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THE PSYCHEDELIC ALTERED STATE OF CONSCIOUSNESS

An Assessment of the Current Status of Psychedelic Research

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Abstract

Classic psychedelic substances, such as lysergic acid diethylamide and the active compound in magic mushrooms, psilocybin, are being studied again in a renaissance of psychedelic research. Psychedelic substances have profound effects on perception, emotion, and cognition, as well as the capacity to induce mystical-type experiences and ego-dissolution. Recent clinical studies indicate that these substances have positive effects on patient populations and healthy participants, both acutely and long-term. Neuroimaging studies show that psychedelics alter neural integration, by the disintegration of normally stable resting state networks, and increasing network connectivity between normally anticorrelated networks. This thesis will review the phenomenological characteristics of the psychedelic-induced altered state of consciousness, the therapeutic potential of the psychedelic-induced altered state of consciousness, and neuroimaging studies on the psychedelic state. Two theoretical accounts are compared on the brain basis of psychedelic-induced altered state of consciousness. From the recent research on psychedelics a novel theory of conscious states has evolved, the entropic brain theory. This theory will be compared to the integrated information theory, a well-established theory of consciousness within cognitive neuroscience.

Keywords: psychedelics, lsd, psilocybin, integrated information theory, entropic brain, entropy, altered states of consciousness

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Introduction

The past decade has seen a resurgence in psychedelic science. Psychedelic substances such as *lysergic acid diethylamide* (LSD) and the active compound in magic mushrooms *psilocybin* are now being studied again after a long hiatus on the topic. Research teams in the US, Europe, and South America are looking into the mechanisms of these substances with new study designs and modern techniques. For example, among the recent findings, LSD and psilocybin have shown promising therapeutic results in the treatment of end-of-life related distress in cancer patients (Gasser et al., 2014; Gasser, Kirchner, & Passie, 2015; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Psilocybin has further shown a significant effect with treatment-resistant depression (Carhart-Harris et al., 2016a, 2018a) and obsessive-compulsive disorder (OCD) (Moreno, Wiegand, Taitano, & Delgado, 2006), as well as an indication of lessening both tobacco (Johnson, Garcia-Romeu, & Griffiths, 2017) and alcohol addiction (Bogenschutz et al., 2015; Krebs & Johansen, 2012). Psilocybin has also been shown to induce mystical-type experiences with a persistent positive outcome in healthy subjects (Garcia-Romeu, Griffiths, & Johnson, 2014; Griffiths, Richards, McCann, & Jesse, 2006; Griffiths, Richards, Johnson, McCann, & Jesse, 2008). By using multimodal neuroimaging techniques psychedelics have been shown to alter resting state networks of the brain (Carhart-Harris et al., 2016b), increase neural signal diversity (Schartner, Carhart-Harris, Barrett, Seth, & Muthukumaraswamy, 2017), decrease oscillatory power (Carhart-Harris et al., 2016b; Muthukumaraswamy et al., 2013) and increase possible brain states viewed through

functional connectivity (Tagliazucchi, Carhart-Harris, Leech, Nutt, & Chialvo, 2014) and connectome-harmonic decomposition (Atasoy et al., 2017; Atasoy, Vohryzek, Deco, Carhart-Harris, & Kringelbach, 2018). Furthermore, psychedelic research has given insight into the serotonin system (Carhart-Harris & Nutt, 2017; Preller et al., 2017; Preller et al., 2018) and given rise to a new theory on conscious states (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). The term psychedelic renaissance has been promoted by both scientists as well as more frequently the mainstream media to describe this new golden age of psychedelic research (Bright, 2017; Carhart-Harris et al., 2018b; Murnane, 2018; Pollan, 2018; Sessa, 2018).

With psychedelic research in its renaissance, the main aim of this thesis is to evaluate what we know today about the psychedelic-induced *altered state of consciousness* (ASC), by covering the recent phenomenological, therapy and neuroimaging studies on LSD and psilocybin. A second aim is to assess how psychedelic research attribute to our understanding of the mind, as the recent neuroimaging studies have given rise to a new theory on conscious states, the *entropic brain theory* (EBT). Thirdly, this thesis aims to evaluate how this new theory contributes to the field of consciousness research, by comparing it to the already well established *integrated information theory* (IIT).

What are psychedelics? Broadly speaking the term refers to a substance that profoundly alters human perception and consciousness. More specifically, *classic psychedelics* refers to a class of psychoactive compounds that cause profound changes in perception, mood, and cognition mediated primarily by agonist or partial agonist activation of the serotonin 2A receptor (Nichols, 2016). The classic psychedelics are the most

commonly known and researched. They include LSD, psilocybin, mescaline, and dimethyltryptamine (DMT) (Murnane, 2018; Nichols, 2016). All of the mentioned, with the exception for LSD, have historically been ingested in ceremonial settings for centuries in American indigenous cultures and are still used today, sanctioned as religious devotion. In western culture, psychedelics can have been said to have had one academic endeavor and one subcultural, with one eventually deflating the other. While the research on LSD as a therapeutic agent showed promising results in the 50s and 60s, the substance was highly associated with the hippie counterculture movement, leading to its criminalization and stigmatization (Johnson, Richards, & Griffiths, 2008; Murnane, 2018).

The stigmatization of psychedelics gained in the 60s and 70s needs some correction as it still has reached into modern society. At the time, campaigns informed about chromosomal damage due to LSD, a statement which is refuted today (Johnson et al., 2008). On the contrary, psychedelics are rated amongst the lowest in an overall harm score done to survey Europe's most popular drugs (van Amsterdam, Nutt, Phillips, & van den Brink, 2015). While psychedelics may increase pulse and blood pressure, and cause unpleasant physical reactions such as nausea, dizziness, blurred vision and weakness, they are generally seen to have low physical toxicity and are non-addictive. The primary safety concern for classic psychedelics in a controlled research setting is their psychological effect. “Bad trips” are best avoided through the preparation of the participant with well-educated personnel in a safe environment (Johnson et al., 2008; Johnson, Hendricks, Barrett, & Griffiths, 2018; Nichols, 2004, 2016).

As previously mentioned, one result from the psychedelic renaissance is EBT, a novel theory of conscious states which have evolved from the modern neuroimaging studies (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). EBT uses the index of *entropy* as a dimensionless quantity of uncertainty to assess the quality of a conscious state. In this view, entropy is synonymous with uncertainty, randomness or disorder. Based on information of brain function, a principle of EBT is then, that a system with high entropy is accompanied by an experience of subjective uncertainty. A principle which EBT maps onto the psychedelic state of consciousness. The system's entropy is also related to the state of *criticality,* in which a system is in a transient zone between order and disorder (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). According to EBT, the psychedelic state is then closer to criticality than ordinary waking consciousness. Furthermore, EBT extrapolates the Freudian concept of *the ego*, or our sense of self, to have a neurological underpinning in the neural resting state of the *default mode network* (DMN) coupled with the *medial temporal lobe* (MTL), and oscillatory activity in the *posterior cingulate cortex* (PCC). This neurological basis of ego is then seen as a mechanism for suppressing entropy, related to *primary consciousness*, and keeping the brain in the subcritical, normal waking state, of *secondary consciousness.*

IIT, on the other hand, is an already well-established and elaborate theory on consciousness with roots in mathematics, philosophy, computation, and neuroscience. IIT is an attempt to conceptualize consciousness in a way that enables computation of its presence and intensity. In IIT consciousness is defined as, and synonymous with, subjective experience and phenomenology (Oizumi, Albantakis, & Tononi, 2014; Tononi, Boly,

Massimini, & Koch, 2016). IIT explains the relationship of mind and brain by first examining experience itself and deriving self-evident *axioms* from introspection. From these axioms, associated *postulates* are formulated which a physical system should support to account for consciousness. With the human brain being one such system IIT predicts certain areas to be essential for conscious experiences, such as the cerebral cortex (Tononi et al., 2016). In its essence, IIT states that the quantity of consciousness refers to a system's capacity to integrate information while the quality lies within the conceptual structure of experience. As such, IIT can conceptualize and explain why consciousness changes as the capacity for information integration changes, like it does when we fall asleep naturally, or under anesthesia, or are under the influence of conscious altering substances (Sarasso et al., 2015). The IIT formalization of alterations in information integration works well to describe the data of changes in the cerebral cortex associated with the different stages of sleep (Casali et al., 2013), and so it would be expected that IIT can have explanatory power on the psychedelic altered state of consciousness.

This thesis is a literature review covering recent studies on classic psychedelic compounds and two theories of consciousness. There are other theories which comment on the psychedelic ASC, both from the previous era of psychedelic research and today (Swanson, 2018). However, in regards to the scope of this thesis, limiting to only these two theories in particular, have been a question of prioritization. The theories were chosen in regards to their differences, IIT being an established theory of consciousness with computational roots and EBT being a novel hypothesis with psychoanalytic influence, and their similarities, both make statements about the neurological correlates of subjective

experience. The literature has specifically been chosen to cover the resting state brain activity of the psychedelic ASC. A further limitation is that studies specifically cover LSD or psilocybin as they are similar in pharmacology and effect, as well as being two of the more studied of the classic psychedelics within brain imaging research and have comparable results (Müller, Liechti, Lang, & Borgwardt, 2018a). To find relevant articles, search engines with material on specifically cognitive neuroscience and psychology was used, for example, PubMed, Web of Science and Google Scholar. Examples of keywords included; 'psychedelics', 'neuroimaging', 'hallucinogens', 'entropic brain', 'LSD', and 'psilocybin'. The search included studies from the years 2000-2019, to ensure the relevance of content and method of design. Older studies lacked proper control groups, and relevant neuroimaging studies have only been conducted the past years. To find updated material on IIT, the website integratedinformationtheory.org was consulted. As the field of psychedelic research is in its renaissance phase, new studies are continuously being published, and there is difficulty keeping up while writing. What is reported in this thesis may very well be old news within the coming years.

Psychedelic research is a converging field of psychology, pharmacology and cognitive neuroscience, and finding the proper balance for this thesis has been difficult. In the following, the aim is to give the reader a sufficient understanding of LSD and psilocybin in regards to their history, safety, psychological effects, and pharmacology. More effort has been directed towards neuroimaging studies of the brain at rest, as they provide the best basis for the theoretical chapters. There is undoubtedly more to be said about the psychedelic ASC, specifically in phenomenological aspects and pharmacological effects.

Hopefully, the following chapters will provide a sufficient inlet to the field of psychedelic neuroscience and its associated theoretical framework.

To initiate the reader the first chapter will introduce the substances known as psychedelics, and provide relevant background on historical and safety aspects. The second chapter will cover their psychological effects and modern therapy studies. The third chapter covers the mechanisms of action, with a brief pharmacological profile and a more detailed coverage of recent neuroimaging studies. After that, the entropic brain theory will be introduced, followed by a chapter on integrated information theory. The last chapter is a discussion, covering the neural basis of the psychedelic ASC, how recent studies have contributed to consciousness research and a comparison of the two theories.

Background

The term 'psychedelics' was initially introduced by psychiatrist Humphry Osmond (1957) and means 'mind-manifesting', from English 'psyche' and greek 'delios' (manifest), and is thought to capture the core of the psychedelic experience. Other nomenclature includes, 'hallucinogens' which highlights the visual perceptual changes induced by psychedelics, and 'psychotomimetic', referring to psychedelics ability to mimic psychotic symptoms (Preller & Vollenweider, 2016). However, considering that actual hallucinations and psychotic symptoms are very rare at standard dosing, and only address a particular aspect of the experientially rich ASC (Johnson et al., 2018; Murnane, 2018; Nichols, 2016), the term psychedelics is arguably a better portrayal (Carhart-Harris, 2018c; Carhart-Harris & Goodwin, 2017).

There are other substances studied today with psychedelic-like effects, known as atypical or non-classical psychedelics. They include the empathogen 3,4-Methylenedioxymethamphetamine (better known as MDMA or ecstasy), the dissociatives ketamine, phencyclidine (PCP), and ibogaine, as well as cannabinoid agonist tetrahydrocannabinol (THC) (Calvey, & Howells, 2018). These atypical psychedelics have different pharmacological mechanisms, and they differ markedly from the experiential profile of classic psychedelics. Therefore, they are regarded to only have a psychedelic-like effect rather than an equivalent classic psychedelic ASC (De Gregorio, Enns, Nuñez, Posa, & Gobbi, 2018; Preller, & Vollenweider, 2016).

History

Considering the historical and cultural use of psychedelics together with their legal status, a section briefly covering some of their backgrounds seems warranted. Historically, psychedelic substances have roots in indigenous cultures. In North American native cultures the use of *peyote*, a cactus containing the classic psychedelic compound mescaline, dates as far back as 5 700 years (Bruhn, De Smet, El-Seedi, & Beck, 2002) and is still used by the Native American Church (Nichols, 2016). In South America, there is evidence for widespread sacramental use of various psilocybin mushrooms in pre-Columbian Mesoamerican cultures. Even today, there is a religious use of sacred mushrooms mixed with Catholic traditions (Carod-Artal, 2015). Another historic psychedelic is the Amazonian brew *ayahuasca*, which is prepared using two different plants. The active ingredient in ayahuasca comes from the Psychotria viridis leaves which contain DMT. Ayahuasca is today

used outside the amazons in the syncretic churches Santo Daime, and União do Vegetal (Johnson et al., 2008; Nichols, 2016). It is noteworthy that within the practice of indigenous use of psychedelic substances there is a common theme of restricted use for sacramental and healing purposes (Johnson et al., 2008), often accompanied by music and song (Carhart-Harris et al., 2018b).

The use of classic psychedelics in western culture is a rather new phenomenon in comparison. The psychoactive effects of LSD were discovered by Albert Hoffman first in 1943, five years after he first synthesized LSD at the pharmaceutical company Sandoz in Switzerland (Shroder, 2014). Psilocybin mushrooms were introduced to the American mainstream in 1957 through a photo reportage titled *Seeking the Magic Mushroom* in the popular magazine Life, portraying the adventure of wealthy mycologist Gordon Wasson (1957) and his wife Valentino partaking in the ceremonial use of sacred mushrooms.

The early research on LSD in the 50s and 60s showed promising results in the treatment of cancer-related stress and addiction (Johnson et al., 2018) and promoted our understanding of how the neurotransmitter serotonin is related to brain function (Nichols, 2016). However, the early therapy studies did not have the rigorous study designs as we have today (with control groups), so the findings are merely suggestive of their therapeutic capabilities (Johnson et al., 2008). Still, there is much to be learned from this first era of psychedelic research. For example, in research where LSD was given to constrained patients without consent, or in the US military's interrogation studies on unknowing civilians, results had a dominantly negative impact on the subjects (Carhart-Harris et al., 2018b; Johnson et al., 2008). These early studies did not take ‘set and setting’ into account.

Where 'set' refers to the participant's mindset, experience, and previous mental preparation while 'setting' refers to the physical environment the subject is in. When set and setting were accounted for results grew positive both for safety and efficacy (Carhart-Harris et al., 2018b).

The use of classic psychedelics is seemingly lower today than in the hippie era of the 70s, at least in comparison to surveys covering college students use of psychedelics in the United States (Johnson et al., 2018). In an epidemiological review by Johnson et al. (2018) data presented from the 2016 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggests that the rate of 'LSD and psilocybin use the past 12 months' is less than 1 % for a population between the ages of 15-34. Accordingly, the latest EMCDDA (2018) drug report confirms that the recreational use of LSD and psilocybin mushrooms are generally low in Europe and have been for the past years. Johnson et al. (2018) also present data from different population-level studies in which the use of classic psychedelics is not linked to any mental health issues. Rather, they are at some level linked with the decreased likelihood of mental health issues, such as suicidality and a decreased risk of opioid abuse. However, Johnson et al. (2018) also state that, based on early research on LSD, rates for developing psychosis after administration "range from .08% to 4.6%, with higher rates among psychiatric patients" (p.3). So, even if some population-based studies portray beneficial results from the use of psychedelics, they are still accompanied by risk.

Safety of Psychedelic Research

Classic psychedelics are considered physiologically safe as they have a low toxicity profile and very low potential for abuse (Calvey, & Howells, 2018; Nichols, 2004, 2016). As previously mentioned, the primary safety concern for psychedelic research today is the risk of a *bad trip* - an acute negative psychological experience, including anxiety, fear, dysphoria, and confusion. Other risks of importance are prolonged adverse psychological reactions such as psychosis, and a cardiovascular event due to the immediate effect of raised blood pressure and heart rate (Johnson et al., 2018). The two latter can best be avoided through screening of participants. Any patient with severe cardiac disease should be excluded from studies to avoid an incident according to Johnson et al. (2018), although it should be noted that psychedelics only moderately increase blood pressure and pulse.

Notably, the risk of prolonged psychosis is scarce, in a survey covering studies in the 60s only one person of 1200 healthy participants had a psychotic reaction lasting more than 48 hours, and this person was the identical twin of a schizophrenic patient. Of the patient groups, the risk of prolonged psychosis was slightly higher, 1.8 per 1000 patients, and in such cases, it is difficult to know if the psychedelic triggered an immanent psychosis or if it caused it (Johnson et al., 2008). Screening should, therefore, exclude any participants with schizophrenia or other psychotic disorders as these patient groups would be expected to be more vulnerable to a prolonged psychosis following psychedelic administration. Depending on the design of the study, other mental health pathologies should be screened as well, both for specific inclusion, and exclusion as their symptoms may confound the effects of psychedelics (Johnson et al., 2008).

To minimize the main risk of bad trips in modern psychedelic research, set and the setting should always be taken into account as the context of a psychedelic experience is indicative of its outcome (Carhart-Harris et al., 2018b; Johnson et al., 2008; Studerus, Gamma, Kometer, & Vollenweider, 2012). This is done by proper preparation of the participant by having multiple therapy sessions before the drug session, to form a bond of trust and report with the study personnel (Carhart-Harris et al., 2018b; Johnson et al., 2008). The environment where the drug session will take place is also an essential factor. In a study using pooled data of 246 healthy volunteers receiving psilocybin in a research setting, Studerus et al. (2012) found that the laboratory setting using positron emission tomography was most indicative of an anxious experience. When possible, experiment rooms are furnished more like living rooms and made so the participant can lie comfortably. It is common that subjects listen to carefully chosen music with eye shades on during drug action for comfort. Depending on the design of the experiment certain precautions are taken into place to ensure the participant's safety. For example, when conducting neuroimaging studies it may be preferable to use participants who have been scanned before and/or non-naive psychedelics users as the setting is strenuous (Carhart-Harris et al., 2018b; Johnson et al., 2008).

Another possible outcome from psychedelic use is *hallucinogen persisting perception disorder* (HPPD), a disorder included in the *Diagnostic and Statistical Manual of Mental Disorder, 5th edition*. The criteria for diagnosis include that the patient experiences perceptual symptoms similar to that of the acute psychedelic experience the patient had while under the influence of a hallucinogen, that this causes significant distress, and is not

related to any other medical treatment or psychiatric disorder. The rate of HPPD is presumed to be very low considering the number of people who have taken psychedelics (Nichols, 2016), and its classification criteria are mainly based on LSD research (Studerus, Kometer, Hasler, & Vollenweider, 2011). In a review of 110 healthy volunteers which had received psilocybin in a research setting, Studerus et al. (2011) found no indication of HPPD, and strong acute adverse effects were limited to the highest dose conditions (315 µg/kg).

Psychological Effects

The ASC induced by classic psychedelics has a wide range of dose-dependent, subjective effects (Studerus et al., 2011, 2012) and is known to have rapid antidepressant effects (Calvey, & Howells, 2018; Rucker, Iliff, & Nutt, 2018). As the duration of psilocybin lasts between 4-6 hours compared with LSDs 8-12 hours, it is the preferred substance for therapy. As yet, there is only one modern study using LSD in the treatment of psychiatric illness (Gasser et al., 2014). The presented studies have primarily used low, moderate or high-doses, whereas there are ongoing studies on the trending microdoses. Psilocybin doses will be referred to as very low (45µg/kg), low (115-125 µg/kg), medium (215-260 µg/kg) and high doses (315 µg/kg) (Studerus et al., 2011). LSD doses are considered low to moderate at 40-80 µg, moderate 75-100 µg, and high at 200 µg or more (Liechti, 2017). This chapter will cover the acute psychedelic effects and long term outcomes of recent clinical studies on patients and healthy adults.

Acute Subjective Effects

The acute subjective effects of classic psychedelics are considered to have the same profile even though they differ in duration (Liechti, 2017; Preller & Vollenweider, 2016). However, it is not until recently that validated psychometric scales, such as the often applied *five dimensions of altered states of consciousness* rating scale (5D-ASC), have been used. The five dimensions are; oceanic boundlessness, anxious ego-dissolution, visionary restructuralization, acoustic alterations, and vigilance reduction (Preller & Vollenweider, 2016). Ratings of which both LSD and psilocybin increase in all dimensions (Liechti, 2017; Studerus et al., 2011). While the 5D-ASC is not exclusive in describing the phenomenology of the psychedelic altered state, it will be used as a foundation to explain the acute subjective effect. Studies also use alternative questionnaires, often complementary to the 5D-ASC, to further evaluate specific aspects of the experience.

Oceanic Boundlessness (OBN) refers to a pleasurable unitative experience with one's surroundings were the sense of self may dissolve, a type of "transcendent of time and space". It is related with pleasurable ego-dissolution and spiritual experiences and includes all positive feelings which may arise during the psychedelic experience, "from bliss to ecstasy" (Preller & Vollenweider, 2016, p. 225). *Anxious Ego-Dissolution* (AED) is then the negative side of depersonalization and loss of control, often felt together with anxiety or even panic. It includes "thought disorder, paranoia, loss of thought control, and loss of body control" (Preller & Vollenweider, 2016, p. 226) and characterizes the notion of a bad trip. *Visionary Restructuralization* (VR) encompasses all the visual alterations typical to the psychedelic state. Changes in visual perception range from elementary such as geometrical

shapes, to complex hallucinations with semantic content and may include objects or people, and even synesthesia may occur. Elementary visual hallucinations, intensity in colors and shapes, and experiencing movement in objects, are much more common with psilocybin and LSD than complex hallucinations. *Acoustic Alterations* (AA) refers to any auditory alterations, sensitivity or hallucinations. Again, actual hallucinations are rare for psilocybin and LSD. A more common experience is that listening to music becomes intensified with psychedelics, however, it could be a consequence of the distortion of time perception or cognition, rather than an auditory alteration. *Vigilance Reduction* (VR) includes any sensation of reduced alertness, such as dreaminess and/or sleepiness (Preller & Vollenweider, 2016).

The psychedelic experience is a dynamic process where the person goes through different stages of perceptual change over time, of which the peak can be an experience of losing one's self, or ego, a process called *ego-dissolution* (Preller, & Vollenweider, 2016). Ego-dissolution is highly interrelated with the dimension of OBN. Another, peak-experience of the psychedelic ASC related to the ego-dissolution, and the OBN dimension, is a *mystical type-experience*. The core features of the mystical experience are described in MacLean, Johnson, & Griffiths (2011) as:

> … feelings of unity and interconnectedness with all people and things, a sense of sacredness, feelings of peace and joy, a sense of transcending normal time and space, ineffability, and an intuitive belief that the experience is a source of objective truth about the nature of reality (p. 1453)

In a study by Griffiths et al. (2006) such mystical-type experiences could be induced by psilocybin in healthy, drug-naive, religious or spiritual, participants. In a 14 month follow-up, the majority of the participants reported the experience to be one of the five most meaningful experiences of their lives and had increased well-being (Griffiths et al., 2008). Furthermore, MacLean et al. (2011) used data from two studies on drug-naive participants receiving a high-dose of psilocybin, and found significant changes in the personality trait openness one year later, and only in participants who reported a mystical type experience. The relevance of these kinds of profound experiences in the research will be referred to throughout this paper.

Therapeutic Effects

The modern psychedelic research era has provided eight relevant therapeutic studies for this thesis, requiring them to cover LSD or psilocybin and be published between 2000-2019. See Table 1 for an overview of these studies and their reported adverse events, in the following their results will be discussed.

Table 1. *Adverse reactions following therapy with LSD or psilocybin*

Reference	Diagnosis	Sample	Drug/ Dosage	Adverse Events (Immediate)	Adverse Events (Delayed)
Bogenschutz et al. (2015)	Alcoholism	10 Alcohol dependence	Psilocybin 300 µg/kg or 400 µg/kg	Mild elevation of BP 1 vomiting, 1 diarrhea, 1 insomnia	1 dropped out after first treatment
Carhart-Harris et al. (2016a)	Depression	20 Treatment resistant major depressive disorder	Psilocybin 10 mg & 25 mg	1 'patient became uncommunicative' during the drug effect (duration not stated) 15 'transient anxiety lasting for minutes' 5 'transient nausea' 3 'transient paranoia	8 'headaches lasting no longer than 1-2 days' No 'flashbacks or persisting perceptual changes' 5 'sought and successfully obtained psilocybin between 3 & 6 months' [after treatment]

Gasser et al. (2014)	Life threatening disease	12 Anxiety disorder secondary to an advanced cancer diagnosis	LSD 200 µg & LSD 20 µg (control)	18 reports of adverse events in LSD group vs. 8 in active placebo group	6 reports of mild adverse events persisting until the next day No 'lasting psychotic or perceptual disorders'
Griffiths et al. (2016)	Life threatening disease	51 Life-threatening cancer with anxiety and depression	Psilocybin 22mg/70 kg or 30mg/70 kg & Psilocybin 1mg/70 kg or 3mg/70 kg	34% systolic BP > 160 mmHg (high dose) 13% diastolic BP > 100 mmHg (high dose) 15% 'nausea or vomiting' 21% 'physical discomfort (of any type) (high dose) 32% 'psychological discomfort (of any type) (high dose) 26% 'anxiety' (high dose) 1 'headache' 1 'transient paranoid ideation' (high dose)	No 'cases of hallucinogen persisting perception disorder or prolonged psychosis' 2/11 'delayed moderate headache after this high dose session'
Grob et al. (2011)	Life threatening disease	12 Anxiety/ adjustment disorder secondary to an advanced cancer diagnosis	Psilocybin 200 µg/kg, & Niacin 250 mg (control)	Mild elevation of HR and diastolic BP	No adverse psychological reactions from the treatment'
Johnson et al. (2014)	Tobacco addiction	15 Tobacco addiction	Psilocybin 20 mg/70 kg or 30 mg/kg	10/42 (23.8%) sessions included strong or extreme feelings of 'fear, fear of insanity or feeling trapped' Mild increases in BP/HR	8/10 participants reported transient, mild post psilocybin headache responsive to simple analgesia No increases in objective Bothersome visual effects at 6 months
Moreno et al. (2006)	OCD	9 OCD	Psilocybin 25 µg/kg, 100 µg/ kg, 200 µgkg & 300 µg/kg	1 transient hypertension (mild) 2 dropped out after session 1 'due to discomfort with hospitalisation'	Not reported
Ross et al. (2016)	Life threatening disease	29 Cancer related anxiety and depression	Psilocybin 300 µg/kg & Niacin 250 mg (control)	Statistically significant increases in BP/HR 28% 'headaches/ migraines' 14% 'nausea' 17% 'transient anxiety' 7% 'transient psychotic-like symptoms'	No 'participants abused or became addicted to psilocybin' No 'cases of prolonged psychosis or hallucinogen persisting perception disorder' No 'participants required psychiatric hospitalisation'

Note. This table is a revised version of the comprehensive "Table 1" in Rucker et al. (2018, p. 206-209). Revisions were made to better suit its purpose here, for example, limiting the studies to be from 2000-2019 and only include LSD or psilocybin. BP = Blood Pressure; HR = Heart Rate; OCD = Obsessive Compulsive Disorder.

The first study investigated the effect of psilocybin on OCD symptoms (Moreno et al., 2006). Patients were given four doses of psilocybin, varying from very low to high, with a minimum of 1 week apart. The first dose was an open-label, low dose (100μg/kg), the following three doses were increased in strength and the very low dose was randomly inserted in this order, in a double-blind setup. Ratings of OCD symptoms was done at intervals 0, 1, 4, 8, and 24 hours after dosing. OCD symptoms were significantly decreased in all dosing conditions, with a significant main effect of time, no differences for the different doses were found.

In an open-label study by Johnson, Garcia-Romeu, Cosimano, and Griffiths (2014) psilocybin were given in conjunction with a 15-week cognitive behavior therapy (CBT) protocol to assist smoking cessation. Psilocybin was administered three times in this program, the first dose was moderate and participants had the option to stay at the same dose or take a higher dose the remaining sessions. The mean weekly cigarette consumption was 19 per day, with a habitual mean of 31 years, and an average of 6 previous attempts to quit. Biological markers and self-report measures were used to assess smoking status. At 6 months, 12 (80%) participants showed smoking abstinence. A later follow-up study (Johnson et al., 2017) showed sustained abstinence in 67% of participants at 12-months, and 60% at 16 months. One patient was referred to further counseling post-treatment due to the resurfacing of childhood trauma during the psilocybin session (Johnson et al., 2017), highlighting the importance of proper support during psychedelic therapy. Compared to other smoking cessation programs these results are highly significant, however, the open-label design, small number of patients and lack of controls, compromises this

generalization (Johnson et al., 2017). Additionally, the positive effects were correlated with the intensity of the psychedelic experience. Garcia-Romeu et al. (2014) reported a significant correlation between the "psilocybin-occasioned mystical experience" and treatment responders. At the 12 months follow up, 13 participants rated the experience to be "among the five most personally meaningful of their lives" (Johnson et al., 2017, p. 58).

Another open-label study (Bogenschutz et al., 2015), administered two high doses of psilocybin to persons with alcohol dependence. In a 12 week intervention, with 14 sessions, psilocybin was given at week 4 and 8. Results showed a significant decrease in drinking behavior after the first psilocybin session at week 4 and were sustained at week 36. Treatment outcome correlated with the quality of the acute experience, both the mystical quality and other acute effects. Bogenschutz et al. (2015) argue that further work is necessary to determine what qualities of the experience is related to therapeutic outcome. Notably, the authors remark that people with alcohol dependence are not as sensitive to psilocybin than healthy participants, a feature that was observed from research in the 60s.

Carhart-Harris et al. (2016a) studied the effects of psilocybin on patients with treatment-resistant depression (TRD). The study used two doses, one lower test dose, and one high therapeutic dose. Psychological support was given before, during and after psilocybin sessions. Significant reductions in depression were seen at "1, 2, 3 and 5 weeks, and at 3 and 6 months follow up" (Rucker et al., 2018, p.211), with maximal effect at 5 weeks post-treatment (Carhart-Harris et al., 2016a, 2018a). The quality of the acute effects predicted the long-term outcome, with a particular quality of high OBN and low anxiety

being positive and high acute anxiety with a negative outcome (Roseman, Nutt, & Carhart-Harris, 2018). Roseman et al. (2018) argue that the mystical type and peak experiences are predictive of outcome and should be promoted in therapy, but also notes that anxiety and resistance is a part of *emotional breakthrough*. Future questionnaires should take this into account in order to assess resolution and not only resistance.

Four independent studies have investigated the effect of psychedelics in the treatment of end-of-life related distress (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). The Grob et al. (2011) study was double-blind, had an active placebo, used a moderate dose of psilocybin, and patients were their own control. All participants had advanced cancer with stress, anxiety and adjustments disorders. Results showed trends for improvement in mood but were non-significant. Ross et al. (2016) did a larger, double-blind, placebo-controlled, cross-over trial, using a slightly higher dose of psilocybin and the same placebo. Patients showed both rapid and sustained decreases in anxiety and depression after their psilocybin session, with an increased quality of life at over 6 months follow-up. Again, the positive results correlated with acute mystical-type experience. The third study, by Griffiths et al. (2016) was the largest, and also had a double-blind, placebo-controlled, cross-over design. The study used two conditions, where a very low psilocybin dose served as placebo to compare the high treatment dose. The high dose condition significantly decreased anxiety and depressive mood, together with a greater quality of life. These results were sustained at a 6-month follow-up and were also suggested as a mediator for positive outcomes. It is noteworthy that with all cross-over trials the blind is broken when the placebo groups cross-over to psilocybin, by the intensity

of the psychedelic experience. The differences in the above-mentioned studies may be due to variations in the degree of psychological support (Rucker et al., 2018).

Lastly, the only modern study using LSD for therapy was done by Gasser et al. (2014, 2015). In a double-blind, randomized, placebo-controlled trial, LSD was given in conjunction with psychotherapy for anxiety related to terminal illness. Placebo was a low dose of LSD. Using the State-Trait Anxiety Inventory, results showed significant state anxiety reduction and non-significant decreased trait anxiety, these results were sustained for 12 months. In a 12 months qualitative follow-up (Gasser et al., 2015) participants reduction in anxiety was sustained and a greater quality of life detected: " the improvement in psychopathological symptoms was accompanied by positive psychological changes in the subjects (e.g. increases in relaxation, equanimity, self-assurance, mental strength)" (p. 64).

Overall, the studies show that these substances can be safely administered to patients with no significant adverse effects. The intensity of the experience is correlated with positive outcome, but it is important to keep in mind that the psychedelic state can also be a challenging experience. Based on their limited sample sizes and design, no certainty can be inferred from these results. Although, they do indicate that the psychedelics LSD and psilocybin may provide a promising tool in psychiatric treatment, and deserves further study (Rucker et al., 2018). Further investigation in dosage and frequency is necessary, phenomenological studies are needed to explore what specific qualities are therapeutic in the psychedelic ASC, neuroimaging can help to characterize the effects of these substances, both acute and long term (Bogenschutz et al., 2015).

Mechanisms of Action

This chapter will present an overview of how psychedelics alter neuronal activity through receptor stimulation, contributing to further change in oscillatory power and resting state brain networks. The main focus will lie on the recent neuroimaging data but first, a pharmacological profile will be presented, for a more detailed account regarding the pharmacology of LSD and psilocybin, the reader is encouraged to read Nichols (2004, 2016) and De Gregorio et al. (2018).

Pharmacological Interaction

The classic psychedelics mainly exert their influence over the brain through the serotonin system, which is also the main neurotransmitter involved in depression disorders (De Gregorio et al., 2018). The main mechanism of action for the classic psychedelics is generally attributed to their agonist, or partial agonist, effect on the serotonin 2A (5-HT2A) receptor (De Gregorio et al., 2018; Nichols, 2016; Preller & Vollenweider, 2016). The subjective psychedelic effect has successfully been blocked by pretreatment with ketanserin, a 5-HT2A receptor antagonist, a result demonstrated with both psilocybin (Kometer, Schmidt, Jäncke, & Vollenweider, 2013; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998) and LSD (Preller et al., 2017, 2018, 2019). They also show further agonist involvement on the serotonin 1A and 2C receptors (Nichols, 2016).

Classic psychedelics indirectly affect the dopaminergic system, primarily through D2 receptors, and the glutamatergic system (De Gregorio et al., 2018; Nichols, 2016). LSD has been shown to have a partial agonist effect on the D2 receptor in rats, similar to that of the 5-HT2A receptors, expressed in a time-dependent manner. Studies on rats further indicated that there are two phases of LSD action, where the first phase is induced by 5-HT2A receptor agonism and the second phase is mediated through D2 receptor agonism (De Gregorio et al., 2018; Nichols, 2016). A newly discovered receptor TAAR1 has also shown to affect the behavioral effects of LSD in rats, however, these are new findings and how they relate to psychedelics mechanism of action in humans remains to be investigated (De Gregorio et al., 2018). Other rodent studies have shown that psychedelics promote structural and functional neuronal plasticity (Ly et al., 2018).

The expression of the 5-HT2A receptor is found across the neocortex (Erritzoe et al., 2009), specifically in the visual, orbitofrontal, medial prefrontal, superior temporal and cingulate cortices (Erritzoe et al., 2009; Forutan et al., 2002), most densely expressed in layer 5 pyramidal neurons (Berthoux, Barre, Bockaert, Marin, & Bécamel, 2018). While the 5-HT2A receptors are not as dense in the hippocampus, this is an area more known for 1A receptor density (Nichols, 2016). Notably, the cerebellum has no binding potential for the 5-HT2A receptor.

Furthermore, there is an indication of the classic psychedelics capacity to affect gene expression and modulation, which may be the mechanism behind their neuroplasticity promoting effect (Calvey, & Howells, 2018).

Neuroimaging Studies

There is far from an abundance of neuroimaging studies on classic psychedelics, and even less so when they are reduced to only LSD and psilocybin. As the main focus of this section is to assess how psychedelics alters brain activity to alter consciousness, the presented material will cover the brain at rest. This is also a more discussed area in the literature. It has a further advantage, at this early stage of psychedelic research, as resting state studies lack the confounding variable between task engagement and normal activation (Whitfield-Gabrieli & Ford, 2012). Notably, there is no encephalography (EEG) studies included in this overview. The two magnetoencephalography (MEG) studies have been chosen to suffice as the more accurate temporal data measures. In the following neuroimaging section, three data sets on LSD and four data sets on psilocybin will be addressed. Covering a total of 19 publications, see Table 2 for an overview of used dosages and how the different datasets reoccur in the literature. Because of their sparse number, even converging results are to be taken with circumspection.

Table 2. *Resting state studies and their frequency in the literature*

Reference	Participants	Dose	Method	Used in these studies
Carhart-Harris et al. (2012)	n=15 healthy adults	Psilocybin, 2 mg, i.v.	fMRI	Atasoy et al. (2018); Carhart-Harris et al. (2013); Lebedev et al. (2015) Petri et al. (2014); Roseman et al. (2014); Tagliazucchi et al. (2014, 2016*)
Carhart-Harris et al., (2016b)	n=20 healthy adults	LSD, 75 µg, i.v.	fMRI + MEG	Atasoy et al. (2017) Lebedev et al. (2016); Schartner et al. (2017)*; Tagliazucchi et al. (2016)*
Carhart-Harris et al. (2017)	n= 15 with treatment-resistant	Psilocybin, 10 mg & 25 mg, orally	fMRI	

	depression			
Lewis et al. (2017)	n=58 healthy adults	Psilocybin, 0.16 or 0.215 mg/kg, orally	fMRI	
Müller et al. (2018b)	n=20 healthy adults	LSD, 100 µg, orally	fMRI	Müller et al. (2017)
Muthukumaraswamy et al. (2013)	n=15 healthy adults	Psilocybin, 2 mg, i.v.	MEG	Schartner et al. (2017)*
Preller et al. (2018)	n=25 healthy adults	LSD, 100 µg, orally	fMRI	Preller et al. (2019)

Note. The amount of participants presented here does not necessarily correspond with how many were used for statistical analysis by the different studies, as they may differ in suitability. fMRI = functional Magnetic Resonance Imaging; MEG = Magnetoencephalography; i.v. = intravenous. *These references appear twice, as they use two data sets in their study.

The default mode network. There is an overall theme in many of the following neuroimaging studies which state that psychedelics specifically alter the *resting state network* (RSN) known as *the default mode network* (DMN). This is a well-defined network representing how the brain acts during rest where we spontaneously arrive at self-referential thoughts and feelings about "the past and present states and possible future states" (Whitfield-Gabrieli & Ford, 2012, p. 51). Anatomically, the main regions of the DMN are the medial prefrontal cortex (mPFC), PCC and retrosplenial cortex (RSP), the inferior parietal lobules (IPLs), and the MTL. These areas are more active during rest than in goal-directed activities. The PCC is considered *the hub* with the widest range of connections. When we engage in a goal-directed task the DMN is suppressed and other, *task-positive networks* (TPNs), are engaged. Therefore, the DMN is also known as *the task-negative network*. Using *functional magnetic resonance imaging* (fMRI) an

anticorrelation of these networks have been found, brain regions active during rest (DMN) are simultaneously deactivated as regions of TPNs are activated (Whitfield-Gabrieli & Ford, 2012). Additionally, there are other identified networks, such as the dorsal attention network, the salience network, visual and auditory networks (Whitfield-Gabrieli & Ford, 2012), often referred to as TPNs (Carhart-Harris et al., 2013). These RSNs show variations in *between* and *within* connection during rest and activity. *Between*-network connectivity or *coupling*, refers to the connectivity between two networks as a whole, such as the normally anticorrelated connectivity between the DMN and TPNs. *Within*-network connectivity refers to the coactivation of a certain network region with the rest of that network (Müller et al., 2018a). A greater DMN hyperactivity and a reduced DMN-TPN anti-correlation is found in both depression and schizophrenia. As well as first-degree relatives to schizophrenic patients, ruling out that this finding is a sufficient diagnostic. It is speculated that this DMN overactivation is related to these pathologies enhanced "focus on the inner mental world" (Whitfield-Gabrieli & Ford, 2012, p. 65).

The resting brain on psychedelics. In a recent review, Müller et al. (2018a) took a closer look at resting state studies of classic psychedelics and found studies which had comparable results due to similarities in methodology. First, these comparable findings will be presented, with a focus on converging or differing results, for a further detailed discussion of possible reasons for these differences see Müller et al. (2018a). After this, further findings from the non-comparable studies with different analysis methods will be addressed, and then post-treatment fMRI scans.

Comparable neuroimaging studies. In regards to *cerebral blood flow* (CBF), comparable results in psilocybin are found in Carhart-Harris et al. (2012) and Lewis et al. (2017). Lewis et al. (2017) had a larger sample size and tested two different psilocybin doses to control for global effects on CBF, with differing results than Carhart-Harris et al. (2012). However, there were also converging results of "decreased CBF in the precentral gyrus, angular gyrus, precuneus, insula, thalamus and putamen" (Müller et al., 2018a, p.165). In the LSD study (Carhart-Harris et al., 2016b), increased CBF was shown in the visual cortex, a very different finding than the psilocybin studies. Müller et al. (2018a) propose these divergent findings between substances may be due to unknown differences in neuronal, or vascular effects.

In regards to *functional connectivity* (FC), increased between-RSN-FC have been found for both LSD (Carhart-Harris et al., 2016b; Müller, Dolder, Schmidt, Liechti, & Borgwardt, 2018b) and psilocybin (Carhart-Harris et al., 2013; Roseman, Leech, Feilding, Nutt, & Carhart-Harris, 2014). One specific anticorrelation between TPNs and DMN was disturbed by psilocybin as their between-RSN-FC significantly increased (Carhart-Harris et al., 2013). While all studies did show increased between-FC for different network couplings, Müller et al. (2018a) found that these studies have inconsistencies in their in RSN-FC alterations. The reasons which are unclear, Müller et al. (2018a) speculate that it may be due to differences in study conditions, methods of analysis, or choice of administration (oral or intravenous). Furthermore, there might be specific differences between LSD and psilocybin, although they found inconsistencies between the two LSD studies as well.

Within-RSN-FC have only been studied in LSD (Müller et al., 2018a). Only decreased within-RSN-FC was found in LSD by Carhart-Harris et al. (2016b), for "DMN, sensorimotor network, two visual networks, the parietal cortex network, and the right frontoparietal network" (Müller et al., 2018a, p. 167). Another LSD study by Müller et al. (2018b) found similar results, with decreased within-FC in DMN, sensorimotor network and visual networks. They differ in that the frontoparietal network was not affected in Müller et al. (2018b) and they did not assess the parietal network. While Carhart-Harris et al. (2016b) found a correlation between decreased within-FC of the DMN and ego-dissolution, Müller et al. (2018b) did not. Notably, Müller et al. (2018a) point out that a study on serotonin reuptake inhibitors showed similar effects on the within-RSN-FC, and therefore, the effects could merely be "unspecific serotonergic" (p. 167) and not a significant characteristic of the psychedelic effect.

Global functional connectivity (GFC) is a measure which calculates "the average correlation" from one brain region to another (Müller et al., 2018a, p. 169). GFC has been comparably studied in both LSD and psilocybin by Tagliazucchi et al. (2016), and further in LSD by Müller et al. (2017). Tagliazucchi et al. (2016) found increased GFC in frontal, parietal, and temporal cortices, as well as the precuneus and thalamus. While these results are also under the scrutiny of being unspecific serotonergic effects, Tagliazucchi et al. (2016) found overlap of FC density with 5-HT2A receptor density but not with other serotonin receptors. Müller et al. (2017) did not find increased GFC in the cortical regions but used "a stricter correction for multiple comparisons" (Müller at al., 2018a, p. 170). They did, however, substantiate the finding of increased thalamic GFC, and found increased GFC

for parts of the basal ganglia. While Tagliazucchi et al. (2016) found correlations between increased FC in the temporoparietal junction and insula with ego-dissolution, Müller et al. (2017) found correlations between FC measures in the thalamus and the right fusiform gyrus and insula that correlated with visual and auditory perceptual changes.

Consequently, from these findings, the psychedelic state can be said to disrupt functional connectivity of the brain. Consistently showing increased GFC in thalamic areas for both LSD and psilocybin (Müller et al., 2018a), as well as disrupting within-RSN-FC and between-RSN-FC, although the latter did not show consistent results on specific RSNs. Müller et al. (2018a) note that two important integration hubs of the brain, the precuneus, and thalamus, are constantly involved in the findings and proposes these structures to be candidates for the neural basis of the psychedelic state.

Further findings. Tagliazucchi et al. (2014) further investigated the psilocybin effect with a new technique on temporal and dynamical changes in *blood-oxygen-level-dependent* (BOLD) signal, and "dynamical functional connectivity states" (p.4). They found significant variation of BOLD signal power in the hippocampus and anterior cingulate cortex (ACC), and notably, the novel dynamic functional connectivity analysis revealed an increased repertoire of new possible brain states for the psilocybin condition compared with placebo.

In another alternative analysis of the psilocybin data, Petri et al. (2014) examined the effects of psilocybin on networks through *homological scaffolding*. This investigation found that the psilocybin state showed less constrained and more integrated scaffolds than

placebo, and that novel structures appeared with wide brain connections in the psilocybin condition.

Lebedev et al. (2015) used the same psilocybin fMRI data to investigate the neural correlates of ego-dissolution, with a special interest in MTL region of the DMN. Lebedev et al.'s (2015) findings showed a specific correlation between ego-dissolution and the disintegration of the within-network connectivity between the MTL and the neocortex. Furthermore, they did not find a correlation of the disintegration of DMN and ego-dissolution, but an association between the salience network and ego-dissolution. The salience network has previously been indicated to be impaired in addiction (Lebedev et al., 2015), and this lends support to the therapeutic role of ego-dissolution or mystical-type experiences in psychedelic treatment of addiction. Another association found was that between ego-dissolution and "reduced interhemispheric connectivity" (Lebedev et al., 2015, p.11), implying that MTL interhemispheric connections may be important for the coherent sense of self. In another study, Lebedev et al. (2016) analyzed the data from LSD neuroimaging and found that acute global effect brain entropy could predict the significant two-week follow-up changes in trait openness, with more acute brain entropy followed a larger increase in openness. Lebedev et al.'s (2016) finding lends neurobiological support for the change in personality found by MacLean et al. (2011).

Using MEG to explore psilocybin-induced changes, Muthukumaraswamy et al. (2013) observed a decrease in oscillatory power of the posterior and frontal association cortices, specifically within the alpha frequency range of the PCC. They found a substantial decrease of oscillatory power in areas of the DMN, and no overall increases of oscillatory

power. Using dynamic causal modeling, they investigated the probable neuronal source underlying the psilocybin-induced frequency disturbance in the PCC. This showed an "increase in the excitability of deep-layer pyramidal cells" (Muthukumaraswamy et al., 2013, p. 15177). Muthukumaraswamy et al. (2013) note that this is an area dense of 5-HT2A receptors and propose that a key feature of the psychedelic mechanism of action is through excitation of layer 5 pyramidal neurons in the PCC, which in turn lead to cortical desynchronization and decreased stability of brain networks. Two items on their psychometric rating scales, relating to the sensation of ego-dissolution and the supernatural quality of the psychedelic experience, showed significant positive correlations with the decrease in alpha power of the PCC.

Using MEG data from studies on LSD, psilocybin and ketamine, Schartner et al. (2017) computed their respective neural signal diversity and entropy with Lempel-Ziv complexity, a measure that is reliably lowered in reduced states of consciousness, such as during sleep and anaesthesia (Schartner et al., 2015). All conditions showed increased global signal diversity compared with placebo, while LSD and ketamine had significant increases, and ketamine the highest. Spatially, the strongest signal diversity were measured in occipital and parietal areas for all substances, similar to the locations of alpha decrease found in Muthukumaraswamy et al. (2013). All of the substances showed correlations between the intensity of the psychedelic state and complexity measures, but differed in strength. Schartner et al. (2017) note that these are the first findings of a higher level of signal diversity in a state of consciousness, and further propose that Lempel-Ziv complexity may provide useful as a measure reflecting both level and content of consciousness,

suggesting that “increases in conscious level correspond to increases in the range of possible conscious contents” (p. 10).

Connectome-harmonic decomposition is a novel method of analyzing neuroimaging data using the approach of harmonic patterns, a naturally present mathematical function found in physics, biology, and electromagnetism, on the human-connectome (Atasoy et al., 2017, 2018). Brain activity is described as having frequence-specific repertoires of harmonic brain modes. Using connectome-harmonic decomposition, in the words of Atasoy (2017), is “not very different than decomposing complex musical pieces into its musical notes”. Using fMRI data from studies on LSD (2017) and psilocybin (2018), Atasoy et al. observed significant dynamical changes between the psychedelic state and placebo state. The psychedelic state demonstrates an increase in total power and energy of brain activity, a specific deactivation of low-frequency activity and promotion of higher frequency activity, and a total increased repertoire of possible connectome harmonic brain states. Atasoy et al., (2018) also describe how the brain works near criticality in normal states but “tune toward criticality in both, LSD and psilocybin-induced psychedelic states” (p. 113). These findings also found that the expanded repertoire is associated with the subjective intensity of the psychedelic ASC.

Preller et al. (2018, 2019) have covered a different data set on LSD. In the first study, Preller et al. (2018) examined GFC and compared it with gene expression across the brain to evaluate the role of the 5-HT2A receptor. They found that LSD reduced connectivity in subcortical and higher association networks, including “the medial and lateral prefrontal cortex, the cingulum, the insula, and the temporoparietal junction”

(Preller et al., 2018, p. 3). They further found that the LSD-induced alterations in subjective experience was significantly correlated with the increased connectivity in somatomotor and sensory networks, which include "the occipital cortex, the superior temporal gyrus, and the postcentral gyrus, as well as the precuneus" (Preller et al., 2018, p. 3). Significantly, participants with the most reduced connectivity in association networks also had the highest increased connectivity in somatomotor and sensory networks. Preller et al. (2018) interpret this pattern of reduced contra increased network connectivity as the underlying mechanisms for the LSD induced altered states, as there is an increased amount of sensory information which is not integrated due to a disruption in association networks. This study found that the gene expression of 5-HT2A receptors positively mapped onto areas LSD-altered GFC, supporting the role of this receptor for the psychedelic ASC. They further found a negative correlation with the 5-HT7 receptor expression, a finding worth exploring in future research. The second study by Preller et al. (2019), recently found that the LSD-induced altered connectivity of the thalamus is *directed to* the PCC and that this depends on the stimulation of 5-HT2A stimulation, as its effect was blocked with ketanserin. A new finding was that a decreased directed connectivity from the ventral striatum to the thalamus was evident even with ketanserin pretreatment. Implying underlying effects of LSD which is not 5-HT2A receptor dependent. Preller et al. (2019) propose that activation of 5-HT2A receptor stimulation in layer 5 pyramidal neurons in the mPFC interrupts cortical-striatal-thalamo-cortical (CSTC) feedback loops which affect thalamic gating of sensory and cognitive information to the cortex, resulting in the perceptual alterations of the psychedelic state.

Post-treatment fMRI scans. The resting state fMRI scans from the psilocybin for treatment-resistant depression group showed a significant correlation in decreases of amygdala CBF one day after psilocybin treatment and reduction of depressive symptoms (Carhart-Harris et al., 2017). The results on within-DMN resting state FC were increased compared to pretreatment scans, specifically, an increase in the ventromedial PFC and bilateral inferior-lateral parietal cortex areas of the DMN predicted therapeutic outcome five weeks after psilocybin. This is a divergent finding compared to the acute effects psychedelics have on the DMN. The authors explain this divergence by referring to results of a study in which precuneus-DMN-RSFC were lowered in patients than controls prior to electroconvulsive therapy (ECT), and was found to be normalized in the patients who responded. An analog to ECT is presented, where psychedelics work as "a 'reset' mechanism in which acute modular disintegration (e.g. in the DMN) enables a subsequent re-integration and resumption of normal functioning" (Carhart-Harris et al., 2017, p. 5). Furthermore, these areas are not found to be normally increased in depressed patients, which may strengthen the view of a re-integration approach (Whitfield-Gabrieli & Ford, 2012). Another finding from this study was a correlation between the peak experience and a decrease in parahippocampus-PFC RSFC, which also predicted the therapeutic outcome after five weeks.

General Limitations in Psychedelic Research

Psychedelics research are posed with some general difficulties, varying depending on the objective of a certain study. One big problem is the collection of valid subjective

reports during the acute drug phase without disrupting the experience (Carhart-Harris, 2018c). Many of the results, specifically in relation to the correlation of neurological activity and sensation of experience, lack replication and therefore these results should be regarded as preliminary (Müller et al., 2018a). Further neuroimaging studies in conjunction with psychiatric treatment would increase the understanding of their therapeutic effects. As the psychedelic effect varies over time it is crucial for comparable results that both subjective reports and neuroimaging are taken at similar time frames, as well as taking multiple measures to analyze the varying effects in the duration of the drug effect.

A limitation in the neuroimaging studies may be the possibility of confounding vascular effects which could impact results of CBF, and head motion which always is a problem in neuroimaging but could be more pronounced here due to drug action (Müller et al., 2018a). Furthermore, it is unknown if their difference in receptor affinity may affect neuronal structures significantly. Results from Preller et al. (2018) may indicate the role of the 5-HT7 receptor, as its density is negatively correlated with GFC. Furthermore, Preller et al. (2019) found LSD-induced directed connectivity unaffected by ketanserin.

It is also of worth to note, even if double-blind designs are to be preferred, the subjective effects of psychedelics are so intense that the blind is easily broken, especially without an active placebo (Carhart-Harris & Goodwin, 2017). While the use of non-naive psychedelic users may be a preference in strenuous neuroimaging settings, they are probably even more likely to break the blind as they are familiar with the psychedelic effects (Tagliazucchi et al., 2016).

Entropic Brain Theory

The entropic brain hypothesis is a novel theory on conscious states, originated by Robin Carhart-Harris and colleagues (2014), and further defined by Carhart-Harris (2018c). The theory states that the subjective quality, or *qualia*, of a certain experience is reflected in the measurement of the brain entropy. The theory is heavily influenced by the neuroimaging studies on psilocybin and LSD (Carhart-Harris et al., 2016a, 2016b, 2018a; Muthukumaraswamy et al., 2013; Schartner et al., 2017), from Carhart-Harris' research team at Imperial College London, and has gained further support from research on the classic psychedelics ayahuasca (Viol, Palhano-Fontes, Onias, de Araujo, & Viswanathan, 2017) and DMT (Carhart-Harris, 2018c). While EBT is a speculative hypothesis in development (Carhart-Harris et al., 2014; Carhart-Harris, 2018c), its main aim is to present a "mechanistic account of altered states of consciousness based on the quantity of entropy" (Carhart-Harris, 2018c, p. 17). In this endeavour it also uses Freudian references in regards to the ego, secondary consciousness, and primary consciousness, a state which precede secondary consciousness and which the psychedelic state is a regression into (Carhart-Harris et al., 2014).

Entropy and Criticality

Beyond being synonymous with uncertainty, EBT also considers entropy an index relating to *content*, *information* and *complexity* - all aspects which refer to the *richness* of the psychedelic ASC qualia (Carhart-Harris, 2018c). The psychedelic ASC being a state of

high entropy, lends support from Schartner et al. (2017), as entropy measured by Lempel-Ziv complexity with MEG on spontaneous brain activity is higher in LSD and psilocybin (as well as the psychedelic-like ketamine) condition compared with placebo. Even more so, the magnitude of the entropy level is correlated with the intensity of the experience, fitting the claim of EBT which states that entropy corresponds to qualia.

EBT holds that entropy can reliably differentiate between brain states, and that there are upper and lower limits in the entropy index in which consciousness can be lost. There is yet no evidence for the loss of consciousness of the upper limit of entropy, but it is predicted in the revised version of EBT that this may happen (Carhart-Harris, 2018c). Schartner et al. (2017) could demonstrate enhanced entropy in the content-rich psychedelic ASC, but there is also evidence for entropy being reliably lowered in reduced states of consciousness (Carhart-Harris, 2018c). Schartner et al. (2015) provide one such example, using the sedative propofol and measuring entropy in spontaneous brain activity with Lempel-Ziv complexity, the results showed decreased entropy in the anesthetized state. These results are supported by Sarasso et al. (2015). Casali et al. (2013) also used a version of the Lempel-Ziv complexity (the perturbational complexity index, further discussed in the next chapter), and could further demonstrate its value in distinguishing between disorders of consciousness and waking consciousness.

It is a central concept in EBT that the brain closes in on a state of self-organized criticality, or even *super-criticality*, on psychedelics (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). Systems in criticality have three defining points of interest; (a) they are at a maximum of metastable states, (b) maximally sensitive to both intrinsic and

extrinsic perturbation, and (c) prone to exhibit cascade-like properties which affect the whole system (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). According to EBT all these parameters can be mapped onto the psychedelic state. In argument of (a) studies show an enhanced repertoire of metastable states (Atasoy et al., 2017, 2018; Tagliazucchi et al., 2014). The importance of context and set-setting for the of the acute psychedelic experience is said to relate to (b), the system's sensitivity of perturbation. The neural cascade processes (c) in the critical psychedelic ASC is proposed to be a mechanism in the release of previous inhibited processes and information. These "periodic cascades" may be involved in the disturbance of "functional hierarchies" which when loosened, opens up a "freer communication" between the cortex and limbic system. (Carhart-Harris, 2018c, p. 19). In the zone of criticality the normal waking brain is closer to a sub-critical point, where order is more defining. The psychedelic ASC is then at the other end, closer to disorder and super-criticality (Atasoy et al., 2017; Carhart-Harris, 2018c). Another example of super-criticality, though it was first speculated otherwise (Carhart-Harris et al., 2014), is the brain during seizure (Carhart-Harris, 2018c).

In the revisited version of the theory, Carhart-Harris (2018c) expresses that entropy is "uniquely adept at bridging the physical and subjective divide" (p. 2), and in line with dual-aspect theory, EBT takes the stance that mind is a fundamental part of physical information which can be decoded. Although, there will always be a fundamental difference in aspect. Notably, the results of Atasoy et al. (2017, 2018) and Schartner et al. (2017), showing higher levels of entropy and a brain state tuned toward criticality, are novel and has yet to be documented in the scientific literature.

To summarize, entropy can reliably differentiate between brain states. Brain states with high entropy is according to EBT closer to super-criticality and the content-rich psychedelic state is an example of one. Low entropy is associated with loss of consciousness, and the anesthetized state is an example of a state beyond the lower limit of entropy where consciousness is lost. In the section below, it will be explained how entropy further relates to the psychological mechanisms of primary and secondary consciousness. Thereafter, the suggested mechanism that normally suppresses entropy will be proposed.

Primary and Secondary Consciousness

In an effort to bring psychoanalytic theory into cognitive neuroscience (Carhart-Harris et al., 2014; Carhart-Harris, 2018c), the entropic brain hypothesis lends themes from Freudian ideas. Carhart-Harris et al. (2014) describe the primary consciousness as a pre-ego type of consciousness which is "qualitatively different to the normal waking consciousness of healthy adult humans" (p. 6). EBT claims this *primary state* to be phenomenologically related to cognitive flexibility and unconstrained thought, and it is neurologically related to random, and high entropy, brain activity. Brain states that would fit the description of a primary state are "the psychedelic state, REM-sleep, the onset-phase of psychosis and the dreamy-state of temporal lobe epilepsy" (Carhart-Harris et al., 2014, p. 6). Secondary consciousness is related with ordered brain activity, and corresponds with the normal waking consciousness, which has an evolutionary advantage in reality testing. Secondary consciousness is characterized by a constrained cognition, in

comparison with primary consciousness, and the mechanism which allows this constraint on entropy is said to be the ego.

The Ego

Here, *the ego* is synonymous with the 'sense of self' and defined as "a sensation of possessing an integrated and immutable identity" (Carhart-Harris et al., 2014, p. 2). The secondary consciousness matures from the primary consciousness by the process of self-organizing the DMN, which coupled with the MTLs and synchronized alpha oscillations, constraints entropy and allows a coherent *sense of self*. EBT notes that certain pathologies, such as depression, OCD and addiction, are related to an overactive ego and has correspondingly a more rigid DMN activity (Carhart-Harris et al., 2014). Therefore, the ego and DMN can be seen as an evolutionary advantageous state, but also has a backside when overactive and becomes a pathology.

Disruption of the coupling between the MTL and DMN together with decreased alpha oscillations, which occurs after administration of a classic psychedelic (Muthukumaraswamy et al., 2013), permits unconstrained or random MTL activity which is characteristic of primary consciousness. According to EBT, the therapeutic potential of psychedelics occur because of this critical primary state, where the rigid thought-pattern and control of the ego loosens so depressed thought-patterns can be remolded. This disintegration promotes the possibility of novel thoughts and emotional insight to occur. It is also in this state where one can have mystical-type experiences, feeling more connected

with the universe, as the critical state of primary consciousness is more attuned with the environment which is more critical in nature (Carhart-Harris et al., 2014).

While EBT mainly focuses on whole brain entropic activity, Carhart-Harris (2018c) highlights that 5-HT2A receptors more dense presence in high-level cortical areas associated with DMN, are relevant to the neurological basis of consciousness.

EBT and the Psychedelic ASC

The psychedelic ASC, in the view of EBT, is a regression into a primary brain state characterized by signatures of criticality and defined by high entropy brain activity. The suggested mechanism that normally suppresses entropy is the sensation of self, the ego, which EBT proposes has the neurological underpinning of the DMN coupled with MTL activity and associated alpha oscillations. According to EBT, the disruption of the ego-mechanism is an underlying key for the therapeutic effects of psychedelics (Carhart-Harris et al., 2014).

To ensure the relevance of entropy as an index of a conscious richness, as opposed to an index of alertness or arousal, similar EEG-Lempel Ziv complexity studies should be done on stimulants as those that have shown a reduction in entropy with anesthetics (Carhart-Harris, 2018c). However, Carhart-Harris (2018c) deems it not likely that stimulants would increase entropy, although studies on non-classic psychedelics are more likely to, which the dissociative sedative ketamine has been an example of (Sarasso et al., 2015; Schartner et al., 2017).

In line with the entropy enhancing properties of psychedelics, Scott and Carhart-Harris (2019) propose them to be tested on patients with disorders of consciousness. More specifically, patients that are in a vegetative state or minimally conscious state as they show some level of wakefulness. It is hypothesized that psychedelics may elevate their conscious awareness.

Seeking to further understand conscious states, Carhart-Harris (2018c) makes the case that it is specifically resting state, spontaneous brain activity which is of most useful value of measuring. In contrast to perturbation approaches (which will be addressed in the next chapter), that tend to "detach" from the "phenomena of interest, i.e. spontaneous 'states'" (Carhart-Harris, 2018c, p.7).

Integrated Information Theory

As a theory, IIT has evolved from Giulio Tononi's early work with Nobel prize winner Gerald Edelman (Tononi & Edelman, 1998), to an independent theory of consciousness (Tononi, 2004, 2008, 2011), and has been further developed with more collaborates and peer support (Gallimore, 2015; Oizumi et al., 2014; Tononi et al., 2016). Regarded as one of the more prominent theories in cognitive neuroscience on consciousness it is bound to tell us something about the psychedelic state of mind. IIT defines consciousness as subjective experience, it is "what abandons us every night when we fall into dreamless sleep and returns the next morning when we wake up" (Tononi, 2004, p. 2). With this anchor in phenomenology, IIT infers certain qualities about the substrates of consciousness, which any physical system must account for to suffice as

conscious. These underlying substrates of consciousness are well-defined structures in IIT and, in principle, allow for consciousness to be calculated both in quantity and quality. In line with these definements, IIT proposes that consciousness is generated by the highly interconnected cerebral cortex, and regards the biological structure of the cerebellum to be inadequate for the task (Tononi et al., 2016). As the theory has evolved over the years it has also developed a mathematical foundation (Oizumi et al., 2014). This thesis, however, will only cover a heuristic account of IIT, focusing on the theoretical aspects and neurobiological statements of consciousness, relevant for the discussion of the psychedelic state.

The Cause-Effect Repertoire and Information

In the IIT model a conscious *system,* hereafter only called system, consists of a set of subsystems or *mechanisms*. Mechanisms must in their turn have an intrinsic causal role upon that system to be a part of it. A general rule of IIT is that in order to generate intrinsic information there must be "differences that make a difference" (Oizumi et al., 2014, p. 3). Following this rule, a mechanism must make a difference within a system, and may do so by constraining its past or future states. For example, a neuron or neuronal group may be considered a mechanism if it had a causal role for the systems past or will effect the systems future. Therefore, even if a neuron is inactive, according to IIT, it has informational value for the system as a whole.

At any given time a system has a certain amount of probable causes for its current state, and a certain amount of probable future states it may take. The mechanisms that

constitute the system constrain both the past, *cause repertoire*, of the system and its future states, *effect repertoire*. The *cause-effect repertoire* of a system is the set of probable past and future states of a system at any given time. The amount of *cause information* a state has is measured by "the distance between the cause repertoire and the unconstrained cause repertoire" (Oizumi et al., 2014, p.4), the *effect information* is calculated in the same way. Together, the *cause-effect information* is the generated information by a mechanism in a certain state. Therefor, the longer the distance between the cause-effect repertoire and the unconstrained cause-effect repertoire, the more cause-effect information is generated. On the other hand, if a systems entropy is increased, as we will see in the psychedelic condition, the cause-effect repertoire moves towards an unconstrained state and the information generated is reduced.

Concepts and the Conceptual Structure

The cortex may contain numerous mechanisms but not all of them are part of the conscious experience at all times. As mentioned, to reach consciousness the mechanism has to make a difference to the system as a whole, and it is only the "maximally irreducible cause-effect repertoire" that does so by having the maximum value of *integrated information* of its parts (Oizumi et al., 2014, p.3). When it does, it counts as a *concept*, and may be defined as "the constituents of conscious experience" (Gallimore, 2015, p. 3). The cause-effect repertoire determines what the concept is about, and therefore adds to the qualitative aspect of experience. For example, if a neuronal group is a mechanism, the cause-effect repertoire

which can produce the most integrated information at any given time determines the quality of the concept (such as a color, shape, sound or sensation) (Tononi et al., 2016).

One concept is only one aspect of a conscious experience, which is a constellation of many concepts. Together they form a *conceptual structure*, which is identical with the experience of a current state, equal to consciousness (Tononi et al., 2016). As concepts may come and go, depending on the stability of their own integrated information, the shape of the conceptual structures may change. Again, it is only the maximally irreducible conceptual structure that constitutes consciousness at any given time, generated by the "local maximum of integrated conceptual information", and is referred to as a *complex* (Oizumi et al., 2014, p.4). In IIT, the quality of consciousness corresponds to the shape of the conceptual structure (what concepts it is composed of) and the quantity of consciousness is dependent on its *integrated conceptual information*. The current state of consciousness therefore corresponds with the structure and stability of the complex, and that state is differentiated from any other states by its conceptual structure.

Major and Minor Complexes

The *major complex*, however, does not restrict the possibility of other *minor complexes* to exist at the same time. The major complex merely defines that it is the conceptual structure with most integrated information and is therefore the one most present in the conscious stream (Tononi et al., 2016). Minor complexes may be regarded as minimally conscious or even unconscious processes in comparison. Consciousness and the brain is dynamic and this is expected to be reflected in the complex, varying in shape and size over time. In its

most extreme, a split of the major complex would occur in patients with split-brain surgery where the two hemispheres may have a major complex each, not aware of the other. This is a known phenomenon revealed in carefully designed experiments (Tononi et al., 2016). But in a less extreme scenario, Tononi et al. (2016) propose the complex may condense into two or more complexes even on a daily basis. For example, this may happen when we do two things at once and one action is on auto-pilot, such as driving down a familiar road while simultaneously being in a conversation. Consequently, Tononi et al. (2016) also propose that splits of the major complex may also be due to a deficit in connectivity, as seen in dissociative disorders, may also provide an explanatory basis for the psychedelic ASC.

From this, it can be inferred that IIT considers consciousness as an emergent property of any system with the proper integration of mechanisms. IIT states that the quality of consciousness is defined by the conceptual structure and the level of consciousness is reflected by its irreducibility (high integration). It follows that brain states with reduced integration have reduced consciousness, such as in sleep or during anesthesia (Tononi et al., 2016).

Measuring Consciousness

Tononi with colleagues (Casali et al., 2013) presented a novel technique to measure the level of consciousness, already mentioned in this thesis, called the *perturbational complexity index* (PCI). The PCI uses transcranial magnetic stimulation (TMS) to pertubate the brain at rest and EEG to record its response, the Lempel-Ziv complexity is applied to

compress the data followed by a normalizing algorithm for source entropy. The result is a PCI value where higher values correspond to more consciousness. Casali et al. (2013) could demonstrate that PCI values were reliably higher during wakefulness and reduced during non-REM sleep and anesthesia conditions for healthy participants. In brain-injured patients, PCI values were graded depending on their level of consciousness disorder. Patients with unresponsive wakefulness syndrome (UWS) had PCI values resembling non-REM sleep and anesthesia in healthy subjects. Two patients with locked in-syndrome (LIS) had the same level of PCI as healthy subjects in wakefulness. Patients in a minimally conscious state (MCS) or emerging from the MCS, had values just below the threshold for healthy awake participants. In another study (Sarasso et al., 2015), they could reliably differentiate between unresponsiveness induced by the anesthetic agents propofol, xenon and ketamine. However, ketamine showed a PCI value comparable to wakefulness and is associated with vivid dreamful, even psychedelic-like, experiences during the unresponsive phase. A recent study (Farnes, Juel, Nilsen, Romundstad, & Storm, 2019) used the PCI to investigate the effects of a sub-anesthetic dose of ketamine, with psychedelic-like effects, on brain complexity. Their results showed that there was no significant change in the PCI, but all other EEG measures (including the Lempel-Ziv complexity) were significantly increased. From these findings, Farnes et al. (2019) propose that PCI may be a good measure for the level of consciousness while the signal diversity as measured by Lempel-Ziv may provide a better indication of content of consciousness. As of yet, there has been no research on any of the classic psychedelics using PCI.

IIT and the Psychedelic ASC

In IIT, the quality of consciousness is identical with the systems conceptual structure. To profoundly alter consciousness, psychedelics must somehow have the capacity to alter this structure. Here, it is proposed that psychedelics alter consciousness on the level of concepts by altering mechanisms, and the complex by altering the conceptual structure (Gallimore, 2015).

Gallimore (2015) has made a comprehensive interpretation of IITs capacity to account for the psychedelic-induced ASC. From neuroimaging studies that report a larger brain state repertoire and increase of entropy (Atasoy et al., 2017, 2018; Lebedev et al., 2016; Schartner et al., 2017; Tagliazucchi et al., 2014), Gallimore (2015) suggests that the entropy increase reflects an effect on the level of the mechanism, altering how they constrain the cause-effect repertoire. Gallimore (2015) uses the mathematical foundation of IIT to show how the *psychedelic cause-effect repertoire* is closer to the unconstrained cause-effect repertoire, this implies that it has less constraint on the system. Increasing the cause-effect repertoire may allow new concepts as they "develop a non-zero probability", creating an expanded repertoire of states for the entire system (Gallimore, 2015, p. 7). From the subjective perspective, this implies that certain concepts have changed in quality and even that new novel concepts might appear. Gallimore (2015, p. 7) infers that in the psychedelic state "concepts that were once clear and well-defined become novel, strange and perhaps even bizarre or ludicrous". On the other hand, increasing the cause-effect repertoire, as previously mentioned, consequently decreases its cause-effect information as the mechanism is less informative about the past and future states of the system. While

psychedelics may increase brain states and create novel qualitative material it does so "at the expense of focusing attention, organizing thoughts, and maintaining cognitive control" (Gallimore, 2015, p.10).

On the level of the complex, any significant changes in concepts will alter the shape of the conceptual structure, altering not only conceptual aspects of consciousness but its entire qulia. Considering how psychedelics alter functional connectivity and the stability of RSNs (Müller et al., 2018a; Preller et al., 2018; Tagliazucchi et al., 2014), it can be inferred that they alter the capacity of neural integration. High integration is important in IIT for a complex to be conscious, it has already been proposed that a complex may condense into multiple complexes, and this is reflected in the neuroimaging analysis of disintegration of RSNs and the occurrence of novel structures (Petri et al., 2014; Tagliazucchi et al., 2014). A split in the major *ego complex* may be an explanation for the ego-dissolution phenomena. Lebedev et al. (2015) found that interhemispheric loss in connectivity was associated with ego-loss, and IIT predicts this to be the case in patients with split-brain surgery or dissociative disorders. The psychedelic state may represent a pharmacologically induced state where the ego complex is blurred and/or blended with other concepts to generate either a quality of oceanic boundless bliss or a dread of ego dissolution. Therapeutically, the pathologies of OCD, depression, anxiety and addiction may all have the characteristics of dysfunctional major complexes which can be temporarily disintegrated by psychedelics, giving the patient a possibility to temporarily experience another major complex. Similar to the hypothesis of EBT, the therapeutic mechanism may be the disintegration of a negative pattern which may be altered in the reconstruct.

The level of consciousness of the psychedelic state as seen through IIT is less straightforward to infer from the current research. Since Gallimore's (2015) article there has been more data published on how psychedelics alter neural integration. Although they indicate disintegration they also support a higher integration, and even directed connectivity from the thalamus, a main connection hub (Preller et al., 2019). These results may provide some indication for higher state of consciousness. For IIT, this would ideally be examined with PCI (Gallimore, 2015). However, the current results from subanesthetic doses did not yield a significant increase in the PCI value. So there is reason to doubt that classic psychedelics would, even though their psychedelic effect is arguably more potent. But what would it mean if the psychedelics state did not increase PCI from the perspective of IIT? If they would yield a similar score to normal wakefulness, as ketamine, it would merely imply that it is not a higher state of consciousness. It would be recognized as normal level of consciousness with highly altered conceptual features. However, this speculation relies on that PCI is a valid measure for the level of consciousness.

To summarize, psychedelics have the capacity to alter expand the cause-effect repertoire of the mechanism, leading to alterations in concepts which affects the stability of the complex. Ego-dissolution may be due to a disintegration of the major complex, either by blending and merging with other novel concepts or by condensing into multiple smaller complexes. The level of consciousness is expected to be higher as integration is high, though further research with PCI would elucidate this.

Discussion

Classic psychedelic substances have a long history of sacramental and healing purposes in indigenous cultures (Bruhn et al., 2002; Carod-Artal, 2015), and while classic psychedelics have been researched in a previous era (Swanson, 2018), the more recent years are often referred to as the renaissance of psychedelic science (Murnane, 2018). Following the aim of this thesis, the discussion is divided into three parts. First, what we know about the psychedelic-induced ASC will be discussed on the basis of the results from the modern therapeutic and neuroimaging studies. Then, a discussion of how they have contributed to our knowledge of mind, and thirdly, a comparison of the theories EBT and IIT will end the discussion of this thesis.

What do we now know about the psychedelic ASC? We know that both LSD (Liechti, 2017) and psilocybin (Studerus et al., 2011), reliably induces profound effects on perception, emotions and cognition, and are capable of inducing ego-dissolution and mystical-type experiences (Preller & Vollenweider, 2016). Recent therapeutic studies have confirmed that LSD and psilocybin can be given safely to patient populations. Significant results have been presented in treatment of OCD symptoms (Moreno et al., 2006), tobacco (Johnson et al., 2014, 2017) and alcohol addiction (Bogenschutz et al., 2015), depression (Carhart-Harris et al., 2016a, 2018a), and end-of-life related anxiety disorders (Griffiths et al., 2016; Ross et al., 2016; Gasser et al., 2014). Although many of these studies had a small number of patients, only half had a double-blind design, requiring further testing to generalize the results (Rucker et al., 2018). In patient studies (Garcia-Romeu et al., 2014;

Roseman et al., 2018), and healthy participants (MacLean et al., 2011), the quality of the acute psychedelic experience predicted long-term outcome, with positive ego-dissolution and mystical-type experiences being indicative of a future increase of life quality. Whether the psychedelic-induced ASC is necessary for the therapeutic effects needs further investigation. Future research could solve this question by testing non-psychedelic 5-HT2A agonists (Murnane, 2018) or identifying compounds with similar neurological effects without the psychedelic effect (Calvey, & Howells, 2018). To better understand what characteristics of the psychedelic ASC is necessary for therapeutic action further investigation is needed, mystical-type experiences may be a to general description, as its prencese also indicates high scores on other acute dimensions of the ASC (Bogenschutz et al., 2015). The importance of setting and context is also noteworthy (Johnson et al., 2008), as the transition into and from the psychedelic state should be done in a safe and therapeutic setting (Carhart-Harris et al., 2014). This is however also a constraint on both scientific and economic factors, and the magnitude of psychological support need therefore also be tested to find a cost-effective treatment alternative (Carhart-Harris & Goodwin, 2017).

In regards to the neural basis of the psychedelic ASC, we know that their main effects are mediated through 5-HT2A receptor agonism (Nichols, 2016), as all psychological effects can be blocked by pretreatment with the 5-HT2A receptor antagonist ketanserin (Kometer et al., 2013; Preller et al., 2017). However, recent results on directed connectivity from Preller et al. (2019) showed that ketanserin did not block all effects from LSD, even if these had seemingly no acute psychological effect, they might have further effects not yet

understood. Muthukumaraswamy et al. (2013) found a decreased alpha oscillatory sourced as at deep-layer pyramidal cells, consistent with the density of 5-HT2A receptor distribution (Berthoux et al., 2018). Recently Preller et al. (2019) found a negative correlation with 5-HT7 receptor expression, which needs further investigation to exclude involvement in the psychedelic ASC. Neuroimaging studies consistently showed disruption in resting state functional connectivity, specifically showing a decreased anticorrelation in normally well-differentiated networks (Müller et al., 2018a). Increased GFC has reliably been found in thalamic areas for both LSD and psilocybin (Müller et al., 2017, 2018a; Tagliazucchi et al., 2016). Novel neuroimaging analysis methods have shown increased possible sets of brain states for psilocybin (Atasoy et al., 2018; Petri et al., 2014; Tagliazucchi et al., 2014) and LSD (Atasoy et al., 2017), as well as increased entropy and neural signal diversity (Schartner et al., 2017). Lebedev et al. (2016) found a correlation between acute global brain entropy and an increase in personality trait openness two leeks post-psilocybin, providing neural support for the findings of MacLean et al. (2011). Not surprisingly, all the neuroimaging studies show a correlation in the magnitude of measurement and intensity of the psychedelic ASC. Although, there are some inconsistencies in what areas are involved in the ego-dissolution phenomena (Carhart-Harris et al., 2016b; Lebedev et al., 2015; Müller et al., 2018b; Muthukumaraswamy et al., 2013; Preller et al., 2018). These divergences could be due to differences in measurement techniques, methods of analysis, but also in subjective ratings. As previously mentioned for the therapeutic studies, better measurements are needed to explore the mechanisms behind the mystical-type experiences and this also true for the

neuroimaging studies to find the underlying neural correlates. In comparable studies, Müller et al. (2018a) found two important connectivity hubs in the brain, the precuneus and thalamus, which are consistently involved in the psychedelic ASC. This is supported by the more recent studies by Preller et al. (2018, 2019), which furthermore demonstrated directed connectivity from the thalamus to PCC (2019). The post-treatment fMRI scans show rather different results than acute resting state scans in healthy participants (Carhart-Harris et al., 2017), demonstrating the need for further studies to understand the underlying mechanism of treatment and how these substances may differ in acute and long-term effects. As all of these findings are based on a rather sparse number of data sets, as demonstrated in Table 2 (p. 27), all the results would need to be replicated to draw any firm conclusions. The divergence between psilocybin and LSD neuroimaging results may be due to unknown differences in neural or vascular effect, also differences in study settings, analysis, and choice of administration (Müller et al., 2018a).

How have recent psychedelic research contributed to our knowledge of the mind and consciousness? The answer to this question have partly been addressed in the section above and will be further explored in the discussion below. More generally, the research has produced completely novel results on certain measures of brain activity (Atasoy et al., 2018; Schartner et al., 2017) and even personality (Lebedev et al., 2016; MacLean et al., 2011), indicating a new avenues for scientific exploration. While it may not be a popular expression (Bayne & Carter, 2018), these findings point to a higher state of consciousness than normal waking consciousness (Schartner et al., 2017). Furthermore, studies consistently show that high ratings of ego-dissolution and/or mystical-type experiences

are linked with therapeutic effects and even increase well-being in healthy participants. If the psychedelic ASC are indicating beneficial qualities, what other ASC may have a similar effect? As previously mentioned, there are ongoing studies on non-classic psychedelics and that these may have beneficial properties might be an easy inferral. However, other ways to induce ASCs, such as meditation and floating tanks, may be worthy of further investigation as well. Beyond these findings, the recent psychedelic research has also given rise to a new theory on conscious states, the entropic brain theory.

EBT regards the psychedelics ASC to be a high-entropy, content rich, primary state, that is closer to super-criticality than normal waking consciousness (Carhart-Harris et al., 2014; Carhart-Harris, 2018c). EBT considers entropy to be an index representative of both qualia, content, complexity, and information (Carhart-Harris, 2018c). IIT, on the other hand, has a more intricate definition of information as a function of qualia. Information in IIT, is derived from the qualitative cause-effect repertoire, which may increase its repertoire by entropy but then consequently decreases its informational value. Therefore, IIT ascribes information a defining, and constraining quality, information says something about how a state differs from others. EBTs entropy explanation may fit well with the studies of neural disintegration, but it lacks explanatory power over the studies showing novel, and increased integration of brain activity (Johnson et al., 2018). An aspect IIT can account for, as an increase in the cause-effect repertoire also alters concepts and allow for new concepts to appear, which is reflected in a split of the major complex. There has been critique directed at EBT for its entropy index of consciousness as a "complexity measure depurated of its integration" (Papo, 2016, p.1). In which EBT, responds that the

explanatory power of IIT is mainly due to its entropy component (Carhart-Harris, 2018c). However, here it is proposed that entropy and integration is two aspects which have inherently inseparable properties. To say that entropy is increased is equivalent to saying that there is a loss of integration. EBT claims that there are upper and lower limits of entropy in which consciousness is lost (Carhart-Harris, 2018c). This can just as well be translated to an IIT framework of upper and lower limits of entropy which consciousness is lost due to loss of integration. Furthermore, Carhart-Harris (2018c) makes another statement against IIT, claiming PCI is not explanatory powerful as it does not look at the system at rest. However, using psychedelics a type of pharmacological perturbation to the system. When it comes to studying conscious states, observing the normal waking consciousness at rest can only give as much information, using perturbation methods to this state can yield even more knowledge of its properties. EBT favors the Lempel-Ziv complexity as a measure of entropy (and therefore also level and content of consciousness) (Carhart-Harris, 2018c) and IIT favors PCI, which is Lempel-Ziv complexity with a perturbational element (Casali et al., 2013). While Schartner et al. (2017) claim Lempel-Ziv complexity to measure both level of consciousness and content. Farnes et al. (2019) used both measures and found that PCI was a better measure for the level of consciousness and Lempel-Ziv complexity a better indication for content richness.

Gallimore (2015) states that IITs framing of the psychedelic state is advantageous over EBT as it can explain the qualitative increase while still formulating a loss of information for a system which has lost an advantageous feature of “organizing and constraint cognition, categorizing and differentiating concepts” (p.14). In an attempt to

bridge theories aiming for a unified theory of the psychedelic ASC, Swanson (2018) includes both EBT and IIT as the main attributes of 21th century neuroscientific theories. From Swanson's (2018) work a transition from psychoanalytical theories of earlier years to modern neurobiology is illuminated. Here EBT can be seen as the bridge from psychoanalytic aspects into neuroscience, and IIT may provide a computational phenomenological contribution. While IIT is a more comprehensive theory of consciousness, with many years to its advantage, EBT is perhaps more accessible with its psychoanalytic terminology. EBT has a leverage in being more approachable for a wider audience than IIT, which requires a certain level of attention for its comprehension.

As a closing comment, psychedelic substances can arguably be said to provide a specifically unique tool for neuroscience to explore the biology of consciousness as they can reliably switch the mental state into an alternate state of consciousness. While there is a great need for replications of studies and further investigation of underlying mechanisms of action, current finding present promising results for the new treatment interventions of difficult mental pathologies. Although psychedelics substances are illegal in many countries, including Sweden, there is a large misinterpretation regarding the legal obstacle for doing research. In fact, there is no legal obstacle for studying any illegal substance in Europe in accordance with the UN drug convention (Kieseritzky, 2018). So there is great potential for this field to grow. Just recently the first official center for psychedelic research launched at Imperial College London. There might be a different kind of psychiatry on the horizon with psychedelic therapy. The Multidisciplinary Association for Psychedelic Studies is currently working towards making the empathogen MDMA an approved

prescription medicine within two years. Psilocybin may very well be next, if further studies can replicate the current findings.

Conclusion

The psychedelic ASC can reliably induce profound changes in perception, emotions, and cognition, even to a degree that promotes mystical-type experiences and ego-dissolution. These experiences are associated with beneficial changes for both healthy participants and patient populations. A significant characteristic of the psychedelic ASC is its capacity to disrupt neural integrity, both disintegrating normally stable networks and adding novel integrations, which is also correlated with the intensity of the psychedelic experience. Both therapeutic and neuroimaging studies are in need of replication and development to generalise any findings. Entropic brain theory is a novel theory on conscious states that has evolved from psychedelic research and brought psychedelics into neuroscientific consciousness research. However, compared with the well-established integrated information theory, it is in need of development to further contribute to the field of consciousness research.

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