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PSILOCYBIN AND LSD IN THE TREATMENT OF DEPRESSION AND ANXIETY

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Abstract

Psychiatry is in a crisis. Mental health disorders are on the rise worldwide and there are currently not enough efficient treatment methods that would meet the patients' needs. Hence, the societal and economic costs of mental health problems are enormous, as well as the suffering of individuals afflicted by mental health problems. Lysergic acid diethylamide (LSD) and psilocybin are substances that create an altered state of consciousness characterized by altered sensory perception and on some occasions, ego-dissolution, and mystical experiences. In recent studies, LSD and psilocybin have been shown to carry significant therapeutic potential in the treatment of depression and anxiety disorders in conjunction with psychotherapy. The therapeutic effects of LSD and psilocybin have also been shown to persist for between 3-12 months post-treatment. LSD and psilocybin, like other classical hallucinogens, increase serotonin availability, which has been suggested to attenuate symptoms of anxiety and depression. In addition, LSD and psilocybin alter the activity of the default mode network, which has been suggested to be overly active in depressed and anxious patients. This essay is a literature review of the neural mechanisms of LSD and psilocybin, their potential therapeutic effects in the treatment of depressive and anxiety disorders, and how insights about said neural mechanisms may be useful in understanding the possible application of psychedelics in the treatment of depressive and anxiety disorders. In sum, recent studies have provided converging and convincing evidence on therapeutic potential of LSD and psilocybin. Yet, few conclusions on the exact neural mechanisms of how LSD and psilocybin alleviate depressive and anxiety symptoms can be made. Although the future of this research field looks promising, archaic national- and international regulations continue to be a hindrance to research into psychedelic drugs. Yet, due to the psychiatric crisis and the promising results so far, more studies in this field are warranted.

Keywords: LSD, psilocybin, cognitive neuroscience, psychedelic-assisted therapy, depression, anxiety, 5-HT_{2A}, Default Mode Network

1. Introduction

Mental illness is a major health concern worldwide and is currently on the rise. In 2018, 264 million people suffered from depression, while 284 million people from anxiety disorders (Ritchie & Roser, 2018). There is a shortage of new treatment methods for depression and anxiety. Furthermore, studies show that pharmacological antidepressant and anxiolytic treatments are not effective at curing the underlying condition, and often they fail at providing relief to sufferers (Griffiths et al., 2016; Ritchie & Roser, 2018). In addition to psychological suffering, depression and anxiety carry great economic and social burdens on society (Rucker et al., 2016; Schenberg, 2018; dos Santos et al., 2016).

Early studies of psilocybin, lysergic acid diethylamide (LSD), and mescaline, i.e., classical hallucinogens or psychedelics, showed that these agents may have anxiolytic and antidepressant properties (Rucker et al., 2016; dos Santos et al., 2016). Because of the mind-altering capabilities of psychedelics, the interest in them was high in psychiatry during 1950s until the 1970s (Rucker et al., 2018).

All classical hallucinogens eventually became banned by a UN convention known as the Convention of Psychotropic Substances (Amsterdam et al., 2011; Law and Government Division, 2001; Schenberg, 2018). As a result, research on these substances declined and the regulations resulting from the treaty are still intact. Finally, the declaration of the "war on drugs" by former US president Richard Nixon ultimately led to the ban (Doblin et al., 2019; Grinspoon & Bakalar, 1997; Law and Government Division, 2001).

Despite the convention, research into the behavioural effects of psilocybin and LSD has rekindled recently, and new neuroimaging techniques have allowed scientists to gain novel insights on the innerworkings of these drugs. Recent studies on psychedelics have provided evidence that these drugs could potentially be efficacious treatment methods for mood disorders when combined with a therapeutic setting (Rucker et al., 2018; dos Santos et al., 2016). New insights on the neural mechanisms of LSD and psilocybin are crucial to advance our understanding of the behavioural and potential therapeutic effects of psychedelics. The knowledge gained will be useful for assessing the risks and benefits of using LSD and psilocybin as treatment methods for depression and anxiety disorders.

My essay will provide a review of the neural mechanisms of LSD and psilocybin, and the substances' therapeutic potential in treating depressive and anxiety disorders. The review will start by explaining depression and anxiety and their correlation with changes in neural activity, and then cover the classification of psychedelics, their receptor mechanisms and effects on brain activity patterns. The thesis will next focus on older clinical trials conducted

with LSD and psilocybin and then proceed with descriptions of modern studies. In the Discussion, conclusions about the potential benefits of psychedelic-assisted therapy will be presented, and the possible mechanisms on how psychedelics may alleviate depressive and anxiety symptoms discussed. The databases that were used in finding the articles included Scopus, Web of Science, Pubmed, and Google Scholar, and search words were: psilocybin, LSD, psychedelics, depression, anxiety, and neural mechanisms.

2. Depression, Anxiety, and Brain Activity

According to Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) 5th edition, major depressive disorder (MDD) is a unipolar mood disorder that is characterized by one persisting major depressive episode without a manic or hypomanic episode that may last for six to nine months. However, MDD may also last for several years (National Institute of Health, 2018). An episode of MDD may be mild, moderate, or severe (American Psychiatric Association, 2013; National Institute of Health, 2018). A depressive episode is characterized by feelings of sadness, agitation, and guilt. The patient often has problems with excessive sleeping or insomnia symptoms, increased or diminished drinking or eating, and recurrent suicidal thoughts. Further, depression is composed of a broad spectrum of unipolar depressive disorders, and thus, its symptoms and phenomenology are different depending on what kind of depression is discussed. Different kinds of depressive disorders include dysthymia, a less intensive form of depression that is chronic; seasonal affective disorder, a depressive episode occurring at specific seasons; atypical depression, depression with heightened reactivity to both positive and negative events; and psychotic depression, a type of MDD characterized by hallucinations (American Psychiatric Association, 2013).

Anxiety disorders are disorders that are characterized by fear and anxiety in response to stimuli. The stimulus can either be specific, such as social situations (social anxiety disorder), or anxiety can be triggered by an event that is non-specific, as is the case in generalized anxiety disorder. Anxiety disorders are either synonymous with panic disorder, agoraphobia, a specific phobia, social anxiety disorder, selective mutism, generalized anxiety disorder, or separation anxiety disorder, or anxiety disorder can be associated with a life-threatening disease (American Psychiatric Association, 2013). However, the type of anxiety that this essay will concern itself with is generalized anxiety disorder.

The functioning of serotonin is suggested to be disrupted in depression and anxiety (Andrews-Hanna et al., 2014). In both disorders, there is a tendency for serotonin depletion in

the synaptic clefts, which is why serotonin selective reuptake inhibitors (SSRIs) are frequently used to treat the two disorders. The main psychological effect of serotonin is mood regulation, though, serotonin is involved in cognition, reward-seeking, and memory as well (Carhart-Harris & Nutt, 2017). Long-term effects of serotonin deficiency are a part of the clinical manifestations of depression and anxiety and cause changes in cognition, reward-seeking, and memory.

Research has provided new knowledge about how disorders related to depression and anxiety are potentially related to dysfunction in the default mode network (DMN). Activity in DMN is negatively correlated with activity in attentional networks, and DMN is not only important to mind-wandering and introspection but to social cognition (thinking about others), autobiographical memory (thinking about one's past), and self-thought related to the future (Andrews-Hanna et al., 2014). Depression is correlated with an increased tendency to mind-wander and to think about ones' past, and activation in the temporal areas of DMN is positively correlated with negative affect (Kopala-Sibley & Zuroff, 2019). Altered brain activity in areas related to self-processing is associated with negative thinking about oneself, which is a recurring element in both depression and anxiety (Andrews-Hanna et al., 2014). Furthermore, patients with late onset depression exhibit decreased functional connectivity between the DMN and cingulo-opercular network (Yin et al., 2016).

Naturally, the neural mechanisms of depression and anxiety are more far-reaching, complex and controversial than what has been acknowledged here, and detailed coverage of these mechanisms is beyond the scope of the present thesis. However, the monoamine-deficiency hypothesis seems to still be the most clinically relevant neurobiological theory of depression (Hasler, 2010). Given the effects classic psychedelics have on serotonergic systems and DMN activity, the serotonin deficiency-hypothesis and the DMN hypothesis were selected to be presented and discussed in this thesis.

3. Classical Hallucinogens

Civilizations have used hallucinogenic agents in religious contexts for thousands of years. For example, the ayahuasca drink was widely, and still is to this day, used by native tribes in South America during religious rituals. Another example is the soma drink, which was used in religious rites in ancient India, and is mentioned in ancient Vedic hymns (Nichols, 2004). The use of hallucinogenic substances has not been limited to just religious rites, but they have also influenced medicine as well. For example, in Pre-Victorian times, mandrake root and belladonna, which are deliriant hallucinogens, were used by pagan

physicians since the Middle Ages as treatment methods for mental and physical disorders (Sessa, 2016).

The classical hallucinogen peyote cactus plant was discovered by the western world in the mid-1800s (Grob, 1996), but it was not until late 1800s that Arthur Carl Wilhelm Heffter isolated and synthesized the active compound mescaline (Sessa, 2016). Albert Hofmann was the first to synthesize LSD derived from ergot fungus in 1938, in an attempt to create a stimulant at Sandoz laboratory in Switzerland, and he was also the first to experience its behavioural effects five years later, when he ingested it by accident (Hofmann, 1959). About two decades later Hofmann also isolated psilocybin and psilocin from the Psilocybe Mexicana mushroom (Hofmann et al., 1959).

3.1 Classification

Classical hallucinogens are substances whose effects are mind altering and hallucination-inducing. LSD, psilocybin, DMT (N, N-Dimethyltryptamine) and mescaline are categorized as *classical* hallucinogens because of similar behavioural effects and mechanisms of action. While psilocybin, mescaline, and DMT are naturally occurring tryptamines, LSD is a semi-synthetic drug. Another word for classical hallucinogen is ‘psychedelic’, which literally translates to “mind-altering” (Baumeister et al., 2014). For a substance to be called hallucinogenic, in addition to be able to induce hallucinations, the substance must have the potential to alter brain activity in such a way that the experience can be called ‘mystical’ (Griffiths et al., 2011).

3.2 Behavioural and Physiological Effects of LSD and Psilocybin

The behavioural effects of LSD and psilocybin include perceptual changes and feelings of joy/intense happiness, as stated by the authors (Griffiths et al., 2016; Griffiths et al., 2011; Griffiths et al., 2018). One of the first systematic studies on the behavioural effects of LSD and psilocybin, involving nine study subjects, showed that both drugs caused perceptual changes in all participants (Isbell, 1959). However, the experience is not always pleasant: anxiety was reported by nearly all participants in the study.

The experiences and insights that people report in conjunction with classical hallucinogens are often spiritual and appear ineffable, i.e., the subjects often have difficulties in explaining their experiences. One such experience caused by LSD and psilocybin is ego-dissolution where the boundary between one’s consciousness and the surrounding world is loosened (Carhart-Harris, Kaelen et al., 2016; Hasler et al., 2004; Shulgin, 1978; Studerus et al., 2010). Sometimes hallucinations can occur that are fantastical in nature, such as imagining

going to the moon or living in gorgeous castles (Isbell, 1959). Mental changes also tend to cause decreases in critical thinking and sometimes cause alterations in body image. In exceptional cases, a bad trip can result in a psychosis or panic attack which can later be followed by flashbacks (Amsterdam et al., 2011).

Even though LSD and psilocybin cause similar mental states, the effects of psilocybin are shorter and less intense. The effects of psilocybin are usually gone after 4-6 hours, while the effects of LSD may last as long as 10-12 hours (Nichols, 2004; Passie, 2002). Psilocybin seems to evoke a mental state of a more dreamlike, philosophical, and ruminative nature (Hollister, 1961; Isbell, 1959). LSD has been estimated to be 100-150 times as potent as psilocybin which has been attributed to LSD's more complex structure (Hollister, 1961). The metabolite of psilocybin called psilocin is about 1.4 times as potent as its pro-drug (Hollister, 1961). Wolbach et al. (1962) also found, similarly to later studies (Carhart-Harris, Bolstridge et al., 2016), that the effects of psilocin and psilocybin peak at around 30-50 minutes after ingestion. For LSD, the effects peak after roughly one and a half hour (Isbell, 1959; Hollister, 1961; Wolbach et al., 1962).

At medium doses of 6 – 20 mg, psilocybin leads to a state of altered psychological functioning when introspection is enhanced. LSD's effects become visible with 0.05-0.20 mg, but an appreciable effect can be observed in doses as low as 0.025 mg in some individuals (Nichols, 2004). In addition, attention seems to be diminished, the sense of self becomes loosened, introversion increases, broadening of perception occurs, and these result in a state of dreaminess. The mentioned symptoms are especially apparent at higher doses (0.2-0.3 mg) of LSD, and a dose of 0.35 mg is enough to make the symptoms especially noticeable (Fuentes et al., 2020; Nichols, 2004). The introspective state is often preceded by a state of extroversion and high emotional excitability where the subject may experience transient anxiety (Hasler et al., 2004; Studerus et al., 2010).

Overall, the risk of adverse effects resulting from the ingestion of LSD and psilocybin are lower than many other drugs in schedule I (A category of illegal narcotics in the UN Convention of Psychotropic Substances). The risk of dependency resulting from long-term use is low (Aday et al., 2020) with no signs of withdrawal symptoms are absent (Amsterdam et al., 2011). However, tolerance to these substances may develop quickly after frequent ingestion (Amsterdam et al., 2011), and tolerance may develop to such a degree that a few days of LSD renders the user insensitive to the physiological and psychological effects after four days of daily administration (Nichols, 2004)

The physiological effects of psychedelics were first described by Isbell (1959) who

showed that both substances result in increases in systolic blood pressure, body temperature, and dilation of the pupils. In a study on healthy volunteers, ingestion of psilocybin caused somatic effects including nausea and increased tendon reflexes in 80% of the cases, and dysmetria (coordination problems), tremors, and irregularities in arterial blood pressure at doses of between 8-12 mg per oral dose total (Passie et al., 2002). These somatic symptoms could be due to increased secretion of cortisol, prolactin, thyroid stimulating hormones, and adrenocorticotropic hormones (Hasler et al., 2004).

4. Effects of Psychedelics on Brain Activity

Since research on LSD and psilocybin began in the 1950s many insights have been gained regarding the receptor mechanisms of the drugs. The development of brain imaging techniques has allowed researchers to investigate and learn how these substances affect brain metabolism, blood flow and functional connectivity between brain areas. These issues will be covered below.

4.1 Receptor Mechanisms

All classical hallucinogens regulate monoamine neurotransmission, and more specifically, they are serotonergic and act on specific serotonin receptors by causing excitatory activity (Baumeister et al., 2014; González-Maeso et al., 2007; Preller et al., 2018; Vollenweider & Kometer, 2010). Researchers agree that LSD and psilocybin are receptor 5-HT_{2A} and 5-HT_{1A} agonists. Antagonists of 5-HT receptors, such as ketanserin and haloperidol, have been observed to reverse the psychedelic state resulting from classical hallucinogens (Baumeister et al., 2014; González-Maeso et al., 2007; Preller et al., 2018; Vollenweider & Kometer, 2010).

It is now known that 5-HT_{2A} receptors are primarily located in apical pyramidal neurons throughout Layer V, and most densely packed in posterior cingulate cortex, prefrontal cortex, medial prefrontal cortex, and association cortices (Carhart-Harris & Nutt, 2017; Nichols, 2004; Vollenweider, 1997; Vollenweider & Kometer, 2010). In addition to serotonergic effects, 5-HT_{2A} receptors modulate glutamatergic and GABAergic systems (Müller et al., 2017; Nichols, 2004). Researchers increasingly believe that 5-HT_{2A} receptors increase the firing rate of both glutamatergic neurons and GABAergic interneurons and pyramidal neurons thus causing excitatory and inhibitory effects on brain networks. In addition, pyramidal neurons project to subcortical areas such as the thalamus, the basal ganglia, the amygdala and raphe nuclei in the brainstem (Baumeister et al., 2014; Carhart-Harris & Nutt, 2017; Carhart-Harris et al., 2014; Müller et al., 2017; Preller et al., 2018; Smigielski et al., 2019).

Animal studies and post-mortem studies on patients with depression have also demonstrated that LSD and psilocybin might have some affinity for 5-$HT_{1, 4, 5, 6, \text{and } 7}$ receptors (Nichols, 2004). In addition, receptor 5-HT_{2C} has been implicated in rat studies where activation of 5-HT_{2C} receptors reduced territorial behaviour in response to LSD (Baumeister et al., 2014; Nichols, 2004; Preller et al., 2018). Other than serotoninergic receptors, Moreno et al. (2011) showed that disruptions of mGlu2 glutamate receptors disable any neural activity by classical hallucinogens. As far as dopaminergic activity is concerned, activity of receptors D1 and D2 has been found to increase in striatal areas in healthy volunteers (Carhart-Harris & Nutt, 2017; Vollenweider et al., 1999). Recently, several original studies and review articles have suggested that LSD and psilocybin trigger neuroplastic mechanisms that enhance glutamatergic neurotransmission (Baumeister et al., 2014; Carhart-Harris & Nutt, 2017; dos Santos et al., 2016; Vollenweider & Kometer, 2010). Even more recently, an in vitro study on various cells suggested that this mentioned neuroplasticity may be rooted in an increased rate of neurogenesis and dendritic growth in the prefrontal cortex (Ly et al., 2018). Additionally, Ly et al. (2018) suggest that the amount of brain derived neurotrophic proteins (proteins that promote neuronal growth) increases, which then causes new synapses and synaptic connections to be formed. These new synaptic formations are thought to influence 5-HT signalling pathways.

4.2 Neuroimaging Studies on LSD and Psilocybin

The advent of positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and electroencephalography (EEG) has provided new ways of understanding the neural mechanisms and neurophysiological effects of psychedelics (Deco et al., 2018). Currently, neuroimaging research into how LSD and psilocybin affect the DMN is of great interest to researchers. The DMN is a network that has been shown to be largely active during introspection and daydreaming when the subject is not focused on any task. The main hubs in the default mode network are the medial prefrontal cortex, lateral frontal cortex, medial parietal cortex, medial temporal lobe, lateral parietal cortex, and lateral temporal cortex (Andrews-Hanna et al., 2014). Under the influence classical hallucinogens, brain regions have been demonstrated to exhibit a de-coupling effect: there's decreased functional connectivity and cerebral blood flow in the DMN (Barnett et al., 2020; Carhart-Harris et al., 2014; Müller & Borgwardt, 2019) with thalamus and amygdala (Carhart-Harris & Nutt, 2017; Müller et al., 2017).

4.2.1 Neuroimaging Studies on Clinical Populations

In one double-blind open-label study, there were 20 participants with moderate to severe MDD who had been antidepressant-free for at least two weeks before the study commenced. Nineteen participants underwent two psilocybin-assisted therapy sessions, followed by two fMRI-scan sessions (see Table 1). In the first therapy session, psilocybin, as active placebo, was administered in a dose lower than the effective dose followed by the second therapeutic session. The researchers obtained fMRI-data from the participants one day after both sessions. Compared to baseline scans made before the treatment, the increased reactivity towards fearful and happy faces corresponded with increased activity in the right amygdala, posterior cingulate cortex and areas related to DMN (Roseman et al., 2018). The change in the right amygdala activity were significantly correlated with decreased scores of depression as measured by the HAM-D-scale (Hamilton, 1960).

A follow-up fMRI study using psychophysiological interaction (a type of analysis to reveal changes in functional connectivity between brain regions) was made several years later, which revealed increased connectivity between amygdala and calcarine sulcus in response to happy faces. The analysis also found increased functional connectivity between ventromedial prefrontal cortex and lateral occipital cortex, occipital pole, and occipital-fusiform gyrus when participants viewed fearful faces. However, the psychophysiological interaction analysis showed increased functional connectivity to left cerebellum in response to neutral faces, and increased connectivity between ventromedial prefrontal cortex and cuneal cortex when the participants viewed happy faces (Mertens et al., 2020).

In another study, Carhart-Harris, Roseman et al. (2017) collected fMRI scans from participants with treatment-resistant MDD (see Table 1). The original sample contained 19 participants but three were excluded due to excessive movement. In this study, there were two sessions. All participants received either a low or a high dose of psilocybin one week apart. None of the patients took any other medications during the time period of this treatment. To measure the degree of depression, the researchers administered the Quick Inventory of Depressive Symptomatology (QIDS) (Rush et al., 2003) at baseline and one week and five weeks post-treatment. The researchers collected fMRI-scans one day after each session, and five weeks post-treatment. Analyses of CBF and resting state functional connectivity were conducted. Scores on QIDS-SR16 showed a treatment response (<50% reduction in QIDS-scores) at the one-week follow-up and the effects sustained at the final five-week follow-up post-treatment for five of the 16 participants, but all participants showed significant reductions at the final follow-up. However, these reductions did not meet criteria for treatment

response. The fMRI post-treatment scan showed significantly decreased cerebral blood flow in auditory cortex and parietal areas. However, the increased functional connectivity observed in the post-treatment scan in sub-genual anterior cingulate cortex, amygdala, ventromedial prefrontal cortex, and hippocampus was not significant.

Table 1

Neuroimaging studies with psilocybin on participants with TRD

Study	***(N)***	***Age***	***Sex***	***Diagnosis***	***Dosage***	***Sessions***	***Results***
(Roseman et al., 2018)	19	44.7 (SD=10.9)	6 females 13 males	TRD MDD	10 mg and 25 mg	1 preparatory session+2 therapeutic sessions+4 integration sessions+1 baseline scan session+1 scan session 1-day post-treatment.	Increased BOLD response in right amygdala towards happy (p=0.022) and fearful faces (p=0.001) after 25 mg compared to baseline at one day after second session; Scores in QIDS-SR16 decreased in patients (47.3%) after five weeks.
(Carhart-Harris, Roseman et al., 2017)	16	42.8 (SD=10.1)	4 females 12 males	TRD	10 mg and 25 mg	1 baseline scan session+1 scan session 1-day post-treatment.	Reduced CBF in left amygdala left pre-central gyrus, Heschl's gyrus, left planum temporale, left superior temporal gyrus, right parietal operculum, and right supramarginal gyrus 1 day post-treatment (p=0.01); QIDS-SR16 scores reduced (47%) five weeks post-treatment (p<0.001).

Note. Blood-Oxygen-Level Dependent Signal (BOLD), Cerebral Blood Flow (CBF), Quick Inventory of Depressive Symptoms (QIDS), Default Mode Network (DMN) Major Depressive Disorder (MDD), Treatment-Resistant Depression (TRD).
Clinical response is a >50% reduction in depressive symptoms in QIDS.

4.2.2 Neuroimaging Studies on Healthy Volunteers

Carhart-Harris et al. (2012) found that psilocybin (0.215 mg/kg), in 15 healthy hallucinogen-experienced volunteers, resulted in a decrease in cerebral blood flow in thalamus and posterior cingulate cortex. Relatedly, another study found overall decreased global functional connectivity after doses of LSD and psilocybin were compared to ketamine (Barnett et al., 2020). Yet, a previous study (Müller et al., 2017) reported that 0.1 mg of LSD might disrupt thalamocortical gating and might have resulted in increased global connectivity

between thalamus and sensory regions: an observation previously found in other studies (Müller & Borgwardt, 2019; Müller et al., 2017). Carhart-Harris, Muthukumaraswamy et al. (2016) used fMRI and magnetoencephalography (MEG) to study the effects of LSD and found that LSD resulted in increased activity and oscillatory power in primary visual cortex. Decreased connectivity between retro-splenial cortex and para-hippocampus was also noted, along with decreased delta- and alpha power in the visual cortex- and posterior cingulate cortex (Carhart-Harris et al., 2012). The results of the MEG-study (Carhart-Harris, Muthukumaraswamy et al., 2016) pointed to lower oscillatory power in areas related to DMN during a psychedelic experience with psilocybin. In addition, Muthukumaraswamy et al. (2013) observed a de-synchronization of neural activity in posterior cingulate cortex after 0.075 mg of LSD.

The hallucinogenic effects are explained by deficient gating mechanisms of sensory inputs between cortical- and thalamo-cortical regions of the brain (Baumeister et al., 2014; Müller & Borgwardt, 2019; Vollenweider & Geyer, 2001). Potential evidence comes from studies pointing to that antipsychotics reduce symptoms of the psychedelic state induced by psilocybin – due to their receptor 5-HT_{2A}-antagonistic effects (Vollenweider & Geyer, 2001). Vollenweider (1997) found earlier that the effects of psilocybin could possibly be reflected in increases in cerebral metabolic rate of glucose in fronto-medial and fronto-lateral cortex. These brain regions are part of the areas that have the highest density of 5-HT_{1A} and 5-HT_{2A} receptors (Vollenweider, 1997). The authors interpreted the data as evidence of hyper-frontality being important to the psychedelic state. A smaller increase in metabolic rate in somatosensory cortex was also noted, as well as increases in anterior cingulate cortex and temporo-medial cortex (Vollenweider, 1997).

To conclude, neuroimaging studies have yielded new insights regarding the neural mechanisms of LSD and psilocybin. It is well-documented that 5-HT_{2A} is the most important receptor in bringing forth the psychedelic state since; 1) while the receptors are widely located throughout the cortex, they are also located in DMN-related areas, which are affected by LSD and psilocybin; and 2) the observable effects of LSD and psilocybin are partly blocked by 5-HT antagonists, such as ketanserin and haloperidol (Baumeister et al., 2014; González-Maeso et al., 2007; Preller et al., 2018; Vollenweider & Kometer, 2010). In addition, data from animal studies and autopsies suggest that 5-HT_{1A} and 5-$HT_{1, 4, 5, 6, \text{and } 7}$ receptors might be important in conveying the effects of psychedelics (Baumeister et al., 2014; Nichols, 2004; Preller et al., 2018). The research that has been carried out suggest that reduced cerebral blood flow and increased de-coupling of areas in the DMN underlies the psychedelic state, and that

LSD and psilocybin affect the main hubs of the DMN, in posterior cingulate cortex, medial pre-frontal cortex, and association cortices (Andrews-Hanna et al., 2014; Barnett et al., 2020; Carhart-Harris et al., 2014; Müller & Borgwardt, 2019).

5. Therapeutic Use of LSD and Psilocybin

Classical hallucinogens were introduced into psychotherapeutic studies in the first half of 1950s (Sessa, 2016), and research on psychedelic drugs was intense during 1950s until early 1970s. These early studies generated optimistic results, but they were frequently influenced by different research standards which were set by psychodynamic approaches in contrast to current research standards. Thus, the early studies do not hold up to scientific scrutiny and mainly serve as anecdotal evidence (Grob, 1996; Fuentes et al., 2020).

5.1 Early Studies on LSD and Psilocybin in Therapy

The implications of LSD and mescaline in therapy were, among others, discussed by Osmond (1957). He thought that new forms of psychotherapy should be developed based on new scientific instruments and insights about LSD. Overall, the author was carefully optimistic in his assessment regarding the usefulness of LSD and mescaline in therapy (Osmond, 1957). Most of the older studies described below only investigated LSD due to it being more popular than psilocybin at that time. At the time, there were very few experiments on psilocybin as it was newly discovered at the time.

The main points of interest in studies conducted in 1950s and 1960s were the behavioural effects and how hallucinogens were to be classified considering their behavioural effects. In a study done by Sandison et al. (1954), 36 patients received around 0.02-0.1 mg/kg of LSD. The disorders in the patient group consisted of depression, anxiety, antisocial, hysteria, schizoid personality, and homosexuality (which was considered a disorder at the time) disorders. Each patient started to experience mental and behavioural symptoms after receiving high doses of LSD, which included hallucinations, flashbacks, and increased emotional activity. Behavioural symptoms included a catatonic state, along with occasional giggling, uncontrollable laughter and crying. Data on the frequency of the behavioural effects were not reported. Out of the 36 patients, 14 were considered as recovered from their condition after ingestion of LSD. Overall, the results were considered a success (Sandison et al., 1954). The authors' conclusion was that LSD tended to bring 'repressed memories' (as stated by the author) into surface and that many hallucinations were related to the research setting. However, the study lacked a placebo group and a proper time frame to determine improvement.

In an ambitious experiment, LSD was given to 110 patients with various psychiatric diagnoses, including psychoneurosis (mood disorders), personality disorders, personality trait disturbances, and sociopathic (antisocial) disorders (Chandler, 1960). One group was placed in a miscellaneous category. Each patient started with a dose of 0.025 mg or 0.05 mg, and gradually increased their dosages by 0.025 mg per session, with the highest dose being 0.15 mg. However, sometimes the researchers decreased the dosage with 0.025 mg between two sessions. Each participant had four or five sessions. Feelings of 'mild euphoria' (as stated by the authors) with transient phases of anxiety were common. Hallucinations were also a common occurrence. However, the rate in which these behavioural effects occurred were never reported. Of all 110 patients, 69% improved, with 45.5% showing "considerable or better improvement". However, 20% of patients showed "little or no improvement". The results showed that the group where psychoneurosis, i.e., mood disorders, improved the most. The sociopathic group also showed improvement (Chandler, 1960). No placebo groups were used.

In a long-term study of the use of LSD and clinical and non-clinical settings, McGlothlin and Arnold (1971) recruited 247 Americans. The participants were interviewed regarding their recreational use of LSD. They were divided into four groups; the therapy-initiated group; the non-medical group (who had used LSD outside of medical settings); and two control groups. About 90% of the sample were white. The goal of the study was to assess the value of using LSD in therapy and separate the symptom-relieving effects of LSD from confounds such as personality traits, attitudes, values, and social settings. Thus, the authors used personality traits, attitudes, values, and social settings as dependent variables in their study. The Sensation-Seeking Scale (Zuckerman et al., 1964) was used to measure the participants' proneness to seek out novel experiences. Finally, the participants also took the Myers-Briggs Type Indicator (Myers, 1962) to measure sensing-intuition (a preference of concrete facts vs abstract ideas), and judging-perception (a preference to live an orderly and systematic life vs a preference to live a casual and spontaneous life). McGlothlin and Arnold (1971) found that there was no significant change associated with LSD regarding personality and sensation-seeking in the therapy-initiated group and the control group. Yet, the authors report that most participants felt that taking LSD had led to "some" change (McGlothlin & Arnold, 1971). However, the group who received LSD in a non-medical setting reported significant change in dependent variables such as increase in intuition, perception, and sensation-seeking.

A recent re-analysis and review (Rucker et al., 2016) investigated the results of 19

studies published between 1950 and 1970, in which altogether 423 participants partook in. The authors concluded that 335 participants (79.2%) showed improvements in reducing symptoms of depression and anxiety, but that new double-blind experiments with proper placebo groups are needed.

5.2 Modern Studies on the Use of LSD and Psilocybin in Therapy

During the early to mid-1990s, research on psychedelic drugs continued after the previously mentioned hiatus. Since the old studies were performed according to different research standards, researchers largely revised the way psychedelic research is been carried out. Researchers started to include control groups and adopt tighter restrictions to control for extraneous variables (Garcia-Romeu & Richards, 2018). As a result, the quality of the studies below is more in line with modern research standards. In psychedelic-assisted therapy, the general outline for the therapy bears similarities to the psychodynamic approach to therapy. The general outline consists of a pre-treatment session, at least two therapeutic sessions, and post-treatment sessions (Garcia-Romeu & Richards, 2018; Sloshower et al., 2020).

First is the pre-treatment session that serves to prepare the patient for the therapy sessions (Sloshower et al., 2020). The main goal of the pre-treatment session is to: 1) let the patient talk about what they think are the main causes of their mental illness, their history with mental illness, and how long the patient has been ill; 2) give information to the patient about what may happen during the therapeutic session and discuss the patient's expectations; and 3) to make sure that the patient is in a relaxed state of mind. The latter is called 'the set': a key concept in psychedelic-assisted therapy (Garcia-Romeu & Richards, 2018).

In psychedelic-assisted therapy, the setting and the approach of the therapist towards the patient have a significant impact on how the behavioural effects of the drugs might be experienced and what kind of emotions might arise (Garcia-Romeu & Richards, 2018). Therefore, the setting usually resembles a private living room that is supposed to be relaxing, safe, and inviting where only the therapist and patient are present. The setting is a key concept in psychedelic-assisted therapy since the setting influences the experiences the patient might have with the drug (Garcia-Romeu & Richards, 2018). After the drug has been administered, the patient will spend the rest of the session lying down on a sofa, often with eyeshades. Sometimes, the patient will also listen to pre-selected music that is supposed to reflect their mental state (Garcia-Romeu & Richards, 2018). In this session, the therapist is not supposed to approach the patient, unless the patient feels discomfort. However, if any thoughts or feelings arise that the patient wants to talk about, the therapist should be ready to do so

(Garcia-Romeu & Richards, 2018).

Finally, the post-treatment sessions serve to follow up on changes in symptoms of depression, anxiety, and measures of mood and happiness, typically by scales and interviews. These are integrative sessions where patients can freely talk about their experiences (Garcia-Romeu & Richards, 2018; Sloshower et al., 2020).

5.2.1 Psilocybin in Psychedelic-Assisted Therapy

In a double-blind placebo-controlled study investigating the usefulness of psilocybin on participants with anxiety and depression due to cancer, 12 participants with advanced stage cancer who all had clinical levels of anxiety and depression were recruited (Grob et al., 2011). Only four of them had never taken a hallucinogen before. All participants received two therapy sessions where they were given psilocybin (0.2 mg/kg) or 250 mg niacin first spaced several weeks apart (see Table 2). In the end, all participants received both dosages. Level of anxiety was measured by employing the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). The state component of the scale measures anxiety in response to events, and the trait component measures anxiety as a personality trait. The Beck Depression Inventory (BDI) (Beck et al., 1961) was used to measure levels of depressive symptoms, and transient mood states of the patients during the week were assessed by the Profile of Mood States (POMS) developed by McNair et al. (1971). All scales were administered at baseline, one day after each drug session, then two weeks after every drug session, and finally every month for six months after the final drug session. Reduced scores on the STAI trait component reached significance one month after treatment. Grob et al. (2011) found that the reduced STAI-scores persisted even after six months, along with significantly improved scores on the BDI at six months after treatment. However, increases in POMS-scores did not reach a level of significance during the six months.

In an open-label feasibility study, Carhart-Harris, Bolstridge et al. (2016) investigated 12 participants (six men and six women) with either moderate depression or severe MDD. Previously, all participants had taken two courses of antidepressant treatments for at least six weeks each and had completed antidepressant treatment before this study. All participants received two doses of psilocybin (10 and 25 mg total dose) each one week apart (see Table 2). The low dose was administered on the first session, while the high dose was administered on the second session. There was no control group. Before the drug sessions, scores for all scales were established at baseline. The participants were screened for MDD and anxiety disorder by BDI, QIDS, 21-item Hamilton Depression Rating scale (HAM-D), Montgomery-Åsberg

Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), and STAI, respectively. The Snaith Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) was also used to measure the degree of anhedonia. All participants completed a Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994) one week after the second session. The other scales were also administered one week after the second session. QIDS was employed after two, three and five weeks after the second session. Three months after treatment, the researchers used QIDS, BDI, STAI (trait anxiety), and SHAPS, which were the final follow-up scales. The researchers observed significant reductions in depression severity according to QIDS, BDI, MADRS and HAM-D after one week, and most of the subjects remitted (67%) when QIDS and BDI were used as the primary outcome measurement. After two weeks, seven participants reached requirement for remission (58%). For most of them, the changes lasted for three months post-treatment when 42% met requirements for remission. The trait-component of anxiety as measured by STAI also decreased significantly in intensity from the first week up until three months. However, five of the 12 subjects relapsed after three months according to QIDS-scores. Significant reductions in SHAPS-scores could be observed after one week and scores were further diminished after three months (Carhart-Harris, Bolstridge et al., 2016).

Eight new participants, along with the original 12 participants, entered the researchers' follow-up study where 19 out of 20 participants completed the treatment (Carhart-Harris, Bolstridge et al., 2017). The research design was the same for this follow-up study with one exception: the researchers employed the QIDS-SR16, BDI and STAI in a six-month follow-up. All 19 participants improved significantly according to decreased BDI, QIDS-SR16, STAI (trait), and QIDS-scores one week after treatment and the effects were shown to persist in the three- and six-month follow-ups (see Table 2). The GAF- and HAM-D scores also improved in the one-week follow-up. Anhedonia symptoms, as measured by SHAPS, were also significantly reduced one week after treatment, and the effects persisted even after three months (Carhart-Harris, Bolstridge et al., 2017).

Finally, 51 cancer patients with clinical levels of depression and anxiety were enrolled in a double-blind cross-over study on the effects of psilocybin on mood symptoms (Griffiths et al., 2016). In the sample, 69% of the participants met criteria for clinical depression, while 63% fulfilled criteria for anxiety disorder. Of all participants, 51% had taken courses of antidepressants before the study, but no numbers on how many courses or when they were taken were provided by the authors of this study. The participants were divided into two groups based on whether they received the low dose (1 or 3 mg/70kg) which was the active

placebo condition, or the high dose (22 or 30 mg/ 70kg) first (the dosages were decreased from 3 to 1 mg/70kg, and 30 to 22 mg/70kg, after the study had started) (see Table 2). To measure symptoms of depression BDI, GRID Hamilton Depression Rating Scale (GRID-HAMD-17), and Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) were used. The researchers also used HADS to measure anxiety, and secondly the Hamilton Anxiety Rating Scale (HAM-A). To assess short-term mood, the researchers also administered POMS. After baseline scores had been established, scores from the scales were collected five weeks after each session, and six months after the last session. In addition to the scales, structured interviews and telephone calls were also carried out before the study, five weeks after both sessions, and six months after the last session. Reductions in depressive and anxiety symptoms were significant for the patients according to GRID-HAMD-17, HADS, BDI, HAM-A, and STAI-scores (trait anxiety) (see Table 2). As for measures of well-being, McGill Quality of Life Questionnaire -scores (Cohen et al., 1995) were significantly improved. Changes to more transient positive moods were significant, as measured by POMS. The changes were visible in the first follow-up and were shown to be sustained in the six-month follow-up after treatment, and the changes were more significant in the high-dose condition.

Lastly, Schenberg (2018) reviewed four recent psilocybin-assisted therapy-studies which focused on depression and existential anxiety (Carhart-Harris, Bolstridge et al., 2017; Carhart-Harris, Bolstridge et al., 2016; Grob et al., 2011; Griffiths et al., 2016). In all studies, most participants got remitted after one to two doses of psilocybin. Schenberg (2018) reported that in all experiments, psilocybin was regarded as safe to use in a clinical environment.

Table 2

Double-blind clinical trials with psilocybin

Study	***(N)***	***Age***	***Sex***	***Diagnosis***	***Dosage***	***Sessions***	***Results***
(Grob et al., 2011)	12	36-58 (age range)	11 females 1 male	Depression and anxiety	0,2 mg/kg and 250 mg niacin (as placebo)	1 preparatory session+2 treatment sessions+6 post-treatment sessions.	Significantly lower BDI scores after six months (p=.03); Lower STAI (trait) scores after one month (p=.001); no significant changes in POMS scores after six months.
(Carhart-Harris, Bolstridge et al., 2016)	12	no data found	6 females 6 males	MDD	10 mg and 25 mg	1 preparatory+2 treatment+5 post-treatment sessions.	Lower QIDS (p=.003), BDI (p=.002), and SHAPS-scores (p=.002) after 3 months. Lower STAI (p=.004), HAM-D (p=.003), MADRS (p=.002), and GAF-scores (p=.003) after one week. Most met requirements for

							remission (42%).
(Carhart-Harris, Bolstridge et al., 2017)	19	mean age=44.1 (SD=11)	6 females	MDD	10 mg and 25 mg	1 preparatory+2 treatment+3 post-treatment sessions.	Lower QIDS ($p<.001$) and STAI-scores ($p<.001$) after 6 months. Lower SHAPS-scores ($p=.005$) after 3 months. Lower HAM-D ($p<.001$) and GAF-scores ($p<.001$) after 1 week.
(Griffiths et al., 2016)	51	mean age=56.3 (SD=1.4)	25 females	Depression and anxiety	1 or 3 mg/70kg 22 or 30 mg/ 70kg	2 preparatory+2 treatment+3 post-treatment sessions follow-up sessions	Lower GRID-HAMD ($p<.001$), BDI ($p<.001$), and HAM-A-scores ($p<.001$) at 6-month follow-up.

Note. Beck Depression Inventory (BDI), Quick Inventory of Depressive Symptoms (QIDS), Spielberg's State Trait Anxiety Inventory (STAI), Profile of Mood States (POMS), Snaith-Hamilton Pleasure Scale (SHAPS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Hospital Anxiety and Depression Scale (HADS), Montgomery-Åsberg Depression Rating Scale (MADRS), GRID-Hamilton Depression Rating Scale (GRID-HAMD), Global Assessment of Functioning (GAF), Hamilton Anxiety Rating Scale (HAM-A).

5.2.2 LSD in Psychedelic-Assisted Therapy

The number of recent studies using LSD compared to psilocybin is relatively sparse; thus, newer studies on the therapeutic mechanisms of LSD were significantly harder to find. In this stage of research, the therapeutic benefits of LSD are yet to be determined (Bershad et al., 2019). Despite the lack of new clinical trials, one double-blind experiment was found which will be presented below.

Gasser, Kirchner et al. (2014) conducted a study on LSD for treating anxiety associated with life-threatening disease. Twelve participants (six males; mean age=51.1) participated in the double-blind, active placebo-controlled randomized clinical trial and received either a moderate dose (0.20 mg, N = 8) or a low dose (0.02 mg, N=4, active placebo condition) across 6-8 therapy sessions. None of the participants took antidepressants or any other medications during the study. The participants answered the trait and state scales of STAI at baseline and one week after each session. After the last session, the participants took the STAI scale again at two-month and 12-month follow-ups. Interviews were also carried out in the Long-Term Follow-Up (LTFU) investigation 12 months after the last session, and a qualitative content analysis was also used to measure changes in levels of positive mood. The LTFU-study did not control for concomitant antidepressant use. Ten patients (two had died) had reductions in STAI trait-scores (77.8%) and reported enhanced positive mood (66.7%) 12 months after the treatment was finished. These results were also replicated in the interviews. Compared to the low-dose placebo condition, LSD administered in the high-dose condition had a bigger impact on the patients with more significantly reduced scores according to STAI-trait scale after a two-month follow-up. The changes sustained even after 12-months post-

treatment and no adverse effects were reported. Four participants, who were first in the active placebo group and received the low dose, were later told about the drug dose they ingested, and they also received the moderate dose.

A 12-month follow-up analysis was made by the same research team, were Gasser, Holstein et al. (2014). Results from other scales such as European Quality of Life Questionnaire (Aaronson et al., 1993), HADS, and Symptom Checklist-90-R (Schmitz et al., 2000) were reported. The results showed that the significant reductions in STAI (state) persisted for two months during the blinded two-month follow-up. However, the reductions were not significant during the crossover follow-up (after all participants received both the high and low dose), nor for any other scales regardless of either follow-up. Neither did the reductions in STAI-scores sustain for the 12-month follow-up. Regarding the scores on the other scales, no significant changes could not be reported either.

As in the case with psilocybin the number of participants in this study is too low to draw any definitive conclusions because it is a pilot study. However, the study was a double-blind experiment, which increases the potential replicability and generalizability of the results. Therefore, the results look promising when it comes to the potential therapeutic benefits of LSD. Notably, no studies on depression and LSD were found.

6. Discussion

The aim of my thesis was to provide a literature review on the neural mechanisms of LSD and psilocybin and investigate whether LSD and psilocybin can be applied efficaciously in the treatment of depression and anxiety disorders. Clinical and neuroscientific results indicate that there is significant potential for LSD and psilocybin to be used as treatment for depression and anxiety. Evidence that activity of 5-HT_{2A} receptors and the de-coupling of DMN seem to underlie the therapeutic therapy of the drugs is supported.

6.1 Application of LSD and Psilocybin in Therapy

Psilocybin seems to be a viable treatment method for patients with anxiety and depressive disorders. Furthermore, the decreases in depressive and anxious symptoms lasted for at least three months in all four studies, and tended to last for at least six months in three studies (Carhart-Harris, Bolstridge et al., 2017; Grob et al., 2011; Griffiths et al., 2016; Griffiths et al., 2011). Moreover, the psychedelic experiences resulting from psilocybin were deemed by most of the participants across all studies to be positive. Even healthy volunteers tended to report positive experiences associated with psilocybin (Griffiths et al., 2011). When used in a controlled fashion, psilocybin does not put the patient in significant risk of long-

term side-effects due to treatment.

Pilot studies that have used LSD as treatment have shown comparable therapeutic results to psilocybin. Since I only could find one recent study on LSD as treatment for anxiety associated with life-threatening disease, even less conclusions can be drawn from these results. Despite that, the data on LSD also looks promising. As is the case with psilocybin, there seem to be no safety issues with administering LSD in a therapeutic setting. Further, the effects that LSD had on anxiety as a personality trait (trait anxiety) rather than in response to an event (state anxiety) were long-lasting but reductions in both state and trait measures of anxiety were equally significant (Gasser, Kirchner et al., 2014). Since only one modern study on LSD could be found, caution should be taken when interpreting the data.

Finally, there is an important discussion to be had about the role of the therapist in psychedelic-assisted therapy. In this therapy paradigm, it is crucial that the therapist succeeds in developing a positive rapport with the patient: especially since therapeutic sessions usually last for several hours (Garcia-Romeu & Richards, 2018). Furthermore, each session lasts for several hours, depending on which psychedelic is used and how long the effects last. The relationship between the therapist and the patient is especially important since patients are supposed to share their experiences in the integration sessions. The therapist should be able to help the patient address any traumatic memories or experiences that may arise. The therapist may achieve this by helping the patients gain insights about their experiences, and then support them in developing self-acceptance, regardless of the patient's experience with the drug, by giving unconditional positive regard (Garcia-Romeu & Richards, 2018). The task of the therapist also relates to the concepts of set and setting, as these concepts need to be taken into consideration to establish a sense of safety on behalf of the patient. Finally, another important task for the therapist is to deal with potential adverse effects that may arise during therapeutic sessions, which will be discussed in the next paragraph.

Even though LSD and psilocybin carry low risk of drug abuse, there are safety concerns that are worth mentioning. Transient anxiety in participants was common in all studies (Carhart-Harris, Bolstridge et al., 2017; Grob et al., 2011; Griffiths et al., 2016; Griffiths et al., 2011), which is a factor that therapists should take into concern if psilocybin and LSD are to be classified as viable treatment alternatives. Furthermore, the risk of a panic attack, although a rare occurrence (Amsterdam et al., 2011), might deter a few patients from seeking psychedelic-assisted therapy. Still, panic attacks can be managed with NMDA-agonists, which cancel the effects of psychedelics, and serotonin-antagonists and support by the therapist. Because of the nature of how LSD and psilocybin affect the user, people with

increased vulnerability to psychotic episodes, i. e., people with schizophrenia, should not be given LSD or psilocybin, as these substances might exacerbate the already increased risk of a psychotic episode (Vollenweider & Geyer, 2001). Lastly, hallucinogen persisting perception disorder (HPPD) may occur from repeated psychedelic use, and although it seems to be rare, the rate of occurrence remains uncertain (Müller & Borgwardt, 2019).

6.2 The Role of Serotonin and DMN Activity Changes

Based on neuroimaging data from the last two decades, the activation of various types of 5-HT receptors in producing the psychedelic state is strongly supported, and placebo studies where 5-HT antagonists have been used serve as evidence for the involvement of these receptors (González-Maeso et al., 2007). The increased level of serotonin release in fronto-cortical structures, after ingestion of LSD and psilocybin might explain why patients consistently become less depressed and anxious after exposure (Baumeister et al., 2014; Carhart-Harris et al., 2012; Vollenweider & Kometer, 2012). According to the monoamine deficiency theory, LSD and psilocybin may reverse symptoms of depression and anxiety since studies show that both substances increase serotonin availability (Hasler, 2010). The therapeutic results from clinical studies lends support to this theory (Hasler, 2010).

Neuroimaging studies on the effects of LSD and psilocybin have shown that reduced activity in the DMN relates to the psychedelic state as shown by decreased blood flow in brain regions related to the default mode network (Carhart-Harris, Muthukumaraswamy et al., 2016; Carhart-Harris et al., 2012). The results are the same for both LSD and psilocybin. Adding to this, the DMN usually consumes 40% more energy than the rest of the brain. However, in the psychedelic state the energy consumption is significantly reduced. Possible converging evidence comes from studies that have shown that the psychedelic state is associated with decreased functional connectivity in DMN in healthy volunteers (Barnett et al., 2020; Carhart-Harris et al., 2012; Carhart-Harris et al., 2014; Carhart-Harris, Muthukumaraswamy et al., 2016; Müller et al., 2017). However, the DMN activity in patients with clinical depression and anxiety is significantly increased, which is associated with increased sad mood and rumination (Andrews-Hanna et al., 2014; Kopala-Sibley & Zuroff, 2019). Yet, how the alterations in the DMN activity induced by psychedelics affect patients with clinical depression and anxiety is currently unspecified.

On the topic of functional connectivity, recent neuroimaging evidence suggest that the thalamus might act as a gatekeeper that blocks information from the DMN, while at the same time allowing more sensory information to arise in consciousness. Here, the evidence mainly

seems to suggest that functional connectivity between the thalamus and the DMN decreases. Meanwhile, functional connectivity *within* sensory networks and between sensory networks and the thalamus increases (Carhart-Harris et al., 2014; Carhart-Harris, Muthukumaraswamy et al., 2016; Carhart-Harris, Roseman et al., 2017; Smigielski et al., 2019). The data carry implications for anxiety and depression since it suggests that increased functional connectivity between these networks serve to attenuate symptoms of depression and anxiety (Andrews-Hanna et al., 2014).

The Entropic Brain Theory (Carhart-Harris et al., 2014) may be useful for understanding the neural mechanisms of the psychedelic state. Entropy began as a concept in physics and chemistry and refers to the tendency of a system to gravitate towards disorder. In the case of mental states, entropy is the degree of disorder present in brain networks. Altered states of consciousness is defined as 'primary state' by the entropic brain theory: ASC are states characterized by a higher degree of entropy (Carhart-Harris et al., 2014). According to the theory, the subjective quality of any 'primary state' can be measured by the level of entropy present in a brain network (or several networks). In this theory, entropy is a unit of information processing that can be quantified and indexed (Carhart-Harris, 2018). In their theoretical article, Carhart-Harris et al. (2014) propose that the psychedelic state is a primary state of consciousness with relatively high entropy that is caused by decreased interconnectivity between posterior cingulate cortex and brain areas that are part of DMN (Carhart-Harris et al., 2014). Independent studies of how the DMN is influenced by LSD and psilocybin reinforce the probability of the theory on a theoretical level. According to Carhart-Harris et al. (2014), the organized information processing in the human brain is characterized by relatively low entropy. However, when the functional connectivity within the DMN and with the thalamus decreases, the level of entropy increases. The psychedelic state is thought to be closer to criticality compared to the normal state of consciousness. In the Entropic Brain Theory, it means that the higher entropy found in the psychedelic state is closer to the level of entropy found in nature, as stated by the authors (Carhart-Harris et al., 2014; Carhart-Harris, 2018). Since patients with depression might have even lower brain entropy (Sessa, 2016), LSD and psilocybin may serve to loosen functional connectivity, which in this case could refer to higher brain entropy. Most of the studies presented in this essay did not use the Entropic Brain Theory as a framework. Thus, the theory is mostly indirectly supported by other review articles and studies of the DMN that did not use the theory as a framework. It should be noted that, since the entropic brain theory has received little empirical evidence, its causal explanations and the implications of the theory should be taken with caution. As far as

this essay is concerned, few attempts have been made to quantify entropy. In addition, research into the neural mechanisms of LSD and psilocybin is still in its early phase. Hence, no causal explanations based on the theory can be made at this moment

The problem about neuroimaging studies, however, is that there is still little data. Much of the work done on how the DMN is influenced is theoretical and based on original studies on healthy volunteers. The same can be said about the data on resting state functional connectivity. Furthermore, the data about the neural mechanisms are contradictory. It is not proven yet whether decreased functional connectivity underlies the behavioural effects of LSD and psilocybin. There is a lack of neuroimaging studies done on patients with depression and anxiety. There are reasons to believe that the neural mechanisms of LSD and psilocybin affect clinical and healthy populations differently. In both studies presented in this essay, resting-state functional connectivity increased in clinical populations, which appear to contradict what other researchers have said (Carhart-Harris, Roseman et al., 2017; Mertens et al., 2020). Functional connectivity in healthy volunteers tended to decrease, which suggest a stark contrast in mechanisms of actions on clinical- and healthy populations, and this observation challenges the Entropic Brain Theory (Barnett et al., 2020; Carhart-Harris et al., 2012). Due to these inconsistencies, no conclusions about the exact alterations within the DMN can be made.

Finally, while the data on the neuroplasticity effects of LSD and psilocybin is fascinating, it is also inconclusive. Evidence of neuroplastic effects have only been observed in animal studies and in vitro studies (Ly et al., 2018). There are no studies on neuroplastic effects on humans other than the observed behavioural effects of LSD. However, based on the observable long-term effects of psychedelic use, it is likely that neuroplastic effects occur (Ly et al., 2018). Yet, the exact mechanisms of these neuroplastic effects remain to be investigated.

6.2.1 Limitations of LSD and Psilocybin in Therapy

A conclusion one can draw from the older studies conducted between 1950s and 1970s is that, although the results are positive, they do not hold up to scientific scrutiny. There is an over-reliance on personal observations made by the researchers and subjective reports from the participants. In addition, the samples included participants with different disorders and diagnoses and not just patients who suffered from depression and anxiety disorders. To further complicate this dilemma, the criteria and definitions for depression and anxiety have changed since those studies were conducted. For example, psychoneurosis (or neurosis) is an

outdated umbrella term for other disorders than anxiety, such as obsessive-compulsive disorder. Hence, the participant samples are not comparable to the samples used in the modern studies. Furthermore, the studies lacked placebo or comparison groups. In addition, the studies lacked a proper time frame for assessing improvement in symptoms. The results, however, give positive anecdotal evidence – and make the investigations worthwhile, nevertheless. Even though anecdotal evidence never substitutes scientific rigor the results still deserve interest.

Since the dawn of neuroimaging techniques, significant insights have been made in this research area. New results on the therapeutic benefits of LSD and psilocybin look promising. The experimental standards are updated in the newer compared to the older studies and the replicability of the present studies is higher. Although important strides have been made in this research area, generalizations about the therapeutic effects of LSD and psilocybin cannot be made in this moment of writing. A significant problem is that the research area is in its early phase, and very few studies on clinical populations have been made thus far. Other significant flaws include small participant samples. The issue of co-morbidity is also an obvious flaw since many participants met criteria for both MDD and anxiety, making it more challenging to meaningfully distinguish between the therapeutic benefits for the disorders individually. On a similar note, the majority of the participants suffered from moderate to severe MDD, and the degree of anxiety disorders present in the samples remains questionable since STAI can never be a proper tool to diagnose any anxiety disorder. At best, STAI is an important indicator of the degree of anxiety present as a state or trait factor.

The risk of suggestibility as a confounding variable can also not be ignored. The risk of suggestibility is a complex problem in all the presented studies. Since the preparatory sessions are supposed to make the patients relaxed, these sessions might increase their susceptibility to the behavioural effects of psychedelic. Hence, it remains a challenge to meaningfully separate effects caused by suggestibility from effects that are the result of LSD and psilocybin. In a way, suggestibility is integral to psychedelic-assisted therapy since the preparatory session is needed to make the patient aware of the behavioural effects. What further complicates this issue is that the behavioural effects of LSD and psilocybin are influenced by the setting, making it hard to separate between the objective effects of the drug and the setting. Thus, suggestibility remains a confound that is challenging to control for.

A related issue is that several of the patients were not hallucinogen naïve, which could have resulted in expectancy bias among the patients. In this instance, the therapist could also be guilty of such an expectancy bias. The combination of expectancy bias, along with

increased suggestibility could have distorted the results towards positive outcomes. On a similar note to expectancy bias, there is the issue of self-selection bias. In most of the studies, the participants volunteered for the experiments. People who volunteered for these studies may be more likely to have tried a hallucinogen at least once. These mentioned methodological flaws are important reasons to believe that LSD and psilocybin's therapeutic effects might in fact be less significant if made available to larger participant samples.

6.3 The Future of LSD and Psilocybin in Therapy

There are still challenges for the neuroscientific community to overcome in the research on psychedelics, both practical and scientific problems. The practical challenges stem from the 1971 Convention on Psychotropic Substances. Scientific understanding of these drugs has not advanced as much as it could have. Even though research into psychedelics is technically legal, the restrictions on LSD and psilocybin contribute to an effective ban. The practical difficulties have not only arisen from the placement of LSD and psilocybin under Schedule I but also because of legal justifications. Currently, the only true legal justification that exists to gasserban drugs, from a government's perspective, is for harm prevention, which is the only justification a government needs (Nutt et al., 2013). Thus, the nature of the ban of LSD and psilocybin are certainly political and not based on any data because the scientific standards in psychology were not as well-established back when this treaty was crafted. The regulations resulting from the treaty are still intact even though classical hallucinogens are among the least dangerous psychotropic drugs, substances that causes alterations in mental functions. The substances are not addictive, and the risk of abuse and the perceived societal harms is among the lowest of all narcotics (Amsterdam et al., 2011; Bonson, 2017; Nutt et al., 2010; Stewart & Kalueff, 2013; Studerus et al., 2010). The laws create a circular problem were researchers cannot investigate the risks and benefits of LSD and psilocybin because governments perceive the substances to be much more dangerous than they actually are. This leads to difficulties getting ethical approval for studies, and doses becoming more expensive which, in turn, leads to fewer participants, and in turn lower the validity of the experiments. Thus, any attempts to put both drugs under a different schedule, like Schedule II, would make research into the drugs easier. Another solution could be to make the obtaining of licences easier, or just lift the ban on psychedelics for research altogether.

Aside from the practical and legal challenges, more data on the functions of the DMN are an important part of understanding the neural effects of psychedelics. At the time of writing, new double-blind clinical trials were psilocybin is used on patients with MDD, is

currently ongoing. In one of the clinical trials, LSD is used as a treatment method against patients with MDD for perhaps the first time in years (see Table 3). Furthermore, the Entropic Brain Theory is worth investigating due to the context it provides to the mechanisms of functional connectivity. Due to the inconsistent findings provided the DMN alterations, another interesting area of research is the differences between how DMN is affected in clinical and healthy populations as a result of LSD and psilocybin. In addition, a better understanding of the mystical experiences that LSD and psilocybin give rise to is also necessary. Insights about the psychedelic experience will help therapists meet the patients' needs so they can help the clients understand what they are experiencing. Generally, more studies that provide insights about altered states of consciousness are needed because, in the end, the subject of psychedelic drugs is a subject that relates to consciousness. More insights about altered states of consciousness increase our understanding about the neural mechanisms that give rise to consciousness.

Of course, more clinical, and therapeutic studies with bigger participant samples are needed to strengthen the replicability and generalizability of the data. On a similar note, LSD and psilocybin as treatment for alcohol and drug addiction is an ongoing area of research, whose results have shown significant promise (Carhart-Harris, Kaelen et al., 2016; Schenberg, 2018). Once researchers have access to bigger participant samples scientists might be more able to conduct studies with more specific samples, like participants with late onset depression and dysthymia (a milder form of depression that is longer-lasting than MDD). Likewise, distinctions between different types of anxiety disorders, like social anxiety and specific phobias, can be made. Then, distinctions between sub-types of depression and anxiety, and their corresponding neural mechanisms can be made, and with that, new variations of psychedelic-assisted therapy might emerge.

Table 3

Summary of on-going clinical trials.

Sponsor	***Substance***	***Diagnosis***	***Dosage***	***Study design***	***Placebo***	***Status***	***Ending***	***Trial number***
Usona Institute	Psilocybin	MDD	25 mg	Phase II, Randomized, double-blind trial	100 mg niacin	Recruiting	February 2021	NCT03866174
Johns Hopkins University	Psilocybin	MDD	No data found	Phase II Randomized, double-blind trial		Active, not recruiting	dec-20	NCT03181529

Yale University	Psilocybin	MDD	0.1 mg/kg, 0.3 mg/kg	Phase I, randomized, double-blind cross-over trial	Microcrystalline cellulose	Recruiting	apr-20	NCT03554174
University Hospital, Basel	LSD	MDD	0.025 mg 0.10 mg	Phase II, randomised, double-blind, active-placebo-controlled trial	Low dose of LSD	Recruiting	July 2023	NCT03866252
University Hospital, Basel	LSD	Anxiety	0.20 mg	Phase II, randomized, double-blind, placebo-controlled, crossover	Participants acting as their own control	Recruiting	May 2021	NCT03153579
NYU Langone Health	psilocybin	Anxiety	0.3mg/kg	Phase I double-blind, placebo-controlled pilot study	Niacin 250 mg	Active, not recruiting	dec-19	NCT00957359

One final point is that, if LSD and psilocybin are to be accepted into therapeutic use, the education of the therapists will need to change for therapists who wish to practice psychedelic-assisted therapy. The primary focus would be placed on the neural and behavioural effects of classical hallucinogens, and what long-term benefits and drawbacks to expect of these substances. The knowledge is important for the therapists to deal with potential adverse effects that may arise in therapy.

7. Conclusion

To conclude, this essay reviewed the neural mechanisms of LSD and psilocybin and discussed how the neural mechanisms seem to underlie the behavioural effects that might make these drugs effective in therapy. In this essay, findings showed; 1) LSD and psilocybin act on 5-HT_{2A}, 5-HT_{1A}, and other 5-HT receptors that underlie the behavioural effects of the drugs; 2) the DMN is a region of interest because both drugs exert much of their influence on posterior cingulate cortex and medial prefrontal cortex; and 3) when administered in therapeutic setting, the behavioural effects of LSD and psilocybin show reductions in anxiety and depressive symptoms. These results serve as guidance for how the framework for psychedelic-assisted therapy may look like, as well as how LSD and psilocybin may be administered in a therapeutic setting. More studies on the neural mechanisms and therapeutic effects of psychedelics are urgently needed to understand the potential benefits and side-effects of these substances. However, despite a societal need for new treatment methods for mood disorders, current national and international regulations are obstacles in doing research

on LSD, psilocybin, and other classical hallucinogens. So far, the future for research into LSD and psilocybin looks promising and the scientific community has years and decades of intriguing findings to look forward to.

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