Cognitive mechanisms of psilocybin:

Review and theoretical framework for future research

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"Those who love wisdom must investigate many things"
- Heraclitus

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PART ONE

Review of the effects and biochemical pathways of psilocybin

Introduction

Altered states of consciousness have fascinated human beings since ancient times. Methods like meditation, dance, breathing rhythms, and ingestion of certain plants and fungi have been used to achieve these states. Many traditions hold these plants as sacred, and often believe that these states may provide an expansion of consciousness or a type of enlightenment. One may, for example, have a deeply spiritual or religious experience while in such a state. This paper will be concerned with one substance that has the capacity to induce altered states of consciousness, psilocybin. More specifically, it will focus on the effects this substance has on humans.

The cognitive and biochemical pathways behind the effects of psilocybin have come under investigation again after some decades of strict prohibition of psychedelic substances. The research cited in this paper may therefore appear old in some cases, though it should not be forgotten that rigorous banning of psychedelic substances has effectively halted research from roughly the 1970s to mid-1990s, and the illegal status of many of these substances continues to make research into psychedelics difficult in present times.

This paper centres around the following research question: how can the effects of psilocybin be explained in terms of cognitive pathways? Part one of this paper starts by introducing the substance psilocybin, followed by a discussion and review of research to date regarding its effects and related biological pathways. Additionally, potential uses in pharmacology and therapy will be investigated. Part two will comprise a small-scale experiment based on a questionnaire assessing subjects' previous experiences with psilocybin-containing fungi. The discussion at the end of this part will attempt to integrate knowledge from both parts to sketch a model of the mechanisms of psilocybin. This model is intended to incorporate some of the previous research into a coherent structure, while also taking into account the variety of individual experiences. Additionally, the author hopes that it may help identify aspects of psilocybin's actions that require further research.

1. Background

Psilocybin is a psychoactive substance found in over 200 species of Basidiomycota mushrooms. The most commonly known of these mushrooms are those of the *Psilocybe* genus, commonly called "magic mushrooms" or simply "shrooms" in the vernacular. Psilocybin belongs to a category of substances that may be called "psychedelics" (mind manifesters), "hallucinogens" (hallucination generators), "entheogens" (generating god within) or "psychotomimetics" (psychosis mimickers), although neither of these terms is fully appropriate (Schultes, 1976). The most commonly used term, "hallucinogen", carries the connotation that the experience is merely an illusion and has no significance to reality, which is debatable. The author believes that although "psychedelics" is an incorrect combination of Greek roots, it encapsulates most accurately and most widely the effects of the drug, in addition to its relatively neutral connotations. Therefore, 'psychedelic' will be the preferred umbrella term used throughout this text.

In order to provide the necessary information for complete understanding of the later sections, this section is devoted to a brief history of psilocybin use, its chemical structure, serotonin receptor subtypes involved, and general metabolism within the human body.

1.1 Historical overview

Psilocybin-containing fungi have been used since ancient times for religious and spiritual purposes. Some of the earliest support to date of the use of mind-altering fungi dates thousands of years back, as interpreted from cave drawings of "mushroom-men" at the Tassili n'Ajjer plateau in Northern Algeria (fig 2*) and the mushroom rock art of ancient Egypt (fig 1*). It should be noted that other types of psychedelic mushrooms exist, for example the fly agaric (*Amanita muscaria*)[1]. The use of psychoactive

Figure 1. Mushroom rock art of Ancient Egypt.

***** These images were forwarded by an acquaintance; the origin of these images is unfortunately unknown to the author of this paper.

[1] Because this mushroom exerts its influence through different pathways than psilocybin, this paper will devote relatively little attention to it.

mushrooms (and plants) was known to various indigenous people all over the world since ancient times. Native Mexican tribes, for example, are known to have been *Psilocybe* mushroom users, and some have been reported to continue their (religious) use of the psychoactive mushroom to this day (Schultes, 1998).

Figure 2. Rock art from Tassili n'Ajjer. A person (thought to be a shaman because of his mask) is depicted with mushrooms sprouting from his arms and legs.

Knowledge of the *Psilocybe* mushroom came to the modernised West in 1955, after Gordon Wasson and his wife Valentina had actively partaken in an indigenous mushroom ceremony in Mexico (Wasson, 1957). They brought back a sample of the psychoactive mushroom, which was identified as *Psilocybe* in 1956 by Roger Heim[2]. In 1957, the Wassons published an article about their experiences in *Life*, and in the following year Albert Hofmann identified the active components psilocybin and psilocin of the psychedelic mushroom (Hofmann et al., 1958; Hofmann & Troxler, 1959; Wasson, 1957).

The interest for this peculiar mushroom increased and was further popularised by supporters of the hippie subculture in the 1960s. Outside of Western culture there was considerable interest in collecting, cultivating and using *Psilocybe* mushrooms as well. Even the CIA took interest in the mushrooms, albeit to investigate the presence of any potential 'mind-controlling' properties that could be used against enemies in times of war (Allen, 1997).

While the Mazatec tribes have always respected the *Psilocybe* mushroom as sacred, in the West they easily became desacralised (Metzner, 2005). On the one hand this can be explained by a lack of 'roots' in Western culture; there was no (religious) tradition or folklore associated with the use of the fungus, making profane use more likely. On the other hand, the failed attempts of the CIA to isolate a mind-controlling drug from Psilocybe mushrooms, along with the excesses of the hippie subculture of the 1960s, contributed further to the desacralisation of the mushroom (Lee & Shlain, 1992).

[2] Refers to the subtype *Psilocybe mexicana* Heim.

Due to this explosion in popularity, desacralisation of the experience and the subsequent widespread recreational use during the 1960s, the mushrooms became increasingly seen as a recreational drug of abuse associated with rebellious social movements in industrialised countries (Vollenweider & Kometer, 2010). The social problems related to the hippie subculture became linked to the use of mind-altering substances like LSD and psilocybin in the eyes of politicians, who then sought to ban all psychedelic substances (Vollenweider & Kometer, 2010; Morris, 2008).

The rigorous banning of the substance between the 1970s and 1980s that ensued also choked scientific research into the *Psilocybe* mushroom and other psychedelic substances while the research was still in its early stages, as well as terminated its use in psychotherapy[3] (Passie et al., 2002; Jerome, 2007). Research and practices that had found a beneficial use for psychedelics in the treatment of various psychiatric diseases were discontinued now that all these substances became highly restricted (Morris, 2008). It is worth mentioning that experimental and therapeutic use had been extensive, yet without complications (Passie et al., 2002).

Since the mid-1990s, there has been a regained interest in psychedelic research (Jerome, 2007). There has been an increase in publications investigating the pathways of action of these drugs and their possible therapeutic applications, and the knowledge gained from this research has provided insight in the mechanisms of certain diseases and disorders such as schizophrenia, depression and obsessive-compulsive disorder.

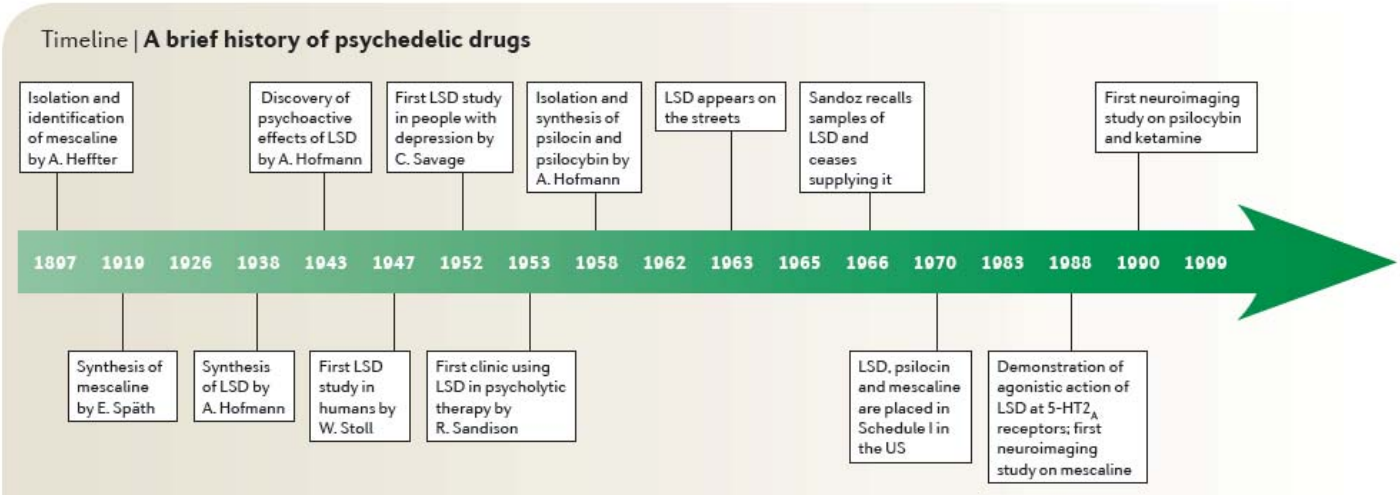


Figure 3. Timeline showing important events in the history of psychedelics.
(Taken and adapted from Vollenweider & Kometer, 2010)

[3] Pure synthetic psilocybin (under the name Indocybin®) was in the 1960s marketed by Sandoz for psychotherapeutic and experimental use (Passie et al., 2002)

Psilocybin is currently the preferred research drug used in studies investigating the effects of serotonergic psychedelics, presumably owing to its short-lived effects and the relatively little stigma they carry as compared to substances like LSD. Slowly, governments have started to tolerate small-scale studies using prohibited psychedelics, improving the quality of research in this field. The aim of this thesis is to provide a review of existing knowledge and to derive a framework that can be used to assess what needs to be researched further in order to better understand the mechanisms behind one of these psychedelic substances, psilocybin.

1.2 Chemical structure

The structure of psilocybin (*4-phosphoryloxy-N,N-dimethyltryptamine*) is based on an indole skeleton[4] with a phosphoric acid group attached to the benzene ring. The methyl groups on the nitrogen ring make the substance more lipophilic, enabling it to cross the blood-brain barrier (see section 1.3).

In the body, psilocybin is rapidly dephosphorylated into psilocin (*4-hydroxy-N,N-dimethyltryptamine*), the biologically active compound. Psilocin is structurally very similar to the endogenous neurotransmitter serotonin (*5-hydroxytryptamine*; 5-HT), binding to and stimulating 5-HT receptors, albeit with different affinities. This difference presumably lies in the fact that serotonin has a hydroxy group on the 5-position of the benzene ring, whereas in psilocin it is located on the 4-position, causing

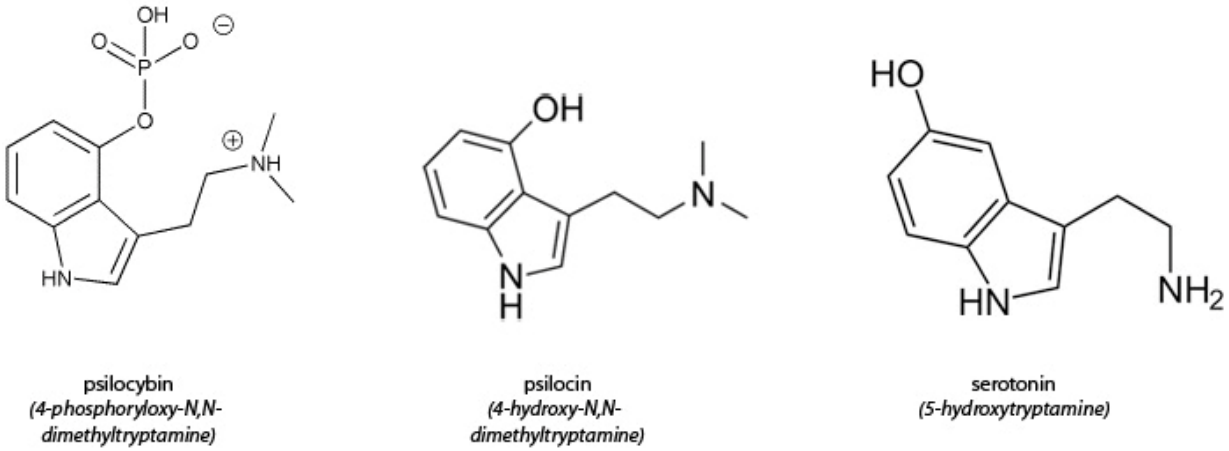


Figure 4. Chemical structures of psilocybin, psilocin, and serotonin.

[4] The indole group consists out of a six-membered benzene ring attached to a five-membered ring which contains nitrogen.

them to interact differently with binding sites on receptors[5] (McKenna et al., 1990; Shih et al., 2000). Indolealkamines with an –OH group on the 4-position exhibit a 25 to 380-fold selectivity for the 5-HT_{2A} receptor over the 5-HT_{1A}, for example, while those with the same group on the 5-position exhibit roughly equal affinities for these two receptors (McKenna et al., 1990).

1.3 Serotonin receptor subtypes

To understand the actions of psilocybin on the serotonergic system, one needs to have a basic understanding of the workings and function of serotonin receptors. In the following paragraphs an overview will be provided of the serotonin receptors that psilocin is known to bind to.

Psilocin is known to be an agonist to 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptor subtypes[6]. The 5-HT_2 receptor family mediates excitatory neurotransmission and consists of three G protein-coupled receptors[7] (GPCRs), named 2A, 2B and 2C. Psilocin is a partial agonist to all three 5-HT_2 receptors, although the 5-HT_{2B} receptor will not be discussed here due to the poverty of information available about this receptor with regard to psilocin. Psilocin also affects receptors of the 5-HT_1 receptor family, which mediate inhibitory neurotransmission. The five subtypes of this family consist of the 1A, 1B, 1D, 1E and 1F receptor subtypes[8], which are also GPCRs[9].

Of the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} receptors, binding affinity is greatest for the 5-HT_{2A} receptor (K_i = 6 nM) (Wittman et al., 2007). This receptor subtype is also understood to account at least partially for the psychedelic properties of psilocin and similar compounds. Notably, this receptor is also the action site of many anti-psychotic drugs (Stahl, 2008). The 5-HT_{2A} receptor is the main excitatory subtype among the GPCRs for serotonin, although it may in some areas have an inhibitory function instead (Williams et al., 2002). These receptors are widely spread throughout the CNS, with an especially high concentration on the apical dendrites of pyramidal cells in layer V of the cortex (Lambe et al., 2000). In addition, 5-HT_{2A} receptors are highly expressed in platelets, fibroblasts, and different cell types of the cardiovascular system, as well as in

[5] Ser242 interacts with the hydroxy group on the 4-position (psilocin), whereas Ser239 interacts with the same group on the 5-position.
[6] Since the mechanisms of serotonergic psychedelics are not fully understood, it is possible that more receptor subtypes are involved than what is listed here.
[7] Coupled to G_q/G_{11}.
[8] No 5-HT_{1C} receptor exists; it was relabelled as the 5-HT_{2C} receptor.
[9] Coupled to G_i/G_o.

the neurons of the peripheral nervous system (PNS). It is thought that overactivity of these receptors in the CNS contributes to the symptoms of schizophrenia, as the 5-HT_{2A} agonist psilocin induces a temporary "schizophrenia-like psychosis" in humans (Vollenweider et al., 1998; Vollenweider & Geyer, 2001).

5-HT_{2C} receptors are widely distributed throughout the central and peripheral nervous system, and are expressed most highly in the epithelial cells of the choroid plexus, as well as in layer V of the cortex (Monti et al., 2008). Upon activation of this receptor, signalling cascades are set in motion that inhibit dopamine and norepinephrine release in some areas of the brain (Alex et al., 2005; Stahl, 2007). These receptors are also involved in regulation of mood, anxiety, reproductive behaviour and feeding (Heisler et al., 2007; Glennon et al., 2000). Unfortunately, not many studies have been conducted to directly assess the effects of psilocin agonism on this receptor, but it has been suggested that many actions previously ascribed to the 5-HT_{2A} receptor could be attributable to the 5-HT_{2C} receptor instead (Glennon et al., 2000).

The 5-HT_{1A} receptor subtype is also widely distributed; it is highly expressed in the cortex, hippocampus, septum, amygdala and raphe nucleus (Ito et al., 1999; Glennon et al., 2000; De Almeida & Mengod, 2008). The receptor is also present in the thalamus and basal ganglia, though in lower densities (Ito et al., 1999). Activation of this receptor produces an increase in dopamine release in the prefrontal cortex (PFC), striatum, and hippocampus (Rollema et al., 2000). Agonist activity at 5-HT_{1A} receptors is also associated with anti-anxiety and anti-depressive effects; this knowledge is used in the development of drugs meant to alleviate anxiety and depression (Kennet et al., 1986; Parks et al., 1998). Furthermore, 5-HT_{1A} activation impairs cognition, learning and memory by inhibiting the release of acetylcholine and glutamate in various areas of the brain (Ögren et al., 2008). Next to that, stimulation of this receptor subtype is associated with decreased aggression, increased sociability, increased impulsivity, facilitation of sexual arousal and behaviour, decreased food intake and inhibition of addictive behaviour[10] (Fernández-Guasti & Rodríguez-Manzol 1997; Haensel & Slob, 1997; De Boer & Koolhaas, 2005; Carey et al,. 2005; Winstanley et al., 2005; Ebenezer et al., 2007; Müller et al., 2007; Thompson et al., 2007). Psilocin has a much lower

[10] The relationship between addictive behaviour and the 5-HT_{1A} receptor is more complex than stated here. For a more detailed overview of the mechanisms involved (and the importance of the pre- or postsynaptic location of the receptor) please refer to Müller et al., 2005 and Carey et al., 2005.

affinity for the 5-HT_{1A} receptor (K_i = 190 nM) than for the 5-HT_{2A} subtype (Wittman et al., 2007).

Having briefly sketched the functions of these different receptor subtypes, the following section will continue with an overview of the basic metabolism of psilocybin.

1.4 General metabolism

Psilocybin can be administered in various ways, though oral administration is most common. Pharmacokinetic studies have shown that approximately half of the ingested psilocybin is taken up by the body, giving an indication of the magnitude of uptake (Passie et al., 2002). After uptake, psilocybin is quickly dephosphorylised to psilocin by alkaline phosphatase in the human liver. Psilocin is the active metabolite that subsequently travels through the bloodstream. Based on the polar properties of psilocin and psilocybin, neither of the molecules is expected to pass the blood-brain barrier. Yet psilocin does so, as is evident from its psychoactive properties. It is therefore hypothesised that the lipophilicity of psilocin may be sufficiently increased when the 4-hydroxy group forms a hydrogen bond with the terminal amine, enabling it to pass the blood-brain barrier in this configuration (Foye, Lemke & Williams, 2007).

The effects of psilocybin may be noticed approximately 20-30 minutes[11] after oral ingestion and generally last between 4 to 6 hours, although this may differ depending on the dose ingested and the specific metabolism and brain chemistry of the

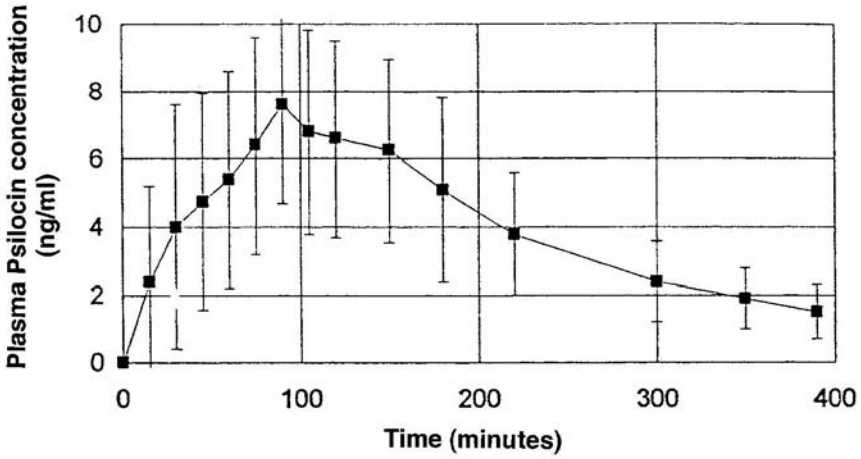


Figure 5. Graph showing plasma psilocin concentration (ng/ml) after ingestion (time in minutes). (Taken from Passie et al., 2002).

[11] Of course, if psilocybin is administered intravenously, the effects are noticed more rapidly after administration.

individual (Hasler et al. 1997; Studerus et al., 2010b). The peak is reached between 60 to 90 minutes (Hasler et al. 1997; Wittman et al., 2007). Figure 5 shows how the plasma psilocin concentration is built up after ingestion, peaks at about 80 minutes, and levels out over time. Metabolism of psilocybin and of its metabolic products continues, until plasma levels are sufficiently low to not generate any obvious effects. After seven days, changes in perception or cognition are no longer detectable (Gouzoulis-Mayfrank, 1999).

Psilocin, like most other serotonergic psychedelics, works as a partial agonist to the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{1A} serotonin receptors in the brain and gut, binding with a higher affinity to the 5-HT_{2A} receptor (Jerome, 2007, Carter et al., 2007). These three receptors are widely spread throughout the central nervous system. Psilocin activates these receptors and mimics the effects of serotonin on these receptors. The psychedelic properties of psilocybin are largely ascribed to the 5-HT_{2A} receptor, as it has been shown that a selective 5-HT_{2A} antagonist such as ketanserin blocks most of the hallucinations (Nichols et al., 2003; Carter et al., 2007; Jerome, 2007).

The physiological half-life of psilocin in the human body ranges between 2 and 3 hours (Jerome, 2007). Psilocin is broken down by monoamine oxidase (MAO) enzymes in the human body, which also breaks down monoamine neurotransmitters like serotonin. Therefore, individual MAO levels may also contribute to differences in the metabolism of psilocin. In addition, this enzyme (or one of its subtypes) may be inhibited by a family of substances called “MAO inhibitors”, which can substantially prolong and potentiate the effects. Chocolate and liquorice, for example, are thought to contain MAO inhibitors. MAO inhibitors were also commonly used as the active ingredient in anti-depressant drugs during from the 1960s until the mid-1980s (Howland, 2006).

Additional breakdown processes such as the deamination to *4-hydroxyindole acetaldehyde* and *4-hydroxyindole acetic acid,* the hydrogenation to *4-hydroxytyptophol* and the glucuronidation to an O-glucuronide form have been documented (see fig. 6) (Jerome, 2007; Yu, 2008). The metabolites produced from the breakdown of psilocin finally leave the body through the kidneys, leaving no substances that accumulate in the body. Psilocybin has an extremely low toxicity, the LD_{50} in rodents being 280 mg/kg (Passie et al., 2002). This corresponds to a few grams in humans (Passie et al., 2002). Rabbits are generally more sensitive to serotonergic drugs, as reflected in the associated LD_{50} being 12.5 mg/kg (Jerome, 2007). The doses used in contemporary human

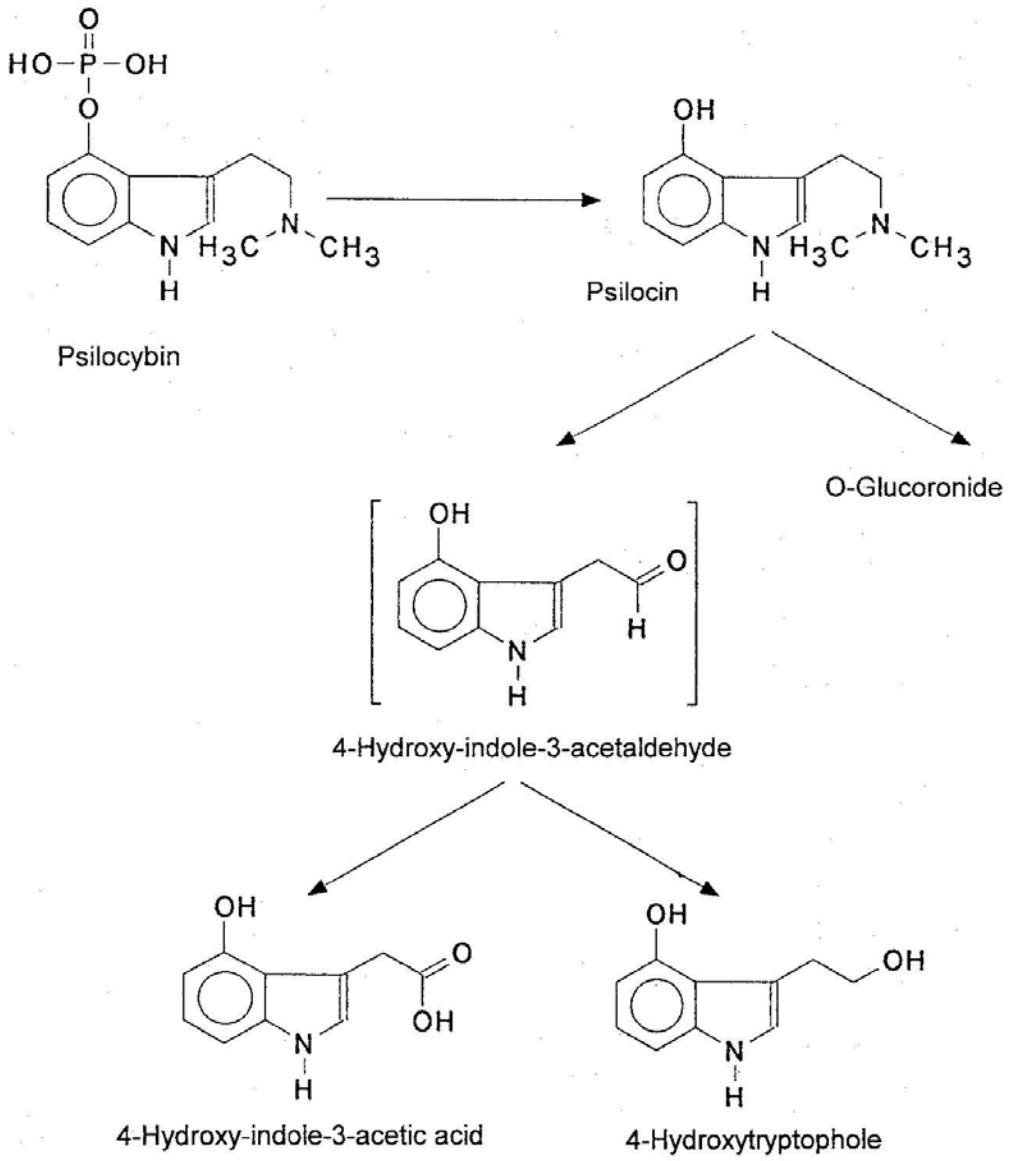


Figure 6. Metabolism of psilocybin in the body. First, psilocybin is dephosphorylised to psilocin, after which additional breakdown processes produce the metabolites 4-hydroxy-indole-3-acetaldehyde, 4-hydroxy-indole-3-acetic acid, and 4-hydroxytryptophol. (Taken from Passie et al., 2002)

research are more than 20 times smaller than the LD_{50} in rabbits, making direct adverse health effects highly unlikely for scientific studies approved by ethical committees. On the contrary, several studies have attributed therapeutic effects within this dose range, although much remains to be elucidated (Moreno et al., 2006; Grob et al., 2010).

Tolerance is built against psilocin, both mentally and physically, but disappears about as quickly as it is built. A second ingestion of psilocybin within a few days of the first ingestion will therefore diminish the effect of the second dose. In addition, psilocybin is not physically addictive, probably because it has no direct effects on the

dopamine system[12] (Vollenweider et al., 1999). The combination of these properties helps prevent abuse of the drug, making addiction very rare.

In the long history of its use, there has not been a single documented instance of a lethality directly associated with the use of psilocybin or psilocin, nor of disease or organ damage (Jerome, 2007). The present author was also unable to find any convincing evidence for a psilocybin-related death. Controversial reports of deaths attributed to *Psilocybe* mushrooms may be based on mistakes in the identification of the mushroom, as the difference between poisonous and edible mushrooms may not be obvious to the untrained eye. Indeed, reports of damage to organs or illness after ingestion of mushrooms have frequently been associated with the accidental ingestion of another, poisonous mushroom (Jerome, 2007). Still, the combination of psilocybin with other drugs – such as MAO inhibitors, alcohol, or other psychedelic substances – may have adverse effects.

[12] Psilocybin likely does, however, increase dopamine levels *indirectly* (Vollenweider et al., 1999).

2. General effects

Psilocybin produces a range of effects that may differ widely among individuals. Its effects may be likened to those of LSD, which is a much more widely researched drug (Isbell, 1959; Jerome, 2007). Psilocybin is, however, approximately 100 to 150 times less potent than LSD and its effects are more short-lived (Isbell, 1959; Passie et al., 2002). The following sections discuss the scope of the effects of psilocybin.

2.1 Short-term effects

Objective effects

The objectively measurable effects are easier to pin down than the subjective effects, and it is naturally easier to make inferences about the dose-response relationship. Mydriasis (pupil dilation), for example, follows a linear relationship with the size of the dose, as found in a study by Isbell (1959). Isbell's study also found an increase in blood pressure, heart rate, and respiratory rate, along with a decreased threshold for the kneejerk reflex indicating increased excitability ("hyper-irritability") of neurons (1959). These findings were partially reproduced by other studies, an overview of which is given in figure 7. These effects are evident of a physiological excitatory syndrome (Passie et al., 2002).

Table 1. *Somatic symptoms*

	Percentage of subjects
Midriasis	93%
Heart frequency	
Accelerated	56%
Slowed	13%
Variable	31%
No change	0%
Arterial blood pressure	
Hypotension	34%
Hypertension	28%
Instability	22%
No change	16%
Nausea	44%
Reflexes tendineae	
Increased	80%
Decreased	6%
No change	13%
Dysmetry	16%
Tremor	25%

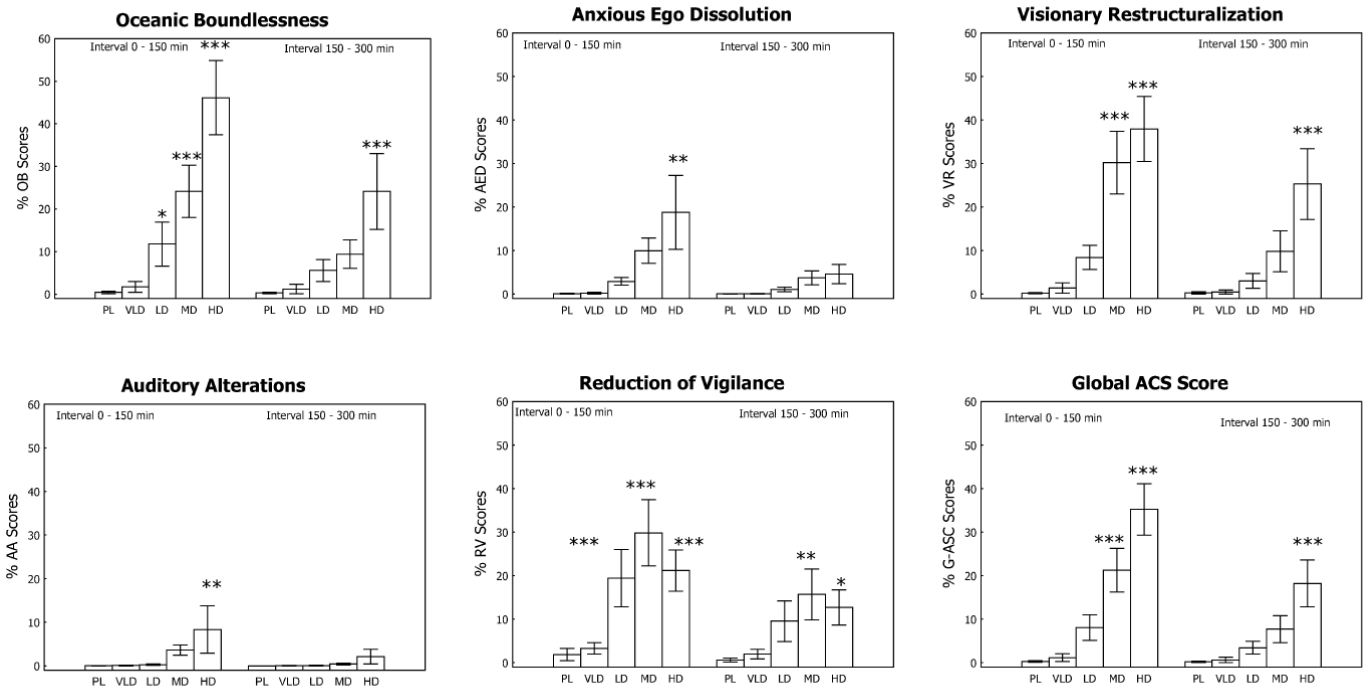
Figure 7. Indication of the prevalence of somatic symptoms attributed to psilocybin. (Taken from Passie et al., 2002)

There is little objective evidence for any direct health risks resulting from psilocybin intoxication. A study by Hasler and colleagues found no somatic dangers related to the use of psilocybin in healthy humans (2004). The author was unable to find any studies researching whether the use of psilocybin could evoke symptoms of latent mental disorders, a property that some other mind-altering drugs possess.

Psilocybin research, in fact, often excludes participants with a (family) history of schizophrenia and other related disorders, just in case. Documented experiences of recreational users could perhaps be used to see if psilocybin has any effect on latent psychological disorders, as experimental research into this on humans would be ethically contra-indicated.

Subjective effects

Summarising previous research, Jerome lists a long list of subjective effects following the administration of psilocybin (2007). In general, subjects report alterations of perception, unusual thoughts, anxiety, euphoria, paresthesias, synethesias, and difficulty concentrating (Jerome, 2007). The effects are variable between and within persons, and may be positive, neutral, or negative[13]. The interpretation of neutral symptoms depends on the user's character and mindset (*e.g.* paresthesias may be an interesting experience for one person, but annoying to another). It would not be possible to cover the entire spectrum of experienced effects here, therefore only the most consistently reported ones will be discussed.



*p<.05, **p<.01, ***p<.001 compared to placebo condition (Tukey HSD post hoc test).

Figure 8. Subjective effects of psilocybin assessed by the 5D-ASC rating scale (mean±SEM). The graphs show the relationship between the dose (from left to right: placebo, very low dose, low dose, medium dose, and high dose) and the scores of participants on the 5D-ASC in percentages of the maximal score. (Taken from Hasler et al., 2004)

[13] As seen from the immense variation of user-reports on sites such as www.erowid.org, www.shroomery.org, and www.psychonaut.com.

In a double-blind, placebo-controlled study by Felix Hasler and colleagues, the acute psychological and physiological effects of psilocybin were investigated. They found that the substance produced alterations of perception, affect, ego-function and attention in all subjects, increasing in intensity corresponding to the dose (Hasler et al., 2004). Figure 8 shows the relationship between dose and participants' scores on the Altered States of Consciousness Rating Scale (5D-ASC).

The three primary dimensions of this rating scale include *Oceanic Boundlessness* (OB), *Anxious Ego Dissolution* (AED), and *Visionary Restructuralisation* (VR) (Studerus et al., 2010a). A high OB score reflects a "state similar to mystical experiences" and the experience of 'oneness', while the AED measures "negatively experienced derealisation and depersonalisation, cognitive disturbances, catatonic symptoms, paranoia, and loss of thought and body control" (Studerus et al., 2010a). A high AED score may therefore be associated with unpleasant experiences similar to 'bad trips' (Studerus et al., 2010a). The VR scale measures visual hallucinations and alterations, illusions, visual/auditory synethesias, and changed meaning of percepts (Studerus et al., 2010a). The remaining two dimensions, *Auditory Alterations* (AA) and *Reduction of Vigilance* (RV) should be self-explanatory.

The graphs in figure 8 show how various dosage levels correspond to the dimensions discussed above. Note that some effects peak at lower doses (RV), and how some dimensions exhibit a dose-threshold effect (VR, AA, RV). It should be kept in mind, however, that the 5D-ASC rating scale has been found too crude to measure subtle alterations in consciousness (Studerus et al., 2010a).

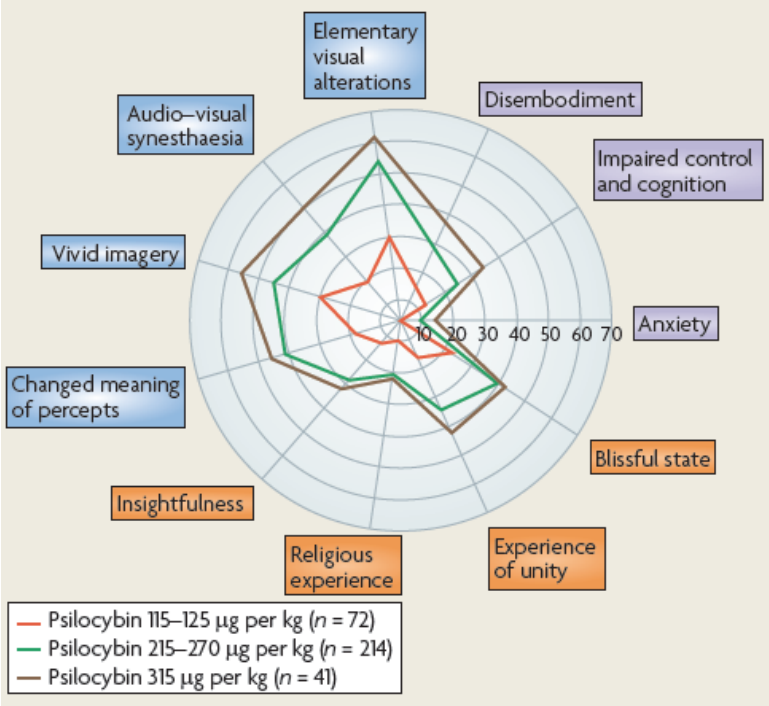


Figure 9. Assessing altered states of consciousness. Orange boxes refer to subdimensions of *Oceanic Boundlessness*, Purple boxes to the dimension of *Anxious Ego Dissolution*, while *Visionary Restructuralisation* is represented by the subdimensions in blue boxes. (Taken from Vollenweider & Kometer, 2010)

Mood may change rapidly under the influence of psilocybin, although most subjects incline towards a positive mood and describe the experience as pleasurable (Vollenweider & Kometer, 2010; Studerus et al., 2010b). Subjects may feel detached from themselves and their bodies, in a positive or negative sense. Things may appear unreal, or subjects may feel like they are in a dream-like state. Yet, subjects under the influence of psilocybin generally retain insight into their condition and the source of the alteration (with the potential exception of very high doses). This insight is further supported by the consistency between self-reports and observer-reports (Gouzoulis-Mayfrank et al., 1999; Griffiths et al., 2006).

Psilocybin has also been shown to be able to invoke mystical or religious experiences in subjects with existing spiritual or religious practices (Pahnke, 1966; Griffiths et al., 2006; Griffiths et al., 2008). The mechanisms behind this experience are poorly understood, but are thought to be linked to the loosening of ego-boundaries, a feeling of insight, and an experience of 'oneness' with the environment. A more detailed coverage can be found in section 2.3 below and in part two of this paper.

2.2 Set and setting

As is common in psychedelics, "set" and "setting" are influential to the effects of the psilocybin. "Set" refers to the mental state and personality of the person, along with the expectations s/he brings to the experience. "Setting" refers to the direct environment, including but not limited to physical features of the environment, music and other sounds, and people present. There is little formal evidence regarding the impact of set and setting, but it is generally accounted for in studies with psychedelics and a great deal of informal evidence exists that suggests it is in fact influential to the experience. One need only take a brief glance at a site or forum where "psychonauts[14]" gather to notice that set and setting are deemed highly influential to any psychedelic experience. While subjects often enjoy the effects of psilocybin, its use can sometimes give rise to what is called a "bad trip", which a good set and setting may help to avoid. A bad trip is marked by a panic response, including intense feelings of psychological distress and anxiety (Jerome, 2007).

[14] Psychonauts: *psyche* (soul, spirit, mind) + *nautes* (sailor/navigator). People who attempt to explore their inner psyche through altered states of consciousness for spiritual or scientific purposes, and often make use of psychedelics.

2.3 Long-term effects and spiritual experiences

There has not been much research investigating the potential long-term changes involved in psilocybin use. A few notable exceptions exist, however. Firstly, the Marsh Chapel Experiment (also called the Good Friday Experiment) investigated the effects of psilocybin on drug-naïve theology students and the occurrence of spiritual, mystical, or religious experiences. It was carried out by Walter Pahnke and Timothy Leary at the Marsh chapel of Boston University in 1962 (Pahnke, 1973). They found that the psilocybin group reported significantly more profound religious experiences than the control group taking an active placebo (niacin) (Pahnke, 1973).

In 1991, Rick Doblin published a follow-up study that criticised the methodology of the Pahnke experiment. However, despite this criticism of the methodological shortcomings of their study, his research supported Pahnke's findings by showing that subjects often reported positive long-term effects of their psilocybin experience and virtually no negative ones after six months, persisting after 24 to 27 years (Doblin, 1991). After more than twenty years, only the subjects in the psilocybin group still recognised their experience as genuinely mystical or religious (Doblin, 1991).

A more rigorously controlled version of this experiment is that of Griffiths *et al*., whose study found that two months after their psilocybin experience, subjects were more likely (64% of volunteers) to report positive attitudes to life and to the world and felt a general increase of well-being and satisfaction compared to the active placebo methylphenidate (Ritalin), persisting undiminished after 14 months (Griffiths et al., 2006; 2008). These improvements were also noted by close relatives or friends, indicating that these changes are not just 'imagined' by the individual. There were no negative changes in the long-term report for either drug.

The "most striking finding" that Griffiths and colleagues mention is that 58% and 67% of their psychedelic-naïve volunteers rated the psilocybin experience as ranking in the top five of most personally meaningful and spiritually significant experiences of their lives, respectively (2008). It should be noted, however, that these participants all had at least some participation in religious or spiritual activities before the study, which may have influenced the interpretation of their experience as personally or spiritually significant (Griffiths et al., 2008).

There is very little evidence concerning any adverse long-term side effects of psilocybin use to be found in the literature, and direct correlations have not been found. Some individuals experience persistent changes in mostly the visual modality lasting from weeks to years after the actual experience. This is commonly referred to as "flashbacks" and currently diagnosed as hallucinogen persistent perception disorder (HPPD). Though mostly associated with the use of LSD, this condition may also occur after psilocybin use, although it is estimated to be very rare (Halpern, 2002; Jerome, 2007).

Now that a profile of the effects of psilocybin has been outlined, the following section will discuss the potentially most important property of this substance: the alteration of human perception and consciousness.

3. Altered consciousness

Humans have always been fascinated by altered states of consciousness. While religious, mythical, and spiritual theories are abundant, the biochemical pathways involved in these states have not yet been elucidated completely. This section will deal with various theories, models and facts that may contribute to an understanding of the mechanisms behind the altered state of consciousness produced by psilocybin.

3.1 Thalamic filter model

In a review by Franz Vollenweider and Mark Geyer, a promising model for (at least part of) the action of psychedelics such as psilocybin was hypothesised (2001). The psychosis-like states produced by psychedelics bear resemblance to schizophrenia disorders, and it is thought that they act through some common pathways. Understanding the processes that contribute to the psychedelic experience may help elucidate factors involved in the development of schizophrenia (*ibid*.).

The two researchers argued that "a fundamental feature of information-processing dysfunction in both hallucinogen-induced states and schizophrenia-spectrum disorders is the inability of these subjects to screen out, inhibit, filter, or gate extraneous stimuli and to attend selectively to salient features of the environment", resulting in a cortical overload of exteroceptive and interoceptive stimuli (Vollenweider & Geyer, 2001; Geyer & Vollenweider, 2008). This overload may then cause a breakdown of cognitive integrity and can cause difficulties distinguishing the self from the non-self (*ibid*.). The impaired sensorimotor gating along with the loosening of the ego boundaries may give rise to symptoms such as hallucinations, thought disturbances and a dissolution of the ego (Vollenweider & Geyer, 2001). The model may also explain the negative symptoms like social and emotional withdrawal sometimes associated with the intake of psychedelics, by implicating feedback processes that attempt to reduce the input overload (*ibid*.).

Mechanisms and pathways

The model Vollenweider and Geyer propose is based on projections existing between the thalamus, frontal cortex, hippocampus, temporal cortex and the basal ganglia, in particular the ventral striatum and pallidum (fig. 10) (2001). The raphe nucleus is thought to influence this loop by exerting a global control over the hippocampus via modulation of local inhibitory neurons (Freund et al., 1990). In order to sketch the

outlines of this theory, first the functions of the thalamus will be discussed, after which the function of the limbic cortico-striato-thalamo-cortical (CSTC) loop will be covered. Finally, the hypothesised effects of psilocybin on the function of this loop will be investigated.

One of the functions of the thalamus is to act as a filter or relay station for incoming information (input) from external and internal sources (Murray Sherman & Guillery, 2001). With the exception of the olfactory system, all sensory systems have a nucleus in the thalamus to which the sensory stimuli are sent (*ibid*.). The thalamus then processes and relays information to the associated primary sensory cortices for further processing (*ibid*.). In addition, through feedback and feedforward connections with other areas of the brain, the thalamus is involved in regulating sleep and waking states, arousal, and level of awareness (Gazzaniga, 2004).

The CSTC feedback loop is thought to protect the cortex from stimuli overload (Vollenweider & Geyer, 2001). It is also involved in memory, learning and self/non-self discrimination (*ibid*.).

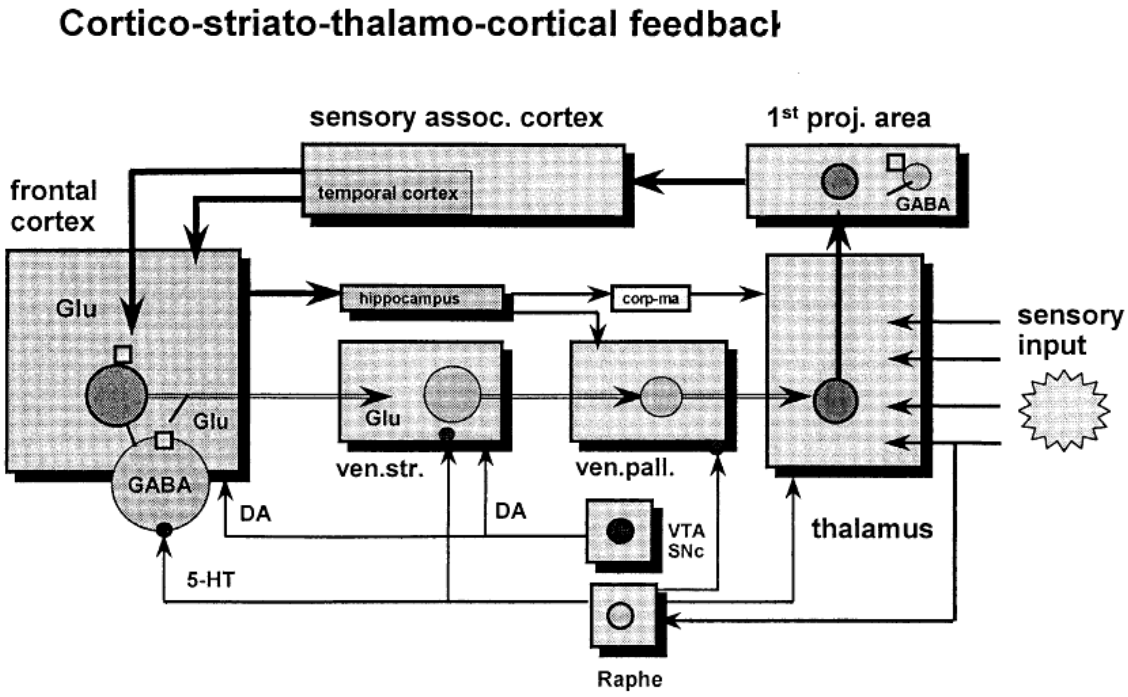


Figure 10. A schematic approximation of the limbic cortico-striato-thalamo-cortical feedback loop is shown here (see text). Legend: ven.str., *ventral striatum*; ven.pall, *ventral pallidum*; VTA, *ventral tegmental area*; SNc, *substantia nigra pars compacta*; corp.ma, *corpus mammillaria*; 5-HT, *serotonin*. (Taken from Vollenweider & Geyer, 2001)

Normally, the sensory stimuli feeding into the CSTC loop are processed as follows. Sensory input from the peripheral nervous system (PNS) is relayed by the thalamus to primary sensory cortices. Primary sensory areas process the incoming stimuli and subsequently connect to higher-order processing areas. Next, higher-order processing areas send the information to association areas in the temporal lobe that are involved in recognition processes. These areas connect to the frontal cortex, which in turn feeds back to the thalamus via the ventral striatum and pallidum, as well as the hippocampus. The neurons of the striatum and pallidum are inhibitory GABA interneurons, producing IPSPs postsynaptically upon stimulation. Regulation of thalamic activity by these areas is therefore dependent on GABAergic inhibition of the thalamus.

The effects of psilocin on the functioning of the CSTC loop are thought to have their origin in pyramidal cells in layer V of the prefrontal cortex, where 5-HT_{2A} receptor density is very high (González-Maeso et al., 2007; Vollenweider & Kometer, 2010). Excessive 5-HT_{2A} agonism – such as occurs in the presence of psilocin – produces a large increase in the frequency of asynchronous, spontaneous excitatory postsynaptic currents (EPSCs) in pyramidal cells in layer V of the prefrontal cortex (Aghajanian & Marek, 1999). These cells increase their (glutamatergic) neurotransmission in response to 5-HT_{2A} receptor activation, increasing stimulation of the ventral striatum. The striatal interneurons consequently increase their inhibitory influence on the ventral pallidum, which in turn lowers its inhibitory influence on the thalamus.

GABAergic neurons in the basal ganglia also possess 5-HT_{2A} receptors, which upon stimulation are thought to increase the firing rate of these neurons (Vaidya et al., 1997). Yet because these neurons exert an inhibitory influence, they generate IPSPs in the cells they project to (*ibid*.). From these findings, one could hypothesise that increased inhibition of GABAergic interneurons in the basal ganglia relieves the inhibitory influence on the thalamus, which in turn may become overactive now that it is no longer restrained.

This unrestrained activity of the thalamus is interpreted by some as ‘opening’ the thalamic filter (Geyer & Vollenweider, 2008). Psilocin generates excessive 5-HT_{2A} stimulation, increasing the excitability of neurons in the prefrontal cortex, striatum, nucleus accumbens, and thalamus, and is additionally thought to alter the neurotransmitter balances in the CSTC loop (*ibid*.). This impairs the feedback system

that normally prevents sensory flooding of the cortex (Vollenweider & Geyer, 2001; 2008). Unregulated overactivity of the thalamus may then be involved in this sensory overload of the cortex, and is suspected to lead to hallucinations and other hallmarks of acute psychosis (Vollenweider & Geyer, 2001; Geyer & Vollenweider, 2008).

In addition, through agonism at 5-HT_{2A} receptors on inhibitory GABA interneurons, the integrative ('binding') functions of cortico-thalamo-cortical (CTC) circuits become disrupted. It is hypothesised that re-entrant[15] information flow through CTC loops – connecting areas related to perceptual categorisation, concept formation, value-related memory, and planning – may be fundamental to a coherent conscious experience (Edelman, 2003). If this is the case, it might be involved in the experienced fragmentation of reality and of the ego during a psychotic experience (Geyer & Vollenweider, 2008).

Indeed, the similarities perceived between the psychedelic experience and psychosis or acute schizophrenia have led researchers to believe that the symptoms of these illnesses may be caused by abnormalities in the serotonergic system, particularly relating to 5-HT_2 receptor subtypes (Vaidya et al., 1997; Aghajanian & Marek, 1999; Geyer & Vollenweider, 2008). It is thought that sensory flooding of the cortex, due to disruptions in the serotonergic system, plays a role in the experienced fragmentation of reality and of the ego during a psychotic experience (Geyer & Vollenweider, 2008).

Firing modes of thalamic relay neurons

In a study by Behrendt, attention is drawn to two different firing modes of thalamic relay and inhibitory neurons, namely a *tonic* mode and a *burst-firing* mode (2003). Tonic firing is characterised by a partial depolarisation and is more prevalent in the wakeful state, while burst-firing is characterised by a hyperpolarisation of the neuron and is associated with states of inattentiveness and drowsiness (McCormick & Feeser, 1990). In the latter mode, information transmission is less effective (*ibid*.). The relevant aspects of tonic firing and burst-firing modes will be discussed below.

In tonic firing mode, thalamic neurons facilitate information flow to the cortex (McCormick & Feeser, 1990). The pattern of action potentials is dependent on the "intensity, duration, and frequency of incoming excitatory inputs", even when they arrive at rates greater than 100 Hz (*ibid*.). Oscillations in the gamma range (around

[15] A re-entrant circuit is a neuronal network (loop) that feeds back to itself, causing reverberation.

40 Hz) have been observed in the membrane potential of these cells during tonic firing, corresponding to their intrinsic resonance frequency[16] (Behrendt, 2003). Synchronised firing in a cluster of neurons can 'recruit' connected neurons to fire in the same rhythm, as overlapping EPSPs increase the chance of occurrence of an action potential and promote tonic firing (*ibid*.). Gamma-range oscillations have been associated with transient sensory integration for the visual and auditory modalities, although it is likely that other modalities are integrated in similar ways (*ibid*.).

In the burst-firing mode, membranes are hyperpolarised, requiring more stimulation before activity is generated. Information transmission is less effective because the hyperpolarised membrane fails to respond to inputs that arrive at a higher rate than approximately 15 Hz (McCormick & Feeser, 1990). EPSPs may, however, use another pathway: they can open low-threshold calcium channels in thalamic relay neurons when these are not firing tonically (McCormick & Feeser, 1990; Behrendt, 2003). The resulting calcium influx generates a large depolarisation spike which causes a burst of action potentials until a repolarising potassium current is triggered (Behrendt, 2003). Burst-firing neurons in the thalamus may also synchronise, which occurs, for example, during slow-wave sleep (*ibid*.).

The regulation of these firing modes is dependent on GABAergic input from inhibitory interneurons. The accumulation of IPSPs causes the thalamic neuron to go into burst-firing mode (Behrendt, 2003). Low-voltage calcium channels become active as a result of hyperpolarisation, which – upon sufficient depolarisation by excitatory inputs – enable burst-firing patterns through the accumulation of calcium in the neuron (Behrendt, 2003).

Looking at the prevalence of both firing modes in different states of consciousness, one finds that tonic firing mode is associated with mental states of "increased alertness and focused attention", is prevalent during REM sleep, and has been associated with hallucinations (Behrendt, 2003; Llinás & Ribary, 1993).

Superimposing this information on the model proposed by Geyer and Vollenweider, the following can be inferred. To begin with, the activation of 5-HT_{2A} receptors in the CSTC loop by psilocybin increases glutamatergic input of the prefrontal cortex to the ventral striatum (fig. 10). These striatal neurons are GABAergic

[16] The preferred input frequency of a neuron; the rate at which efficacy is maximised.

and inhibit neurons in the ventral pallidum to which they project. As the neurons in these two areas are both inhibitory GABA neurons, they cause an inhibition of the inhibition in cells of the thalamus to which they project. As a result, the thalamus becomes uninhibited and hyperactive, facilitating the flow of sensory information to the cortex by tonic firing. The imbalance in neurotransmitters of this loop, caused by psilocin, prevents the feedback connections from regulating the level of arousal and wakefulness that protects the cortex from sensory flooding under normal conditions. The "underconstrained perception" this produces, in combination with a sympathetic state of hyperarousal, could be an explanation[17] for hallucinations (Beherendt, 2003).

Finally, it is important to note that although it is true that most research regarding the effects of 5-HT agonism by psychedelics is concerned with the 5-HT_{2A} receptor subtype, it would be wrong to assume that the 5-HT_{2A} receptor is involved in all the effects of psilocin. Studies using selective 5-HT_{2A} antagonists have demonstrated that other receptors must also be involved (Carter et al., 2007). Candidates include the 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2C} receptor subtypes, for which psilocin is a partial agonist, but it is possible that other, less well researched receptor subtypes of the serotonergic system play additional roles. Further research into other serotonin receptors is necessary to create a full picture of the biochemical pathways involved in the effects of psilocybin.

3.2 Gene expression

Receptor signalling cascades ultimately regulate gene expression (González-Maeso et al., 2007). Changes in gene expression may be measured as early as one hour after ingestion of a psychedelic substance, making it possible that some of the effects could be mediated through gene expression. Because very little information is available with specific regard to psilocybin, only the relevant observations made with serotonergic psychedelics will be discussed here.

Gene expression is potentially involved in some of the effects of psilocybin relating to brain plasticity and neuronal proliferation, survival, and death. Most available data regarding psychedelics-mediated gene expression were obtained using LSD. Since the mechanisms and effects of LSD and psilocybin overlap to a great extent,

[17] The model sketched here provides only a highly simplified idea of some of the effects of psilocybin. A full coverage of all available information would, unfortunately, be far too lengthy for this paper. For more information and further details, please refer to Behrendt, 2003 and Geyer & Vollenweider, 2001.

it is likely that signalling pathways are the same or similar in both compounds, providing at the very minimum a direction for further research.

A study by Nichols and colleagues identified seven genes that are induced by administration of LSD, primarily through effects on the 5-HT_{2A} receptor: *ania3*, *arc*, *c-fos*, *I-Kappa B Alpha*, *egr-2*, *Nor1*, and *sgk* (2003). *Egr-1 and 2* (**e**arly **g**rowth **r**esponse) proteins are involved in neuronal plasticity, as well as in various aspects of development and growth. González-Maeso and colleagues found *egr-1* and *egr-2* to be upregulated by 5-HT_{2A} agonism by psychedelics (including psilocybin), but not by non-psychedelic compounds targeting the 5-HT_{2A} receptor (2007).

The specific induction of *egr-1* and *2* by psychedelic compounds but not non-psychedelic 5-HT_{2A} agonists, has led González-Maeso and colleagues to hypothesise that the effects of psychedelics on the 5-HT_{2A} receptor are mediated through a configuration-specific pathway that is different from non-psychedelics (2007). Their study showed that the effects elicited by psychedelics are largely attributable to stimulation of the 5-HT_{2A} receptor in pyramidal neurons of cortical areas, particularly in layer V where these receptors are most densely expressed. Layer V functions as the "output" layer of the cortex, and it is therefore hypothesised that the neuropsychological response to psychedelics results from their capacity to stabilise a specific configuration of the 5-HT_{2A} receptor (González-Maeso et al., 2007). Through this configuration, it is thought that distinct intracellular signalling cascades are generated.

Another protein involved in plasticity is *arc*, which stands for **a**ctivity-**r**egulated **c**ytoskeleton-associated protein. This protein is recognised as a marker for plastic changes in the brain, and plays a role in learning and memory (McIntyre et al., 2005). *Arc* is, for example, upregulated following long-term potentiation[18] (LTP). The increase in *arc* expression following administration of LSD was the highest among the factors tested, and it was also the most highly expressed factor in absolute terms (Nichols et al., 2003). Expression of *arc* could contribute to the reported increased memory and learning capability during psychedelic states. This will be further addressed in part two of this paper.

In response to 5-HT_{2A} stimulation, BDNF (**b**rain-**d**erived **n**eurotrophic **f**actor) was found to be upregulated in neocortical pyramidal cells, but inhibited in GABAergic

[18] LTP is commonly understood to be one of the mechanisms underlying learning and (long-term) memory processes.

interneurons in the basal ganglia (Vaidya et al., 1997). BDNF is encoded by a gene with the same name. It is one of the most active neurotrophic factors involved in survival of existing neurons and growth and differentiation in new neurons, in addition to its essential role in LTP (Vaidya et al., 1997; Zigova et al., 1998; Pencea et al., 2001; Benraiss et al., 2001; Bekinschtein et al., 2008). BDNF acutely increases synaptic strength and efficacy in neurons, which again may attribute to the facilitated memory reported after ingestion of psilocybin. It could also help explain psilocybin's therapeutic potential for subjects suffering from mental disorders: induction of "long-lasting adaptive processes" might be mediated partly by elevated protein levels of BDNF and other proteins involved in neuronal plasticity (González-Maeso et al., 2007; Vollenweider & Kometer, 2010).

On the other hand, neurons in the hippocampus and basal ganglia decrease their expression of BDNF in response to 5-HT_{2A} stimulation, which would seem to contrast with the reports of increased memory attributed to psilocybin (Vaidya et al., 1997). Future studies will hopefully provide more insight in the mechanisms involved. Lowered BDNF levels have also been linked by various studies to neurological and psychological conditions, including but not limited to schizophrenia, depression, obsessive-compulsive disorder, Alzheimer's disease, and dementia (Brunoni et al., 2008; Dwivedi, 2009; Maina et al., 2009; Xiu et al., 2009; Zuccato & Cattaneo, 2009).

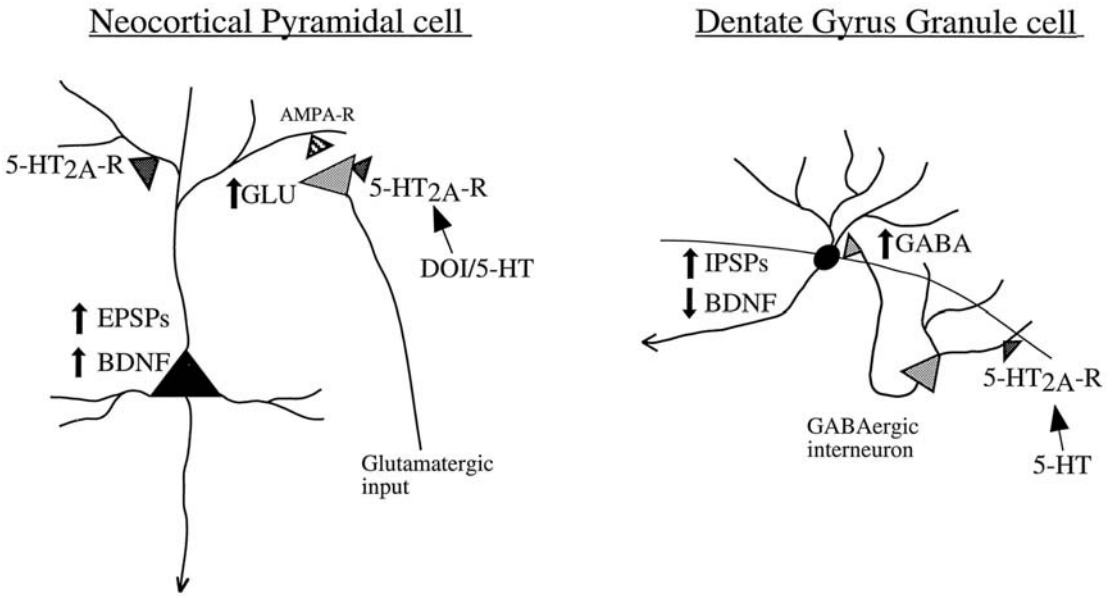


Figure 11. 5-HT_{2A} receptor-mediated pathways of BDNF expression in the neocortical pyramidal cell (left) and BDNF decrease in the dentate gyrus granule cell of the basal ganglia (right). (Taken from Vaidya et al., 1997)

While psychedelic-induced changes in gene expression are very interesting and may account for some of the effects of psilocybin, it should not be forgotten that these gene transcriptions are largely end-products of psychedelic activity and signalling in the brain.

4. Possibilities for pharmacological use of psilocybin

After a period of radio silence, the research into the therapeutic effects of psychedelics has been renewed. Not just psilocybin and LSD are investigated, but also 'newer' drugs like MDMA [19] have been shown to have therapeutic potential (Morris, 2008). Psychedelics in sub-hallucinogenic doses may reduce symptoms of depression, anxiety, obsessive-compulsive disorder (OCD) and chronic pains. In addition, it is hypothesised that psychedelic compounds may also induce "long-lasting adaptive processes" (Vollenweider & Kometer, 2010).

In the following paragraphs the therapeutic uses for psilocybin will be briefly discussed. It should be kept in mind that sessions with psychedelic substances are normally conducted in controlled environments ('settings'), and it is often important for the result of such treatments that patients integrate their experiences afterwards during regular therapeutic sessions.

4.1 Terminal illness

Terminal illnesses can produce heavy emotional and physiological burdens for patients diagnosed with them. Anxiety, depression, and psychological isolation are seen in various degrees in terminally ill patients, yet very little is commonly done to alleviate these problems (Grob, 2007).

A placebo-controlled, double-blind pilot study into the therapeutic effects of psilocybin was recently carried out by Charles Grob and colleagues in advanced-stage cancer patients (2010). Their findings demonstrate a significant reduction of anxiety and improvement of mood in these patients after treatment with psilocybin (Grob et al., 2010). The reduction in anxiety and elevated mood could be attributable to changes in consciousness, which are subjectively reported as 'increased insight' into problems that seemed unsolvable before (see part two of this paper).

[19] Strictly speaking, MDMA is not a hallucinogenic substance. However, it does commonly alter consciousness and is therefore often grouped with the psychedelics.

4.2 Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) has been associated with dysfunctions of the serotonin system, although conclusive evidence for this correlation is not yet available (Zohar et al., 1987; Goodman et al., 1990; Bloch et al., 2008). The first study in the US using psilocybin since the ban was conducted by Francisco Moreno and his colleagues in 2006. They investigated the effects of psilocybin on OCD patients who were unresponsive to regular treatment, partly inspired by accounts of OCD patients who apparently self-treated themselves successfully using psilocybin (Moreno et al., 2006; Grob, 2007). The pilot study showed promising results: psilocybin use in subjects with OCD is safe and may be associated with "robust acute reductions" in central OCD symptoms (Moreno et al., 2006; Grob, 2007).

4.3 Cluster headaches

One of the most debilitating and painful headaches are cluster headaches. Patients suffering from this disease experience periodically returning headaches of great intensity. The causes for these headaches are poorly understood; the most widely accepted theory relates to dysfunction of the thalamus, which is also involved in regulation of the biological clock. Additionally, it is responsive to a great number of inputs, reflecting the many different triggers that can cause cluster headaches in patients.

The substances that are currently used to alleviate symptoms often act upon the serotonergic system, suggesting a serotonergic component in the biochemical pathway. Low (non-hallucinogenic) doses of psilocybin and similar psychedelic compounds have been suggested to be able to abort a cluster headache episode. Scientific interest in this matter was taken up after patients reported beneficial effects upon self-administration.

In a study conducted by Andrew Sewell and his colleagues, patients suffering from cluster headaches who had used psilocybin or LSD in an attempt to treat themselves were interviewed (2006). The study showed that for each drug, more than half (but often more than 80%) of the patients reported that the psychedelics aborted attacks, terminated a cluster period, or extended the remission period (Sewell et al., 2006). Further research, possibly with non-hallucinogenic but similar compounds, could help develop an effective treatment for cluster headaches, as well as provide more insight into the mechanisms of this disease.

PART TWO

Small-scale study investigating the reported subjective effects of psilocybin and recommendations for future research

Introduction

Scientific research has elucidated or made suggestions regarding various aspects of the workings of psilocybin, as was discussed in part one. Yet user-reports are still unexplainably varied. To provide some feedback and a 'reality-check' to the theoretical and experimental data described in part one, the individual effects of psilocybin were researched on a small scale. This was done using a questionnaire that consisted of the researcher's own quantitative and qualitative questions, as well as standardised questions taken from the OAV[20] psychometric evaluation.

First, the methods and experimental design will be discussed, followed by an analysis of the results. The results will be grouped according to the three dimensions stated above. Finally, the discussion will link the findings of this study with the knowledge from part one of this paper and provide a framework to aid future research.

5. Methods

Participants

Participants of various nationalities currently living in Europe were recruited via email and verbal communication. The two requirements for participation in the study were (1) previous experience with psilocybin in any form and (2) relative proficiency in the English language.

Of 29 recruited participants, 20 returned a completed questionnaire. 13 out of these 20 participants were male, 7 female. Subjects had a mean age of 21.6 years (range: 18-28), and were mostly undergraduate or graduate students. The substance taken was in half of the cases a *Psilocybe* ("magic") mushroom, while the other half had experience with *Sclerotia* (truffles). Participants often reported they took both, but did not specify which effects belonged to which experience. Therefore, a comparison between the mushrooms and truffles was unfortunately not possible. A few participants have had only one experience with psilocybin prior to filling in the questionnaire, while another has had almost 50. The average number of past experiences with psilocybin in the sample was 5.8 times.

[20] OAV and the 5D-ASC rating scale mentioned earlier are two different questionnaires that resulted from revisions of Adolf Dittrich's APZ questionnaire (*Abnormer Psychischer Zustand*), which assess altered states of consciousness in retrospect of the experience (Studerus et al., 2010a). "OAV" stands for the German names of the three primary dimensions of altered consciousness: *oceanic boundlessness*, *dread of ego dissolution* and *visionary restructuralisation* (ibid.).

Experimental design

The study assessed the effects of orally taken psilocybin as reported by subjects after the experience. Results were obtained using a digital questionnaire, which subjects were requested to fill in and send back. Participants were free to give as many details as they liked, since the author believes that spontaneously reported effects may be less influenced by potentially biased formulations of questions. Subjects were asked to focus their report on their last 'trip', although participants with more than one experience of taking psilocybin often tended to compare their last trip with previous ones. In addition to the questionnaire, subjects were encouraged to write a trip report, in which they could describe their experiences more freely. Subjects were told they would receive a present as a compensation for writing a trip report, although only one participant was willing to do this.

The questionnaire that was used in this study is the Psilocybin effect questionnaire (PEQ), designed by the author of the present paper. The PEQ consists of eight sections. The first five relate to the sensory modalities of *vision*, *hearing*, *touch*, *smell*, and *taste*. They contain a quantitative measure and an open question, as well as an indication of when – relative to the time of ingestion – the reported effects occurred. Section 6 contains a limited set of closed and open questions related to mind and body, for which subjects were encouraged to provide as much relevant additional information as they saw fit.

Section 7 consists entirely of questions from the OAV questionnaire, as evaluated in Studerus *et al.* (2010a). From the 42 questions that their study evaluated, two were omitted for being of relatively little importance to the topics discussed in this paper. Participants were asked to answer *yes* or *no* to the 40 remaining questions, again with the liberty of providing extra information. The questions relate to 11 dimensions: (1) *experience of unity*, (2) *spiritual experience*, (3) *blissful state*, (4) *insightfulness*, (5) *disembodiment*, (6) *impaired control and cognition*, (7) *anxiety*, (8) *complex imagery*, (9) *elementary imagery*, (10) *audio-visual synesthesiae*, and (11) *changed meaning of percepts* (Studerus et al., 2010a). To help prevent unintended spill-over effects relating to the order of these questions, they were shuffled in a random order using www.random.org.

Finally, section 8 is intended to assess previous experience of the participants with psychedelic drugs. This is important since experienced users of psychedelics often have different ideas, theories, or remarks about the effects of psilocybin than those with

less experience. At the end of the questionnaire, participants are asked to fill in their preferred contact email and/or telephone number in case answers are unclear or incomplete. This has shown to be very useful for the completion of questionnaires that would otherwise remain ambiguous or incomplete.

Statistical analysis

No statistical analysis for possible significant results was performed, as the sample was not considered to be representative for the population at large and the methods used not completely standardised. This will be further explained in the discussion. For these reasons, attributing statistical significance to these data would be meaningless. Furthermore, the goal of this study is not to prove that the subjective effects reported are reliably produced; it is rather a first start to map some of the variation of these subjective effects in order to maintain the balance between the theoretical side of the problem and subjective experiences of users.

6. Results

The collected data show a variety of reported subjective effects after consumption of psilocybin. The results are split up into quantitative and qualitative results and will be discussed in detail in the sections below.

6.1 Quantitative results

The quantitative results pertain to sections 1-5 and 7 of the PEQ. The first five sections deal with the reported increase or decrease in quality of sensory perception, and will be discussed below. Subsequently, the results from section 7 of the PEQ will be covered, which are concerned with assessing dimensions of altered consciousness.

Sensory perception

The first five sections of the questionnaire deal with sensory perception under the influence of psilocybin. They deal with vision, hearing, touch, smell, and taste, respectively. Subjects marked on a scale of 1-7 whether they perceived the quality of perception had improved or decreased during the experience, and how much. 1 on the scale indicates great impairment in quality, while 7 indicates great improvement. ‘No change’ is indicated by a 4. In the analysis and in the graph, the numbers were normalised so that ‘no change’ is now 0, great improvement is 3, and great impairment

-3. The mean results of the influence on the different sensory modalities can be found in figure 12.

Vision was reported to have increased in various degrees in the majority of subjects (75%), and so was touch (76%). Hearing was reported by 58% of participants to be improved, while the remaining two senses scored relatively low: 22% of responses reported improvement for smell and 42% did so for taste, the latter being more variable than any of the other senses. Impairments were reported for taste (16%), vision (10%), and hearing (5%). The mean extent of the improvement or impairment can be seen from the graph; improvement in visual perception is reported to be markedly improved on average, closely followed by touch. Hearing is reported to be moderately improved, while smell and taste again receive low scores.

Responses indicating that the subjects had forgotten about this aspect of the experience or did not pay attention to the sensory modality in question were treated as "no data". Valid responses for other senses have been included in the results.

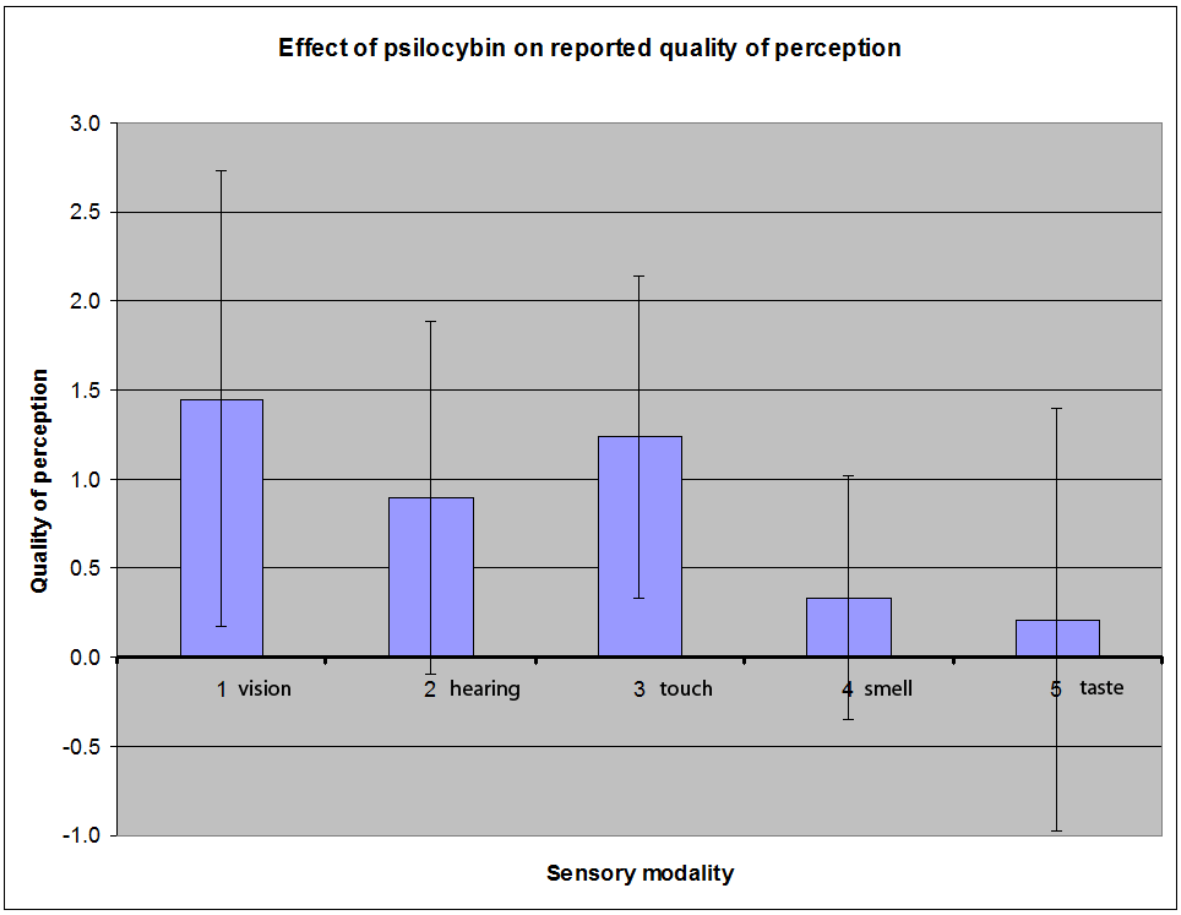


Figure 12. Graph showing mean results and standard deviations for the reported changes in quality of perception of the sensory modalities *vision*, *hearing*, *touch*, *smell*, and *taste*. A seven-point scale was used that ranges from -3 to 3, corresponding to perceived great impairment and great improvement of perception, respectively. A value of zero (*i.e.* the x-axis) indicates no change.

OAV questions assessing altered consciousness

Section 7 uses 40 questions taken from the standardised OAV questionnaire to assess alterations of consciousness according to the 11 dimensions discussed in the Methods section. It should be noted that the questions have a binary format, and as such they are incapable of measuring subtle changes in consciousness (Studerus et al., 2010a). However, analysis of the results can indicate which of these dimensions play a prominent role in the psilocybin experience and which dimensions are of lesser significance.

The responses of participants were averaged for each question, so that percentages could be calculated. This percentage corresponds to the fraction of people who responded "yes" to the question. Next, the 40 questions and their means were sorted per dimension and averaged. An evaluation study[21] of the OAV questionnaire was used to determine to which dimensions the listed questions belonged (Studerus et al., 2010a). Figure 13 shows the mean percentages per dimension, which is referred to as the 'dimension mean' in this paper.

As can be seen from the graph (fig. 13), a *blissful state* and *insightfulness* were most commonly experienced. *Changed meaning of percepts*, *experience of unity,* and

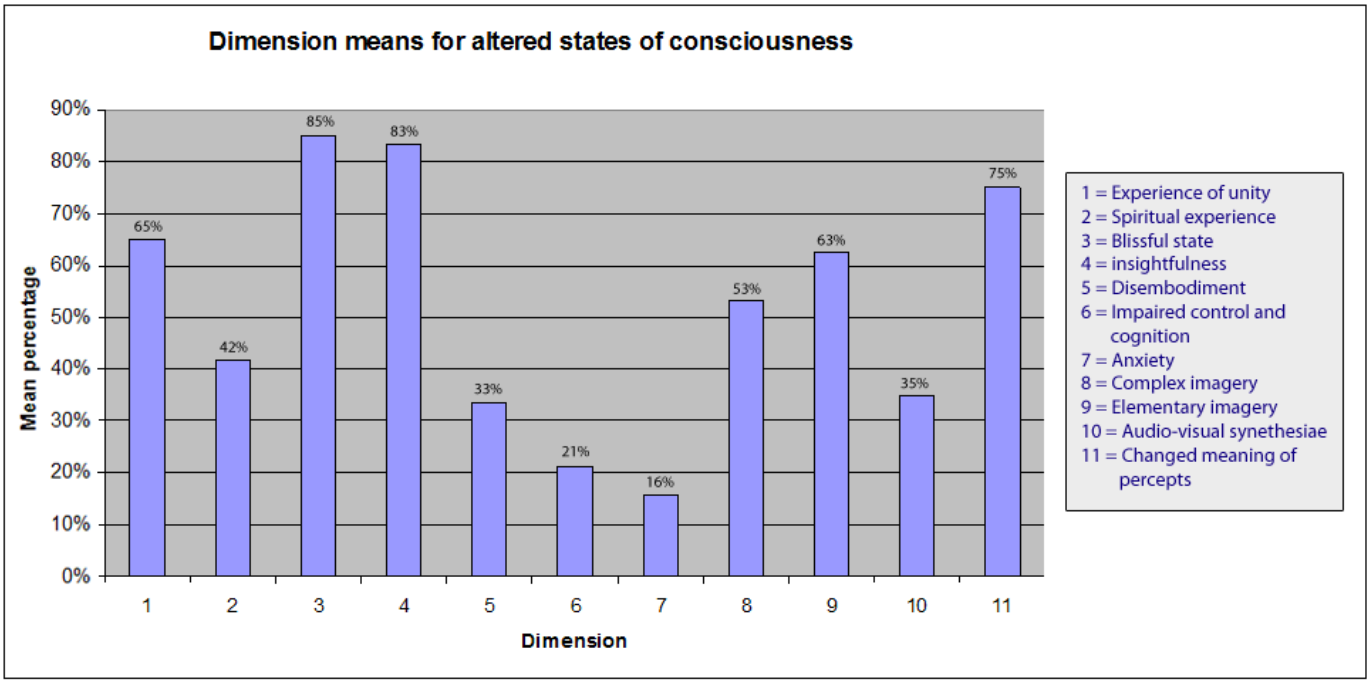


Figure 13. Graph showing the dimension means (in percentages) for the 11 dimensions of altered consciousness listed in the legend on the right.

[21] The 40 OAV questions included in the PEQ were taken from the same evaluation study.

elementary and *complex imagery* also ranked relatively high versus the other dimensions. Surprisingly, negative phenomena such as assessed by the dimensions *anxiety* and *impaired control and cognition* were relatively rare. Possible explanations for these results will be explored in the discussion.

6.2 Qualitative results

The qualitative results of the PEQ include non-numeric data from sections 1 to 5 on sensory perception, section 6 on mind and body, as well as any extra information provided by respondents throughout the questionnaire. Information relating to sensory perception will be covered first, after which the subjective effects on mind and body will be discussed. The latter category takes into account effects on emotion, subjective perception of time, nature, and one's own body, personal significance of the experience, sense of consciousness expansion, and more.

6.2.1 Sensory perception

Vision

A large part of comments regarding sensory perception pertained to the visual modality. Sharper visual perception, contrasts, and intensification of colours were often reported, and in almost all cases these effects were noticed at the onset of the 'trip' (roughly 30 min after ingestion). Increased sensitivity to light was also noticed by participants, though some report being able to look into a light source and clearly see the inner components, apparently not bothered by the brightness. At the same time, these people reported that they were able to see in the dark very well while under the influence of psilocybin.

Depth perception was improved in a proportion of subjects, often even in 2D objects like paintings. Improved perception of patterns was noted as well, and in some cases kaleidoscopic, fractal, or other regular patterns were reported to be seen on 'blank' or smooth surfaces like walls, or in the sky (*i.e.* hallucinations[22]). It is important to note that most of the participants did not experience 'true' hallucinations[23], although

[22] Although at the beginning of this paper it was said that "hallucination" and derivative words carry connotations of something that is not real or a mere illusion, the word will here be used for lack of a better word that carries appropriate meaning.

[23] 'True' hallucinations are defined here as mental images that are little influenced by actual sensory perception and have little basis in the immediate physical environment. The 'perception' of people or things that are not there at that point in time and space, for instance, are true hallucinations.

alterations of normal visual perception were experienced by most subjects, as well as regular patterns superimposed on 'normal' perception as was just mentioned. Some subjects also noticed a kind of aura or colour scatter radiating from objects.

Some specific effects that were noted by participants could provide some knowledge about the scope of effects, as well as help distil underlying cognitive causes. Some interesting individual responses will therefore be discussed here. One participant noted that she could see sharply from extremely close-up, as if looking through a magnifying glass. Another subject mentioned that visual perception was very variable: sharpness of vision depended on whether the visual modality was actively attended. Yet, upon focusing on one element in the direct environment, it appeared to come into view larger, sharper and more detailed as compared to normal. Another participant also reported a very variable effect: he mentions very clear, very detailed vision at some times, but has also had experiences where his visual perception was reduced to mere patterns and shapes. Two subjects noted some intolerance towards hard 'unnatural' colours such as neon pink, which were perceived as bothersome. A remarkable effect was noted by one participant, whose vision shifted to only black and white for about a minute. One such effect was also noted by another subject, who describes what she saw as: "my friend became a charcoal painting". However, the other effects these subjects experienced were relatively common in the sample.

Despite the rather varied responses, the general picture that emerges for visual perception is that of a heightened perception of patterns, colours, 3D-effects, and improved edge-detection, particularly at the onset of the trip. The perception of 'breathing', 'flowing' or 'pulsating' objects was also a relatively common experience. These effects were reported to be most intense around the beginning of the trip (around 30 to 60 min after ingestion), and gradually faded away. Long-distance and depth perception were in many cases reported to be improved, sometimes persisting for some days or more after the experience. In a few cases subjects reported that parts of the altered perception became permanent, possibly relating to a structural change to the neuronal networks dealing with visual perception. Interestingly, this only occurred in the case of improvement; no negative effects were reported to persist after the experience.

Finally, it is relevant to note here that some participants who reported no change in visual perception did experience some of the effects listed above, although they did not necessarily interpret them as improvements or impairments. Similarly, subjects that

noted impairments for vision often experienced similar effects as those who noted improvement, indicating that the interpretation of the experience as improvement or impairment is highly dependent on the context of the experience and on individual personality and mood (set and setting, see section 2.2). In addition, subjects often reported seeing things that they would normally not perceive or pay attention to. This could be called a form of perceptual insight, which could perhaps explain why some subjects permanently retained the novel ways of perception they experienced during their trip.

Hearing

From the responses relating to auditory perception it appears that this modality was less impacted by psilocybin than for example vision or touch. Many subjects reported no changes, while those that did report changes mostly spoke of their perception of music. Music was perceived as more intense and more structured; participants noted a greater appreciation for melodies, rhythms, and patterns in the music. Perception of music was incredibly variable: some say perception of music was "crystal clear", while others refer to it as "wide" or reported they felt "enveloped" by the music. One subject noted that the music sometimes seemed to fit the "moment" and the mood perfectly, as if it was 'meant' to be played at that particular moment, while yet others reported they paid little attention to the music played.

A proportion of participants also reported being more sensitive to loud sounds, especially when these were shrill, hammering or 'unnatural'. One subject reported his hearing was very sensitive overall; he notes he had to turn down the music very low to be able to enjoy it. A relative intolerance to "bad music" was experienced by another participant, who was selectively bothered by instances of sloppy rhythm, false notes, and other things in music that "disrupt the perfection of the patterns" in music. This subject also noted that this was not unique to shrooms, since she also experienced this while under the influence of another psychedelic.

Negative effects were noted by one participant. He describes he experienced a somewhat "impaired perception of speech and 'stand-alone noises' ", although the same participant also noted improved perception of "harmonic" and "melodic" sounds. Another participant reported his overall auditory experience to be slightly impaired but did unfortunately not specify how he experienced this.

The first auditory effects were experienced simultaneously with the visual effects by some participants, while others reported these effects to lag behind the visual effects by 15 minutes up to 3 hours. For some the effects faded away gradually, for others they persisted throughout the experience. It should be noted that many subjects did not remember when they first noticed changes, although it seems clear that the experience is quite variable.

Touch

Touch perception was reported to be improved by most of the participants, although a proportion of subjects reported no changes. Of those who felt it to be improved, the majority noticed this through specific events, while others noted an overall increase in touch perception but did not find it particularly special.

A finer touch perception was reported most often, which was experienced by one participant as a tingly sensation to any body part touched, and by others through a pleasurable experiencing and examining of the texture of various things. One person reported being able to feel the sensations of individual cells while lying down, though for another subject everything just felt 'harder'. Others said it depended on the focus of their attention. Another participant reported that her perception of touch during the experience was fascinating, because she often ignores this sense in daily life.

For some, however, the experience is variable. One participant notes that while he can sometimes greatly enjoy examining textures through touch, at other times his touch is completely blunted, which he describes as being "unable to 'feel' ". No other impairments were reported for touch, although a lower perception of pain was reported by one subject, who nevertheless interpreted this as an improvement. The first effects of altered perception of touch, as reported, are also quite variable: they range from 45 minutes to 3 hours after intake of psilocybin.

Smell

The majority of participants did not notice any changes in their perception of smell. A few subjects reported smell to be improved, of which two reported that they became more aware of smells around them. For another participant this manifested itself as the ability to smell sweet odours from great distances on the one hand, and intolerance to certain subjectively disagreeable smells on the other hand. This subject also notes that the heightened sense of smell persisted for some days. One participant said the effect

was noticed at the onset of the trip, simultaneously with changes in the other modalities, although no other participant reported when they experienced the first effects.

Taste

Changes to taste perception are difficult to study, since psilocybin appears to reduce appetite in most people during the first hours of the experience. Some participants noticed improved taste during the trip, such as one who found fruit to taste "amazingly delicious and sweet". Others noticed a decrease in taste perception, with one participant reporting he was unable to notice the taste in the food he was eating. Food eaten afterwards, or towards the end of the trip, was reported by several subjects to be more tasty than usual. A substantial amount of references were made to a greater appreciation of the texture of food. The real time of onset of these effects is difficult to study, because the perception of altered taste is dependent on when the subject decides to eat something.

6.2.2 Subjective effects on mind and body

In this subsection, a number of subjective effects of psilocybin on the human mind and body will be discussed. Emotional reaction is the first topic to be discussed, after which the perception of one's own body and of time will be covered. Next, the personal significance of the experience will be examined, followed by the perception of nature and structures. Subsequently, this subsection will look into the perception of communication with others, as well as possible changes in intuitive understanding. Finally, some attention will be devoted to subjective changes in thought patterns and the experience of consciousness expansion.

Emotional reaction

Subjects often describe their emotional reaction to the experience as "euphoria", "like being in love" or as general happiness. Subjects felt "energetic", "elated", and/or "at peace with the world". Some subjects noted that emotions overall became stronger, sometimes experiencing intense negative emotions and intense positive emotions at other times. One participant reports the following: "I was generally very happy and a lot more at ease with the world around me and myself. I think I can describe it as a very profound sense of inner satisfaction, guided by the feeling that no matter what it is, it's going to be alright." Another subject notes a similar experience, and adds to this that as

long as she felt happy and at peace, nothing mattered, not even death[24]. The subject noted she could still, however, rationally contemplate her decisions the whole time.

The loss of ego was reported by one subject, which he describes as: "one loses the sense of being a singular being, where the boundaries between yourself and the matter around you dissolve and you are part of everything around you, as much as everything around you is part of you". At this point awareness of emotions is also lost, he notes. Others said they loved everything, or experienced everything as beautiful. While the experience may be quite varied, the general effect – at least in this sample – seems to be a mild to great euphoria, with the possibility of loss of ego boundaries.

Perception of the body

Subjects perceived their own bodies variably. Some felt smaller relative to the world around them, while others felt larger, or ambiguously responded "both". Others did not feel larger or smaller than normal. To some participants it felt like their bodies became larger, or like they became larger than their bodies. Some feel their body is detached or almost inexistent, like a shadow. While some respondents report feeling clumsy or awkward in their bodies, others have the opposite experience: they feel more integrated with and in control over their body. One subject reports: "Matter *is* mind. [I experienced an] increased sense of balance and some intuitive understanding of physical limits [of the body]". A few others with similar experiences add to this that they experienced a great increase in energy along with decreased perception of pain.

Perception of time

The subjective perception of time slowed for many of the participants, which has also been documented in the literature (Wittman et al., 2007). A proportion of participants noted they did not pay any attention to time, while others said time was irrelevant or that time just did not exist during their trip. A few people reported to have understood time in terms of events or actions that happened.

Personal significance

Remarkably, all but three participants considered the experiences they have had while under the influence of psilocybin personally significant. Two of these three reported taking a relatively low dose, suggesting the possibility of a 'threshold' dose for certain

[24] Such effects are highly interesting for palliative medical care, especially in the treatment of anxiety in terminal patients. For some preliminary studies investigating this possibility please refer to Grob, 2007 and Grob *et al.*, 2010.

effects. All others responded "yes", "YES!", or "definitely" to this question. For a number of subjects it strengthened group bonding and understanding, although others were more introspective. One participant in the latter category used the experience to learn more about herself, while another used it to think about his past, present, and future actions. A third participant found the experience therapeutic because it allowed her to free emotions that she had suppressed before, while a fourth says every experience teaches her something. Overall, the reasons given seem to relate to improved insight and understanding, be it manifested consciously or subconsciously.

Perception of nature

Possible changes in perception of nature could not always be reported, as some participants spent the duration of their trip inside a house. Virtually all other participants expressed an increased appreciation of nature, sometimes describing their perception of nature as "warm" and/or "cosy". Feelings of becoming more "integrated with the environment" are often mentioned, along with reports of an increased presence of nature felt by the subjects. To one participant it felt like a "rediscovery of nature", although others experienced their environment as different "areas" that "felt different".

With man-made structures – especially those that do not show signs of wear or age – the opposite was experienced by many subjects. A number of reports indicate some intolerance to being inside; the perception of being inside was described by one subject as "cramped, confined, plain, fake, and incredibly boring". While one participant said he perceived no difference in his perception of nature as compared to man-made structures[25], a strong general tendency towards the appreciation of 'nature' can nevertheless be seen. This might be explained in part by a greater enjoyment of patterns, as one participant aptly put it: "everything which is a product of some emergent process sucks your attention in, so to speak. You can get completely lost in the patterns."

Perception of communication

Communication with other people was noted by many participants to be better with others who were also under the influence. Bonding effects within a group were often reported, facilitated by a reported better understanding of other people's thoughts and feelings. Some note the experience of a kind of 'group mind', where the members of

[25] Technically, one cannot make such a separation, as man-made structures are also built up from nature. The common view in Western culture, however, holds nature as everything that is not deliberately or obviously created by humans. The word 'natural' is also associated with certain mathematical proportions inherent to nature.

the group all seem to understand each other and collectively build the experience. This was only reported to occur with others who were also under the influence of psilocybin. One subject reports that, while in a group of people speaking a foreign language the subject did not master completely at the time, she found herself being able to follow the conversation effortlessly, having no problem with colloquial words or rapid speech. She notes that this effect persisted after the trip had ended, although not completely. A few others report that they had found it easier to convey complex, abstract ideas to people who had also taken psilocybin.

Several participants reported they felt uncomfortable around others who were 'sober', for various reasons. Others note no real difference between communication with sober or intoxicated people, while yet others say their perception of communication was the same as always. Whereas some subjects reported difficulties understanding others at the beginning of the trip and disappearing towards the end, others reported the exact opposite. While the perception of communication varied quite substantially, the reactions indicated a variable tendency for improved communication, though not in all cases. The reports indicate that there was not always a 'sober' or 'intoxicated' person available for comparison.

Intuitive understanding

As was foreshadowed by the quantitative results discussed earlier, intuitive understanding was reported to be increased by the majority of participants. Shifts to a more intuitive pattern of thinking were frequently reported, as well as a "deeper understanding" of people, concepts, and things. Subjects mention being able to pick up "vibes" from people or places, or report being able to understand other people's underlying motives. Some subjects experienced that it becomes easier for them to keep their balance or to learn new things while 'tripping'. One subject adds to this that it felt like subconscious processes were highlighted and more accessible.

Several participants note that they felt enlightened or that they had some other revelation significant to their understanding of the world. One participant mentions she was very grateful for the intuitive understanding she gained during a trip, which she reports has been very useful in daily life. Another respondent described the experience as an "epiphany" and reports he felt for some weeks to months afterwards that he had come to a clearer understanding of the world. That being said, a few participants noted no changes in their intuitive understanding.

Subjective changes in thought

Thought patterns seemed to change remarkably for some respondents, but as with most effects, not all participants experienced changes. Subjects often reported an increase in abstract thoughts, as well as increased speed of thinking. For some this led to rather 'unordered' thoughts and instances where subjects were unable to finish a thought, new ones appearing before the previous one was completed. Others felt their thoughts were more precise, more coherent, or more ordered, some adding to this that it felt like being mentally "hypercharged". There was also some variation to the ability to multitask: some find it to be impaired but report to be able to focus on one thing very well, while others report being able to take in much more different things at the same time or to keep them in focus simultaneously.

Some participants note that they thought differently about things, with more clarity, deeper meaning, and a preference for intuitive thought and feelings. A few subjects declared to be very aware of the "essences" of things[26], while others reported being more occupied with patterns. On the other hand, a few subjects preferred to deal with abstract concepts than with patterns during their trip, while others stated it varied throughout the experience. One should keep in mind that while these reports provide a glimpse into the scope of effects on subjective thought resulting from psilocybin, individual thought remains a very elusive subject for scientific understanding.

Consciousness expansion

A small majority of subjects experienced consciousness expansion, which was defined in the PEQ as the feeling of suddenly being able to oversee everything, as if watching from a higher altitude. The remainder of subjects either experienced some slight changes the direction of consciousness expansion, or reported that they experienced no such changes. One participant fittingly describes what is meant by consciousness expansion. She writes: "I had the 'vision' of myself standing on a hill with reality spreading out before me – just there to be understood".

Many subjects felt as if "everything made sense", often reporting having new insights and feeling calm. Some subjects felt they could suddenly piece the puzzle together and associate concepts that seemed unrelated before. Furthermore, a number of participants report having found solutions to difficult problems during their trip.

[26] *Essences of things:* "essence" can be interpreted in the Aristotelian sense, or as the 'core' that defines a living being, concept, or other thing. "Things" should be interpreted in the broadest sense of the word.

7. Discussion

The results discussed in the previous section show that the experience is often incredibly varied, both between and within participants. Taken together with the theory of the gating function of the thalamus and the overload of perceptual stimuli caused by its disruption (see section 3.1), one could hypothesise that the variability of the psilocybin experience depends for a large part on differences in environment, leading to different stimuli perceived.

In this light, it becomes clear why users of psychedelics stress the importance of set and setting. The set guides the focus of the attention as well as the value given to the perceived stimuli (top-down control). The setting determines what types of stimuli enter the sensory system. These stimuli may subsequently trigger certain affective and rational processes in the brain of the user (bottom-up control). Psilocybin may, by increasing the excitability of some neurons, cause stimuli that normally remain subconscious to enter the conscious mind of the user. An experimental study investigating how setting and set influence the experience could shed more light on this issue. Preferably, the study would include low, medium, and high doses in addition to an active and regular placebo. Mood and expectation tests can be used to assess the subjects' mindset before the experience. Furthermore, since subjective feelings are exceptionally hard to study, observer reports may be beneficial in assessing whether the responses of the subjects reflected their behaviour and attitude.

In addition to the diversity of experiences, some general tendencies were also reported. These include improved (visual) perception, heightened affect, and an increased awareness of patterns. An enhancement of intuitive understanding (cf. OAV dimension *insightfulness*) seems to play a role in many of the effects reported, and could arise from sensory overload of the cortex. This study hypothesises that as the thalamic filter is bypassed (as was explained in section 3.1), subjects suddenly become aware of thoughts, processes, and other inputs that normally remain in the subconscious[27]. For some this may lead to confusion and anxiety, but for others it could provide new insights and a feeling of consciousness expansion. A remark by one of the participants supports this idea: "it becomes easier to notice things that would normally not reach your awareness, for all senses". Therefore, the possibility should be

[27] This likely includes lower-order processes such as shape recognition (cf. the OAV dimension *elementary imagery*).

considered that consciousness expansion is nothing more than an increased awareness of processes that one is normally unaware of.

A few other things are of lesser importance, but deserve a brief discussion here. Several participants reported phenomena that were variably described as 'group mind', 'group feeling', being "in synch" or feeling "connected". It is possible that this is influenced by the reported increased intuitive understanding. Furthermore, increasing understanding of the mirror neuron phenomenon and its response to substances like psilocybin, in combination with a better understanding of the feelings of detachment that are experienced by many under the influence of psilocybin, may provide new insights as to the role of these rather different effects (Ramachandran, 2010). Thus far, little scientific attention has been devoted to the experience of group-mind.

Next, it should be brought to the attention that not all senses are equally dominantly present in Western culture. While it is undeniable that vision and hearing play a large role in Western society, this is less true for touch: rules of etiquette often dictate the use of less intrusive means of perception. This cultural bias may be reflected in the reports of respondents. Lastly, there were no reports of 'bad trips' in the sample, and all participants found the experience to be pleasurable. This study was therefore unable to assess the effects relating to a 'bad trip'[28].

This study was intended to map some of the variation of the psilocybin experience, in order to provide a preliminary reality-check to the theory. However, when one would like to draw conclusions from the current data, the following limitations of the study should be kept in mind. Firstly, the sample size is relatively small and biased. This was unfortunately unavoidable, as the use of psychedelics is not openly accepted in Western culture[29]. In addition, due to time restrictions set to this study, not all ambiguities in the Psilocybin Effect Questionnaire (PEQ) could be resolved before participants filled them in. Additionally, the PEQ did not ask how much respondents remembered from their experience, or in any other way controlled for it. Furthermore, no account was taken of existing religious or spiritual beliefs, interests, and practices of the participants, nor were the respondents' personalities or character

[28] The lack of bad trips in this sample may on the one hand be explained by the sample size, which was not large enough to warrant a negative experience, and on the other hand by the dose. Subjects most commonly took relatively low to moderate doses, while the literature indicates that intense negative experiences occur primarily in high doses (Studerus et al., 2010b).

[29] The author was told that it can be problematic for the social and professional life of individuals to "come out of the psychedelic closet". This makes it more difficult to find enough subjects, and makes it especially difficult to obtain a random sample in this situation.

traits assessed. The age group was relatively limited in range and while the sample included subjects of various different nationalities, most of these are graduate or undergraduate students living in the Netherlands.

While anecdotal evidence generally does not enjoy a very high status in scientific literature, the author believes it to be crucial to a meaningful understanding of the psilocybin experience. Future research is recommended not to shun the subjective side of the problem, as that is where insights pertaining to difficult questions can be found. Consciousness or subjective perception is exceptionally hard to study, which is why the pooling of experiences might be beneficial to point out general effects or tendencies that can be further investigated using more rigorous scientific methods.

Additionally, it was observed that relatively experienced psilocybin users (those with more than two experiences) can often provide a more precise description of their experience. While users with few psilocybin experiences often describe effects in relation to events that occurred, experienced users more frequently relate these to the general effects they attribute to psilocybin. From the data obtained in this study, it appears that anxiety is experienced more often in first-time users than in users with multiple experiences. It is not difficult to imagine why this might be the case: the first time one enters an altered state of consciousness can be frightening, as the user does not yet know what to expect[30]. While there are certainly benefits associated with including more experienced users in experimental studies, most studies to date assessing the effects of psilocybin have been performed with drug-naïve participants. It would be good to perform similar experiments with groups of both inexperienced and experienced users of psilocybin to supplement this data.

There are as of yet many uncharted areas of the psilocybin experience, and therefore many fields of interest for future research. An examination of how changes in gene expression are mediated following stimulation of a 5-HT_{2A} receptor by psilocybin and other psychedelics can provide more knowledge about long-term effects. For instance, the increase of neurotrophic factors and proteins involved in learning and memory may be beneficial in the treatment of neurodegenerative diseases like Alzheimer's disease. The knowledge that would be gained from an investigation into the signalling pathways involved in gene expression may also provide valuable

[30] It is likely that there are little differences in receptor sensitivity or density in experienced users versus inexperienced users, as the user reports showed that the substance was not taken very frequently (up to a few times per year). It would be wise to confirm that there are indeed no significant physiological differences in experienced users.

information regarding the biochemical pathways involved in the action of psilocybin, possibly also providing clues as to the causes of commonly reported effects.

In addition to this, more knowledge is necessary with regard to the effects of various dosage levels. Although this study attempted to compare the effects to the dosage, subjects were often unable to say how much they had consumed. Additionally, psilocybin content per gram may vary in specimens of *Psilocybe* and *Sclerotia*, further complicating the issue. While some experimental studies have already started to assess the effects of various dosages using pure psilocybin in quantities relative to the subject's body weight[31] (Carter et al., 2004; Hasler et al., 2004; Wittman et al., 2007), additional research may provide an understanding of the dose needed for therapeutic effects. Some effects may be therapeutic even in sub-hallucinogenic doses (*e.g.* cluster headaches, section 4.3), which is especially interesting for pharmaceutical use.

Finally, in order to map the current understanding of the effects of psilocybin and to help identify fields for further study, an overview of the current knowledge is provided on the following page (fig. 14). The framework shown is structured as follows. At the top of the diagram the objective effects of psilocybin are listed, while at the bottom the subjective effects can be found. Solid lines and boxes refer to data that have been supported or confirmed by scientific articles, of which a large part can be found in previous sections of this paper. Dashed black lines refer to connections – proposed by the current study or by others – for which there is as of yet no clear support or falsification. These may be seen as uncharted territories, awaiting exploration. Purple dotted lines indicate possible links between objective effects and subjective effects. Future research is urged to investigate the mechanisms that may explain the relation between the objective effects on the one hand, and subjective experiences on the other.

While the ghost of the 1960s has made research into psilocybin rather difficult, psilocybin does appear to have potentially beneficial effects. Additionally, a better understanding of its mechanisms can provide important information regarding neurological diseases, including but not limited to schizophrenia, depression, and obsessive-compulsive disorder. The author hopes that that future research will help elucidate these specific mechanisms of psilocybin, to provide not only understanding, but also valuable knowledge for the treatment of certain neurological disorders.

[31] See Studerus *et al*., 2010b for a list of relevant research in progress.

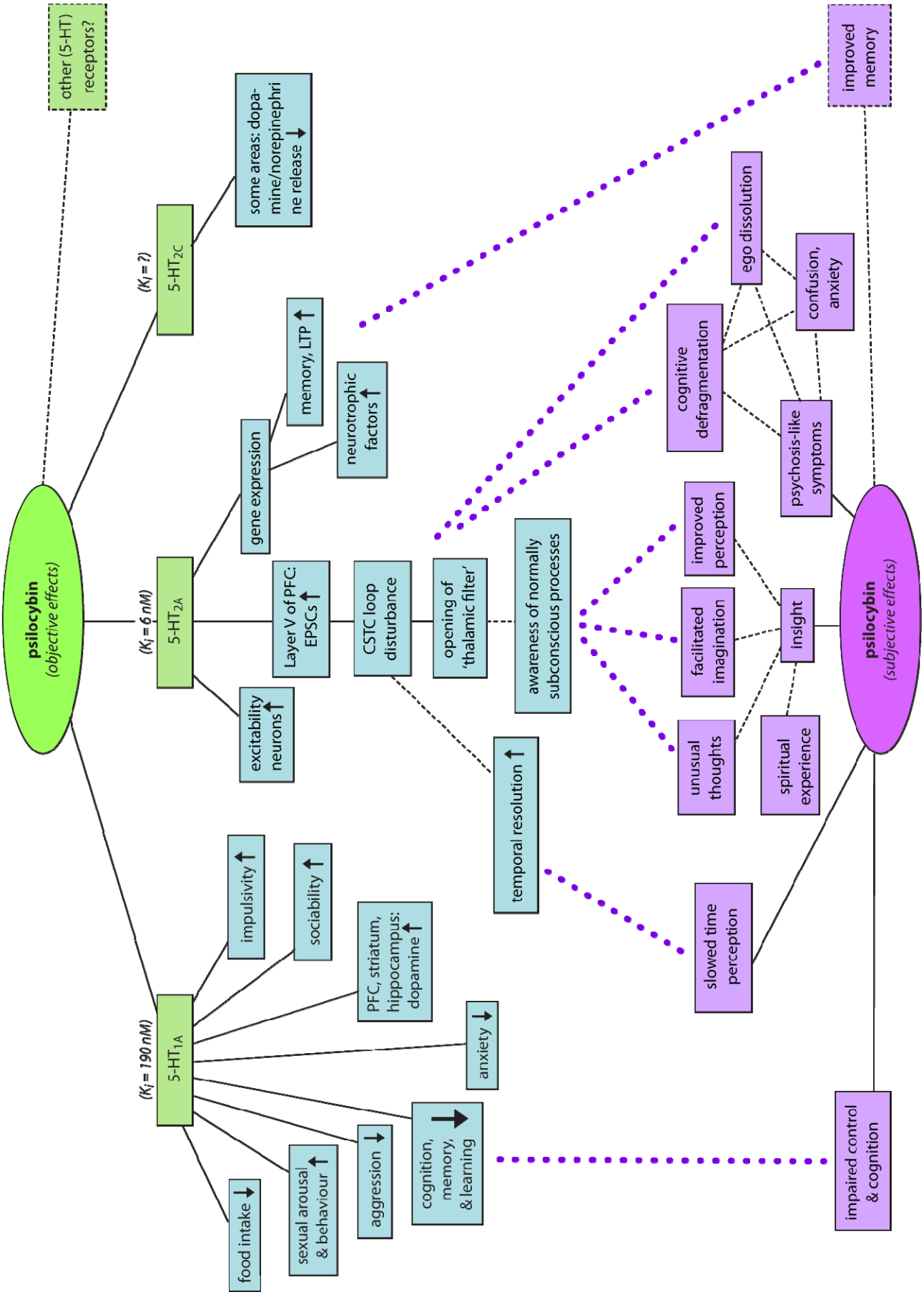


Figure 14. Framework listing many of the subjective effects of psilocybin currently known or hypothesised (see text). Solid lines and boxes indicate that some support for this effect has been found in the literature, dashed black lines indicate that neither substantial support nor falsifications have been found in the literature (*i.e.* gaps in knowledge). Finally, the dotted purple lines indicate potential links between objectively observed effects and subjective effects.

List of abbreviations

5-HT	*5-hydroxytryptamine; serotonin*
5D-ASC	*Altered States of Consciousness Rating Scale*
AA	*Auditory Alterations (5D-ASC dimension)*
AED	*Anxious Ego Dissolution (5D-ASC dimension)*
arc	*activity-regulated cytoskeleton-associated protein*
BDNF	*brain-derived neurotrophic factor*
CNS	*central nervous system*
CSTC	*cortico-striato-thalamo-cortical*
CTC	*cortico-thalamo-cortical*
egr	*early growth protein*
EPSP	*excitatory postsynaptic potential*
EPSC	*excitatory postsynaptic current*
GABA	*γ-aminobutyric acid*
GPCR	*G protein-coupled receptor*
HPPD	*hallucinogen persistent perception disorder*
IPSP	*inhibitory postsynaptic potential*
LSD	*lysergic acid diethylamide*
LTP	*long-term potentiation*
MAO	*monoamine oxidase*
MDMA	*3,4-methylenedioxymethamphetamine*
OAV	*psychometric evaluation test (see footnote on page 34)*
OB	*Oceanic Boundlessness (5D-ASC dimension)*
OCD	*obsessive-compulsive disorder*
PEQ	*Psilocybin effect questionnaire*
PNS	*peripheral nervous system*
PFC	*prefrontal cortex*
RV	*Reduction of Vigilance (5D-ASC dimension)*
VR	*Visual Restructuralisation (5D-ASC dimension)*

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