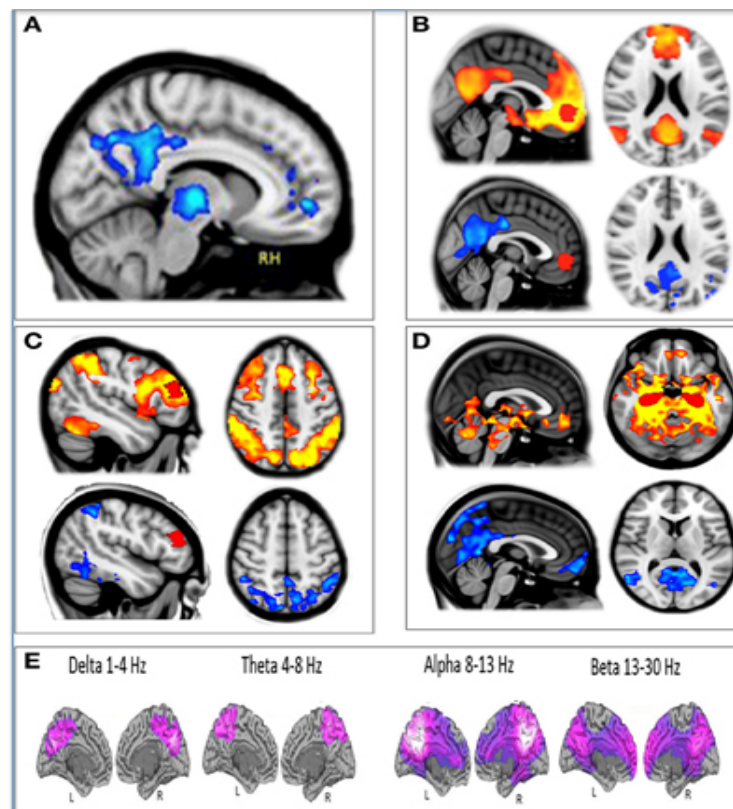


Figure 3. The effect of psilocybin on fMRI and MEG measures of brain activity. (A) Blue shows decreased CBF after psilocybin infusion. (B) Ventromedial PFC resting state

functional connectivity (RSFC), orange shows baseline and blue shows decreases after psilocybin infusion. **(C)** Dorsolateral PFC RSFC, orange shows baseline and blue shows decreases after psilocybin infusion. **(D)** Hippocampal RSFC, orange shows baseline and blue shows decreases after psilocybin infusion. **(E)** Purple shows decreases in oscillatory power after psilocybin infusion measured with MEG. (Adapted from: Carhart-Harris et al., 2014a, p. 6. Reprinted with permission from the first author).

Carhart-Harris et al. (2016) conducted an ASL and BOLD study under LSD in resting-state condition, followed by a magnetoencephalography (MEG) scan. They found decreased alpha power in the visual cortex, increased visual cortex CBF and a significantly increased resting-state functional connectivity in the primary visual cortex (V1). They suggest that the reduced alpha power and increased CBF under psychedelics could facilitate the release of chaotic patterns of excitation that then participate in creating visual hallucinations.

Carhart-Harris et al. (2016) also found increased RSFC between V1 and many cortical and subcortical regions, and between the parahippocampal (PH) and dorsal mPFC and the right dorsolateral PFC (dlPFC). The magnitude of the increase of CBF in V1 correlated positively with the reported eyes-closed visual hallucinations, and the increased V1 activity correlated positively with ratings of elementary and complex imagery. The idea of “seeing with eyes shut” under psychedelics can be explained by the findings of decreased alpha power, expanded RSFC in primary visual cortex, and increased visual cortex CBF. The increase in CBF was limited to the visual RSNs, whereas the decrease was more widespread. The researchers also found decreases in RSFC between the PH and PCC and the retrosplenial cortex (RSC), which correlated with ratings of ego dissolution and altered meaning (Carhart-Harris et al., 2016).

Tagliazucchi et al. (2014) used BOLD signal fluctuation to investigate RSFC between the left and right anterior cingulate cortex (ACC), and left and right hippocampus. They found an increase of novel connectivity patterns when comparing the results before and after psilocybin administration but not when comparing before and after placebo (see Figure 4). More specifically, they found a greater diversity of connectivity patterns after psilocybin infusion,

reflecting increased entropy (irregular variability and intense complexity) in the brain. They suggest that this demonstrates an expansion of new states in the brain under psilocybin.

Tagliazucchi et al. (2014) also found that psilocybin decreased low-frequency power localized to higher-level cortical regions. This implies that the primary action of psilocybin and other major psychedelics is to cause desynchrony through loss of oscillatory power in higher-level cortical regions, most likely through the 5-HT_{2A} receptor. However, the increased activity in the hippocampi and ACC measured with a BOLD signal suggests that these effects do not generalize to deeper structures. The RSNs that showed the most significant changes under the influence of psilocybin corresponded not to motor and primary sensory networks but rather to higher brain systems, such as attention and executive-control networks and the DMN: that is, the areas with the densest distribution of 5-HT_{2A} receptors (Tagliazucchi et al., 2014).

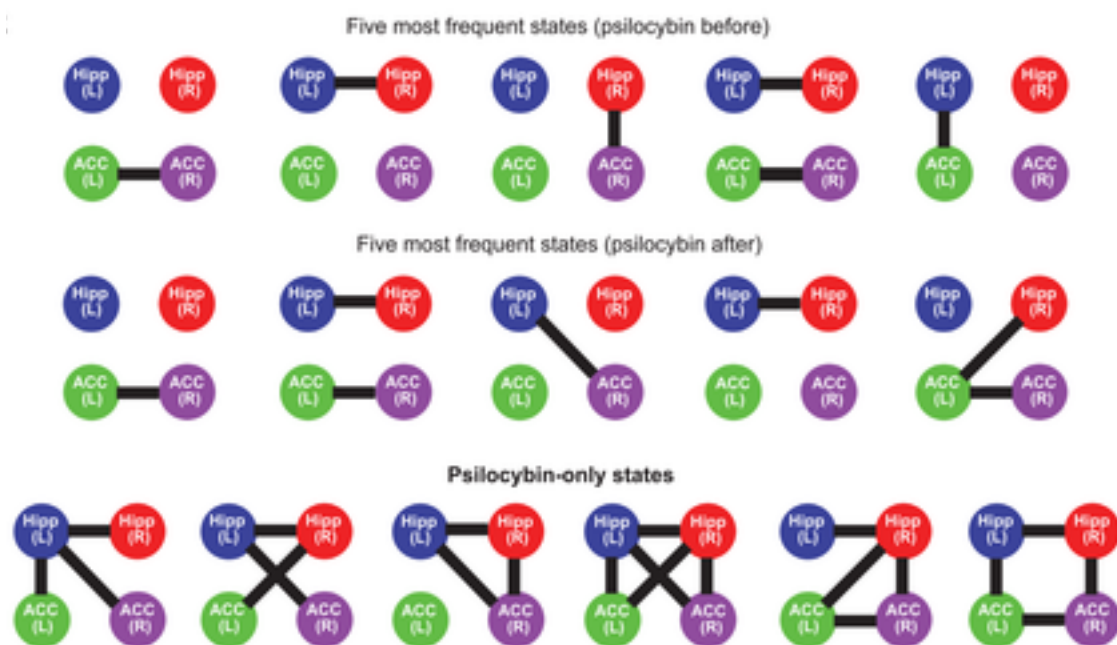


Figure 4. Hippocampal and ACC connectivity. First row: five most frequent connectivity states before the infusion of psilocybin. Second row: five most frequent states after the infusion of psilocybin. Third row: states observed only after the infusion of psilocybin, but absent before the infusion and in the placebo condition. In all cases, the lines are used to indicate a significant transient functional connectivity between two nodes. (Adapted from: Tagliazucchi et al., 2014, p. 12. Reprinted with permission from second author.)

That the temporal cortex and PCC play a major role in the experience of psychedelics is generally acknowledged (Carhart-Harris et al., 2016; Lebedev et al., 2015). Carhart-Harris et al. (2014a) discuss the involvement and coupling of the medial temporal lobe (MTL) in the actions of psychedelics. The temporal lobe processes social and emotional information, and both processes are affected in the psychedelic state (Preller et al., 2019). It is known that the MTLs is strongly connected to the PCC but, remarkably, under psychedelics the decreases in functional coupling are selectively located to the cortical nodes of the DMN (Carhart-Harris et al., 2017).

Another area potentially affected by mPFC activity is the amygdala, which processes the emotional context of stimuli but also participates in generating fear responses (Roseman, Demetriou, Wall, Nutt, & Carhart-Harris, 2018). Roseman et al. (2018) used an fMRI scan to find increased amygdala responses to emotional faces one day after treatment with psilocybin for moderate to severe depression. The increase in amygdala response was greater toward fearful faces compared to neutral faces. The opposite was found in an fMRI BOLD study conducted by Kraehenmann et al. (2015). They found reduced amygdala activation after administration of psilocybin to neutral or negative pictures; this change in BOLD signal was inversely correlated with ratings of increased positive mood. The discrepancy between these results may be due to different stimuli shown, different timing on the test, and differences in individuals participating. In the study Roseman et al. (2018) conducted, the participants were diagnosed with depression. They showed emotional faces, and the results were observed post psilocybin “high”. The study conducted by Kraehenmann et al. (2015) tested healthy individuals in the acute psilocybin “high” showing emotional pictures but not faces. The results need to be interpreted with caution since changes in spontaneous brain function are different during the acute effects of psilocybin compared to before or after.

It is suggested that the effects of psychedelics result from sensory gating deficits in the thalamus (Geyer & Vollenweider, 2008). The thalamus is a part of the diencephalon and function as a processing center that determines what sensory projections exiting and entering the cerebral hemispheres (Franklin, 2017). It gates input from subcortical areas to the cortex and contains cells that likely project to all the regions of the cortex (Preller et al., 2019). The reduced thalamic filtering induced by psilocybin is suggested to cause symptoms such as sensory overload and hallucinations (Vollenweider & Geyer, 2001). Preller et al. (2019) used spectral dynamic causal modeling (DCM) in a resting-state fMRI. DCM is a model of how interaction between neural populations causes fMRI time series, estimating the direction and strength of connections between different brain regions: that is, effective connectivity. Other functional connectivity measures show correlations with no possibility to infer causality, unlike effective connectivity (Preller et al., 2019). Preller et al. found that LSD increased effective connectivity from the thalamus to the PCC, while the connection from the PCC to the thalamus showed reduced connectivity. The increased activity depended on agonist activity on the 5-HT_{2A} receptor. The researchers also found decreased connectivity from the ventral striatum (VS) to the thalamus under the influence of LSD, independently of stimulation to the 5-HT_{2A} receptor. This means increased patterns of information flow to particular areas of the cortex while there is reduced connectivity between the thalamus and other cortical areas in resting state (Preller et al., 2019).

To summarize, psychedelics alter consciousness by exerting their effects on 5-HT_{2A} receptors in the cortical and hippocampal areas and subsequently disorganizing brain activity (Carhart-Harris et al., 2014a). The above findings imply that under psychedelics CBF, is decreased - especially in the cortical nodes of the DMN, mainly the PCC, and the thalamus - but may be increased in the primary visual areas. There is a corresponding decrease in oscillatory power and functional connectivity, as well as effective connectivity from the PCC

to the thalamus, in functionally connected brain regions that normally are highly metabolically active.

The Use of Psychedelics as Therapeutic Tools

Modern societies have high demands on the individual, both physical and cognitive, and leave little time for recovery from intense or heavy workload. The goal for many is to find a fast recovery, an effective way to cope with stress, a way to change from “stressed and tired” to “relaxed and fresh” (Müller & Schumann, 2011). Müller and Schumann propose that mental states can be changed on purpose by psychedelic agents, to facilitate other, non-drug-related behaviours. In healthy individuals, psychedelic drugs might support personal growth and development; and, more importantly, through guidance in controlled conditions, psychedelics might also provide benefits for ill individuals. The use of LSD as an adjunct to psychotherapy, in treatment for depression, anxiety, schizophrenia and addictions, was already explored in the late 1940s. In the last few decades, advances in the neuroscience of psychedelics have rekindled interest in the potential therapeutic use of these agents.

Among the leading causes of disability worldwide are anxiety and mood disorders. This puts society under a massive economic burden (Whiteford et al., 2013). The PFC plays a key role in depression and related disorders, with structural changes such as loss of dendritic spines, retraction of neurites and elimination of synapses (Castrén & Antila, 2017). These can be counteracted by compounds capable of stimulating functional and structural neural plasticity. However, so far not many compounds have been identified as capable of promoting plasticity in the PFC (Castrén & Antila, 2017).

A study conducted by Ly et al. (2018) found that psychedelics robustly promote neuritogenesis (forming of new neurites), spinogenesis (development of dendritic spines in neurons), synaptogenesis (forming of new synapses) and functional plasticity in rats. This means that psychedelics cause both functional and structural changes in cortical neurons. To

test whether the 5-HT_{2A} receptor played any role in the plasticity, Ly et al. co-treated the rats with ketanserin and found that it completely prevented spinogenesis and neuritogenesis.

Serotonergic psychedelics have demonstrated quick and long-lasting effects on changes in mood (Griffiths et al., 2011) and brain function (Carhart-Harris et al., 2017). This raises the question of whether psychedelics could be used to alleviate mood and anxiety disorders.

It has been suggested that LSD binding to the 5-HT_{2A} receptors leads to increased sensitivity of the dopaminergic system (Marona-Lewicka, Chemel, & Nichols, 2009). Novel sensations have been shown to increase dopaminergic (DA) activity in the mesolimbic system, believed to contribute to reward learning as an adaptation to enhance reproduction and survival chances (Martel & Fantino, 1996). The increased dopaminergic activity correlates with euphoria and depersonalization phenomena (Hasler et al., 2004). However, it might also happen that interaction between subcortical 5-HT_{2A} receptors and the mesolimbic DA system affect emotional properties of a stimulus, resulting in a bad trip (McMahon, Filip, & Cunningham, 2001).

Depressed patients focus almost entirely inward, often in a self-critical manner. There is a risk that their cognitive style becomes too fixed and they become unable to behave and think in a flexible manner. In depression brain regions and networks such as the mPFC and DMN becomes over-engaged. Studies have found that psychedelics reduce both connectivity and activity in the same areas (Carhart-Harris et al., 2014a). Biomarkers of depression include downregulation of DA and 5-HT systems. Reduction in DA and 5-HT transmission is linked to reduced motivation and behavioral activity (Carey, Huston, & Müller, 2008). The use of major psychedelics could possibly restore homeostasis in 5-HT and DA systems, improve depressive symptoms and promote motivation (Markou, Kosten, & Koob, 1998). Through stimulation of 5-HT_{2A} receptors, one could expect a decrease in mPFC activity correlated with increased subjective well-being (Carhart-Harris et al., 2012b). It has been shown that the

treatment efficacy from just a few sessions with psilocybin in treatment-resistant depression have large effect sizes with rapidly improved symptoms. Psilocybin treatment is generally well tolerated, and the results remain positive for months after (Carhart-Harris et al., 2018).

In many psychiatric disorders, behavior becomes automated, rigid and hard to break. Consistent with their disorganizing effect on the brain, psychedelics may work to help break down disorders by demolishing the activity patterns on which they rest (Carhart-Harris et al., 2016). Krebs and Johansen (2012) demonstrated the efficacy of using LSD in treatment of alcohol dependence. Another study found that psilocybin significantly reduced depression and anxiety for months after administration in patients with advanced cancer (Grob et al., 2011). Comparable results were found when Griffiths et al. (2016) tested if psilocybin administration would decrease anxiety and depression in cancer patients with life-threatening diagnoses. They found large decreases in measures of anxiety and depressed mood as well as increases in optimism, life meaning, and quality of life.

In a study conducted on test subjects with obsessive-compulsive disorder (OCD) the administration of psilocybin significantly reduced the symptoms of OCD (Moreno, Wiegand, Taitano, and Delgado, 2006). The therapeutic potential for psychedelics rests upon their ability to disrupt stereotypic patterns of behavior and thoughts. It might be that some of the benefits come from having altered experiences rather than the direct effect of changed brain chemistry (Carhart-Harris et al., 2014a).

Hallucinogens enhance memory recollection, sometimes in an overwhelming and vivid way (Carhart-Harris et al., 2012c). Since the MTL is important for storage and recollection of memories, it has been proposed that the effects of hallucinogens are linked to activation of this area (Halberstadt, 2015) - hence the use of psychedelics in treatment for post-traumatic stress disorder (PTSD). PTSD is a chronic condition associated with recall of traumatic memories, with high treatment resistance (Sessa, 2017). Although MDMA is not a major

psychedelic, the use of this substance for treatment of PTSD shows great potential. It seems like MDMA facilitates the recollection of traumatic memories without the negative feelings that usually accompany such reminiscences (Sessa, 2017). MDMA reduces depression and anxiety, allowing the patient to engage in therapy with reduced discomfort and increased positive mood (Graeff, Guimarães, De Andrade & Deakin, 1996). MDMA increases feelings of empathy, trust, and emotional attachment, improving the relationship between the therapist and patient (Dumont et al., 2009). Reduced subjective fear response to the recollection of traumatic and negative memories gives the patient an opportunity to reflect upon painful memories in a more opened and relaxed manner (Carhart-Harris et al., 2014b).

According to Johnson et al. (2008), with the help of psychedelics, in carefully supervised therapeutic situations, it is possible to reach targeted mental states in a controlled way that minimize the risk for long-term psychological and physiological aftereffects. It is important to note, however, that there are both positive and negative implications to using LSD in therapeutic settings, considering that it can enhance suggestibility. In particular, there may be increased risks of inducing beliefs or memories in some clients (Carhart-Harris et al., 2015).

Discussion

The aim of this thesis was to investigate how brain activity and subjective experiences are altered under the influence of major psychedelics, how altered brain activity explains the alterations in subjective experiences, and whether the neuroscience of psychedelics supports the use of psychedelics in therapeutic settings. The typical effects of major psychedelics include altered perception and cognition, hallucinations, magical thinking, enhanced emotionality, ego dissolution, and mystical experiences. The differences in subjective experiences can be partially attributed to the user's current internal state and the environment (set and setting), her reaction styles and personality, as well as the dose ingested.

Chain of Events Triggered by Psychedelics

To clarify the chain of events under the influence of psychedelics, from different activation in signaling pathways to subjective experience, is currently beyond human capabilities (Nichols & Barker, 2016). However, the main mechanism of action is fairly well known, allowing interpretation of the correlation between altered brain activity and subjective experience.

The first site of action of psychedelics is the serotonin receptor 5-HT_{2A}. The highest distribution of 5HT_{2A} in humans is found in the PCC. There are far fewer 5-HT_{2A} receptors in the sensorimotor cortex, and this probably explains why motor actions remain somewhat unaffected during a psychedelic experience (Carhart-Harris et al., 2014a).

Stimulation of the 5-HT_{2A} receptors causes large populations of neurons in the cortex to fire out of phase: that is it leads to desynchronized cortical activity. This disruption in the cortex extends to large-scale brain networks such as DMN, where a decrease in system organization is observed. This disintegration of brain networks leads to an increase in network metastability and in connectivity patterns within the cortex (Carhart-Harris et al., 2014a). When the distribution of connections in the brain is broader and more wide spread it is believed that people have more uncertainty and less confidence - because it is difficult to predict the outcome in a system that behaves somewhat randomly (Carhart-Harris et al., 2014a). This hyper connectivity might make altered perception and magical thinking more possible.

Brain Activity Under Psychedelics

Brain regions that show the most consistent deactivation (the PCC, ACC, and thalamus) after psychedelic administration are areas that, under normal conditions show exceptionally high activity (Carhart-Harris et al., 2012a). During resting state, the PCC shows greater activity than during cognitive tasks in normal conditions. The result of significant decreases in coupling between the PCC and mPFC under psychedelics can be interpreted as either an

increase in bottom-up processing (connectivity from parietal to prefrontal regions) or a decrease in top-down processing (connectivity from prefrontal to parietal regions) (Carhart-Harris et al., 2012b). The reduced ability for emotional processing in the amygdala after psilocybin use could potentially be explained by increased inhibitory top-down control from the PFC (Kraehenmann et al., 2015).

Much is known about the DMN but why it consumes so much energy is still a question (Raichle et al., 2001). One hypothesis that Carhart-Harris et al. (2014a) have put forward is that the DMN is the physical counterpart to the ego: the narrative self, which is mostly unconscious or implicit. Nevertheless, the sense of self is never far from consciousness. Just as there is variance in coupling in the DMN or variance in alpha oscillations in the PCC during the psychedelic state so there is insecurity about one's sense of self (Carhart-Harris et al., 2014a). Decreased functional connectivity between high-level cortical areas and reduced interhemispheric communication are associated with ego dissolution (Lebedev et al., 2015). Decreased DMN and parahippocampal RSFC coupling and a decreased delta and alpha power correlate with ego-dissolution and changes in normal waking consciousness. This suggests that preservation of DMN integrity, communication between parahippocampal (PH) RSFC and higher-level cortical areas, and regular oscillatory rhythms may all be essential to maintaining one's sense of ego or self (Carhart-Harris et al., 2016).

Increased visual cortex CBF and V1 RSFC predict both simple and complex hallucinations, while the quantity of decreased alpha power predicts the degree of visual hallucinations. This findings suggests that under the influence of LSD a considerably greater part of the brain contributes to visual processing than under normal waking consciousness. Increased connectivity between V1 and other brain regions in the psychedelic state may explain how different sensations, such as emotions, can freely “color” the visual experience (Carhart-Harris et al., 2016). percentage

In Sickness and in Health

“The psychedelic state is considered an exemplar of a primitive or primary state of consciousness that preceded the development of modern, adult, human, normal waking consciousness” (Carhart-Harris et al., 2014a, p. 1). It has been suggested that research with psychedelics can help advance knowledge about consciousness in general. Since psychedelics affect the serotonin receptor 5HT_{2A}, which in turn affects perception, attention and affect regulation, this makes psychedelics useful in studying the neural basis of consciousness and cognition (Hasler et al., 2004). Yet the pharmacology and neurobiology of psychedelics are still not fully understood in humans (Preller et al., 2019). While it is acknowledged that 5-HT_{2A} receptors play a crucial role in the psychedelic experience, this does not exclude the possibility that other receptors also participate.

In addition to advancing knowledge about how consciousness works, psychedelics may provide an alternative treatment or an adjunct to therapy (e.g., Carhart-Harris et al., 2014a; Studerus et al., 2011; Lebedev et al., 2015) and increase understanding of psychiatric diseases. According to Grof (1980) could psychedelics be of great importance for psychiatry since they make it possible to study processes that normally is unavailable for direct observation.

Studies consistently find that psychedelics are among the least harmful substances when it comes to societal and personal risks compared to other drugs, including legal drugs such as alcohol and tobacco (van Amsterdam, Nutt, Phillips, & van den Brink, 2015).

Regarding psychedelic, non-addictive drug use appears to be much more common than drug addiction all-around the world and is chosen because of its positive effects (Müller & Schumann, 2011). Compared to the general population, psychedelic drug users do not have increased psychopathology; the evidence actually suggests that they may have better mental health (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015). Long-term consumption of

hallucinogens in ritual contexts shows that hallucinogens do not seem to be associated with personality disorders but instead with differences in personality measures which in turn seem to be related to antiaddictive and antidepressant effects (Bouso et al., 2018). Nevertheless, self-medication (which is when a person turns to alcohol or drugs in order to deal with situations they find emotional, stressful or hurtful) may lead to malaise progression.

Carhart-Harris and Nutt (2010) conducted a web-based study to investigate recreational drug users' perception of the harms and benefits of hallucinogenic drug use. Overall, 60%-67% of psilocybin and LSD users responded that the experience induced by psychedelics had long-term positive effects on their well-being. To get this in perspective, only 6% of alcohol users claimed the same improvements. Carhart-Harris et al. (2014a) suggest that psychedelics could be used in healthy subjects to enhance well-being and divergent thinking.

Limitations of Reviewed Studies

In most studies and experiments the sample sizes are small, which makes it difficult to generalize results to the rest of the population. Moreover, compared to psychedelic use outside the experimental setting, the doses administered may be considered low. Keeping in mind that the psychedelic experiences are highly dose-dependent, experience outside laboratory setting may differ in intensity and other qualities.

In the laboratory, everything is controlled, and the person can feel safe. The environment and mindset of the study participant is likely to have an effect on the psychedelic experience. Informing participants in advance about possible effects such as hallucinations may cause participants to focus on specific aspects of the experience at the expense of missing other effects. It would be unethical not to inform participants about possible effects, so some expectancy effects are inevitable (Griffiths et al., 2006). Social desirability effect may also play a role: that is, participants do not answer questions truthfully but instead answer what they think the experimenter wants to hear.

Participant selection may also have an effect on results. Certain type of people might be more likely to apply to participate in a study using psychedelics, producing a biased sample. Exclusion of some subjects because of potential risk factors (e.g., psychiatric illness, high emotional lability, history of drug abuse, or hereditary risk factors) might be necessary but does not lead to a representative sample of the population. That said, the risk of a participant having a bad trip might be higher if no exclusion took place. Gaining knowledge about adverse effects and how these relate to various factors, is important. Yet research is typically conducted with healthy volunteers, and only later expanded to groups such as patients.

Conclusion

The neural changes observed after administration of psychedelics can help explain the altered subjective experience in this state. These altered connectivity patterns and the emergence of novel patterns might be the reason why psychedelics have so many positive effects, and why their use could be justified in therapies or for autognostic purposes.

With this thesis I want to break the taboo and help people become more openminded. To discover the possibilities with these substances and maybe consider psychedelics to be an opportunity to learn and grow. Psychedelics is not for everyone, but the choice should be up to everyone.

Even though there are still many open questions, what researchers know so far about psychedelic agents shows great potential for these substances. Psychedelic substances can be useful in gaining insight and increasing well-being in healthy individuals, easing suffering and increasing well-being in ill individuals, and maybe - if we are lucky - uncovering some of the secrets of consciousness.

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