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Psilocybin as Treatment for Depression

Bachelor Thesis

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Abstract

Depression is the main cause of disability worldwide and negatively affects the quality of life. It is characterised by a depressed mood and a lack of pleasure or interest in activities. Antidepressants and psychotherapy are used to treat depression, however, these treatments are still unsatisfactory as they have limited effectiveness and adherence. Treatment-resistant depression is therefore sometimes diagnosed in the patients that do not respond to these established treatments. Fortunately, more options are available to treat depression such as brain stimulation therapy and treatment with psychedelics. Research on the use of psychedelics for the treatment of psychiatric disorders flourished in the 1950s and 1960s. However, in the late 1960s use of psychedelics was associated with the counter-culture movement and the use of psychedelics was banned, which resulted in the arrest of research that involved the use of psychedelics. In the past years, the potential of psychedelic drugs for the use of mental disorders has been rediscovered. Psilocybin is a classic psychedelic that can be found in a variety of fungi, and functions as a 5-HT receptor agonist. Administration can result in intense changes in perception and mystical experiences. Research on the treatment of depression with psilocybin has shown very promising results with a fast onset of psilocybin's antidepressant effects and relatively few side effects. This thesis investigates whether treatment of psilocybin is better compared to established methods, such as antidepressants. Unfortunately, based on literature, this cannot be rejected nor confirmed as not enough comparative studies are available to make a solid conclusion. More comparative research is necessary to be able to make such statements.

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Introduction

It is normal for a person to have a depressed mood or a lowered interest and pleasure in activities from time to time. Nevertheless, when this mood state remains for a couple of weeks, it is called depression. Depression is one of the most commonly experienced mental illnesses and negatively affects the quality of a person's life by manifesting itself in productivity loss, lack of interest in activities and increasing the risk of suicide (Jenkins, 2017). Even though depression appears to be among the most treatable of mental disorders, treatment is still problematic (American Psychiatric Association, 2020). Generally, depression is treated with psychotherapy combined with antidepressants. Five different types of antidepressants are used for treatment, with selective serotonin reuptake inhibitors (5-HT SSRIs) being the most commonly prescribed drugs. These drugs are known to have the best tolerability and safety, nonetheless, they still receive a lot of criticism. They are poorly efficacious, have a delayed onset of their effects and sometimes even produce adverse effects. People that take antidepressants often experience a lot of common side effects, such as sexual dysfunction, sleep disturbances and anxiety. This makes the present-day treatment of depression highly unsatisfactory, resulting in the consideration of alternative treatments by research institutions (American Psychiatric Association, 2020; Jenkins, 2017; The National Institute of Mental Health, 2018). Recently the potential of psychedelic drugs has been rediscovered as a treatment for depression. Publications show very promising results regarding the treatment of depression with the hallucinogenic psilocybin, which is present in fungi commonly known as magic mushrooms (Carhart-Harris et al., 2016, 2018; Davis et al., 2021; Tullis, 2021). Researchers at the John's Hopkins Centre for Psychedelic and Consciousness Research are already studying the antidepressant effects of psilocybin in clinical trials (Davis et al., 2021). These new insights give rise to the following question: "Is the use of psilocybin as a treatment for depression better than the currently used treatments?"

Chapter 1 | Depression

Depression is a leading cause of disability worldwide, affecting 264 million individuals of all ages (World Health Organisation, 2021). Depression negatively impacts the quality of life and increases the risk of suicide, making it a major contributor to the overall global burden of disease and a substantial risk for public health (Harris & Barraclough, 1997; World Health Organisation, 2021). Furthermore, the all-cause mortality risk is 1.7 times greater for people with depression than the risk for the general public (Walker et al., 2015). The concerns for depression in Europe are also high with a lifetime prevalence of 9% among European adult men and 17% among European adult women (OECD & European Union, 2018). Additionally, the economic burden of depression is increasing, analysis estimated that the costs of depression in the US are over $210 billion (Greenberg et al., 2015) and the overall mental health costs in Europe were already exceeding the €600 billion in 2018 (OECD & European Union, 2018). These numbers emphasize the severity of depression and the need for effective treatment.

Depression is characterized by having a depressed/lowered mood or feeling sad, together with a loss of interest or pleasure in activities. However, many more symptoms can be included such as changes in appetite and sleep patterns, loss of energy or increased fatigue, feeling restless, reduced concentration, difficulty making decisions, feelings of worthlessness or guilt and even recurrent thoughts of death or suicide (American Psychiatric Association, 2013; Bear et al., 2016). Not every depressed person experiences the same symptoms and some experience more symptoms than others. A person suffers from depression if they experience at least five of these symptoms most of the day, nearly every day, for at least two consecutive weeks (American Psychiatric Association, 2013; Bear et al., 2016).

There are multiple types of depression with Major Depression (MD) being the classic type, containing the before mentioned symptoms. When these symptoms remain present for at least two years it will be called Persistent Depressive Disorder (PDD), the symptoms of this depression may not reach the same intensity as MD but are chronically present. Bipolar Disorder also called Manic Depression distinguishes itself by the presence of extreme low periods, with symptoms compared to those of MD, in alternation with periods of abnormally elevated mood, named mania. When experiencing Seasonal Affective Disorder (SAD) a person has a period of MD which often happens during the winter months. There are also depression types unique to women: Postpartum Depression (PPD) which occurs after childbirth and Premenstrual Dysphoric Disorder (PMDD) which arises at the start of menstruation. (American Psychiatric Association, 2013; Bear et al., 2016; Merz, 2020)

Several factors increase the risk of developing depression. Current research suggests that it is most likely to be caused by a combination of risk factors, these include genetic, biological, environmental, and psychological factors (Rot et al., 2009; The National Institute of Mental Health, 2018).

Chapter 2 | Treatment of Depression

Following a diagnosis for depression psychological and pharmacological treatment are usually used to treat depression, however, these treatments are not always able to relieve the symptoms. Brain stimulation therapies can also play a role in treating mental disorders additionally, other options such as treatment with psychedelics are now studied to help patients with treatment-resistant depression. Within the different possible treatments, there is a diverse offer of options. The wide range of treatment options already implies that the optimal treatment for depression is still hard to find.

Psychological treatment

During psychotherapy, clinical methods and the use of psychological principles will be used in social interaction to help a person change their behaviour, cognition, emotions, and/or other personal characteristics. This will be done in order to guide the participant to their desired personal characteristics (Campbell et al., 2013). Therapy can be an effective form of treatment for depression because it can help people process negative experiences and handle negative thoughts (Institute for Quality and Efficiency in Health Care, 2020). Fifteen different types of therapy may be effective in the treatment of depression (Cuijpers et al., 2019). The most commonly known are; Cognitive Behavioural Therapy (CBT), Behavioural Activation Therapy (BAT) and Interpersonal Psychotherapy (IPT). CBT is the most studied psychotherapy for depression and its approach is used to alter a person's behaviours and attitudes, as well as to work out problems by finding solid solutions (Jenkins, 2017). During BAT the basic elements of the treatment are to increase positive interactions between the environment and the participant along with the appreciation of pleasant activities. IPT in turn focuses on the complication in personal relationships and the acquired skills to handle these problems (Cuijpers et al., 2019).

Pharmacological treatment

Until the 1950s no effective drug treatment for depression was available. It was in the late 1940s that doctors "by chance" noticed an uplifted mood in patients that were treated with a drug used for tuberculosis. A derivative from this drug, iproniazid, was subsequently found to reduce symptoms of depression, however, it appeared to come with harmful side effects (Bear et al., 2016; Carlson & Birkett, 2017b; Crane, 1957; Jenkins, 2017). Fortunately more types of pharmacological treatments to help depressed patients are available nowadays, for example, lithium, which is mostly used for bipolar affective disorders, and antidepressants (Bear et al., 2016). Antidepressants come in various forms that can be classified into five main forms; Serotonin and noradrenaline reuptake inhibitors (SNRIs), Tricyclic/Tetracyclic Antidepressants (TCA/TeCA), Atypical Antidepressants (Aty), Monoamine oxidase inhibitors (MAOIs) and Selective Serotonin Reuptake Inhibitors (SSRIs). The use of antidepressants is continually increasing in most European countries with an increase of on average 19.83% per year (Gusmão et al., 2013). In 2020, about 1.038.610 Dutch citizens used antidepressants and this number is continuously increasing (GIP-databank Geneesmiddelen, 2021).

The different types of antidepressants are mainly named after their functioning. SNRIs inhibit the reuptake of the neurotransmitters serotonin and noradrenaline in the synapse. Serotonin (5 hydroxytryptamine – 5HT) plays a role in the regulation of mood and pain as well as in the control of arousal, eating and sleep. Noradrenaline, also called norepinephrine (NE), contributes to the sleep-wake cycle, memory storage and the response to stress and exercise. NE is also important for the regulation of emotions, especially positive and euphoric feelings. TCA/TeCA are among the oldest antidepressants and also work by inhibiting the reuptake of 5-HT and NE by the brain. Additionally, they partially inhibit the reabsorption of dopamine. Dopamine (DA) has been implicated in several important functions that contribute to the ability to think and plan. Next to their working on 5-HT and NE, Aty's acts mainly on the neurotransmitter DA, which makes them affect the brain differently compared to other antidepressants. SSRI derived the name from the neurotransmitter they act on; serotonin. SSRIs inhibit the reuptake of 5-HT into neurons of the raphe nuclei. Receptors linked to the working of this antidepressant are the 5-HT_{1A} and 5-HT_{2A}. As this form of antidepressants shows the least side effects, they are prescribed the most, compared to other antidepressants. (Carlson & Birkett, 2017a; Jenkins, 2017; Yohn et al., 2017)

Even though the antidepressants used nowadays aim to be as selective as possible, complete selective neurotransmitter medication is not yet achieved. 5-HT elevation does not go without interactions with NE and DA. This interaction therefore may result in undesired and unforeseen effects regardless of the underlying mechanism, which could be a reason why people who are taking antidepressants experience side effects (Jenkins, 2017). Side effects can be physical symptoms such as headaches, sleep disorders, sexual dysfunction and suicidal behaviour (Jenkins, 2017). Furthermore, therapeutic effects usually only appear after multiple weeks of treatment, which could be because the required stabilization of monoamine levels and other neuroadaptation takes time (Popa et al., 2010). Most concerning is the fact that many people taking antidepressants do not respond to this treatment (Jaffe et al., 2019), which will be described shortly.

Treatment-Resistant Depression

In most adults, pharmacological treatment fails to relieve the symptoms of depression. At least half of them will not maintain relief of the symptoms following multiple treatments (McIntyre et al., 2014). If this occurs, it can be speculated that the person has treatment-resistant depression (TRD). Even though no universally accepted definition of TRD exists, it is suggested that TRD can be defined as failure to induce a clinically meaningful remission with the consecutive treatment of two or more adequate antidepressant trials, used at a sufficient dose and tolerable length of time (Jaffe et al., 2019; McIntyre et al., 2014). TRD occurs in 30% of the patients treated for MD (Jaffe et al., 2019), nevertheless, more treatment options are available apart from the psychological and pharmacological treatments for example brain stimulation therapy and treatment with psychedelic drugs.

Brain stimulation therapy involves directly activating or inhibiting the brains activity through the use of electricity, implants, or magnets (Rausch, 2021; The National Institute of Mental Health, 2016). Electroconvulsive therapy (ECT) uses an electric current that is being passed through the brain to trigger a seizure. Improvement in symptoms occurs more rapidly compared to the use of antidepressants, however, relapse is a common problem (Carlson & Birkett, 2017b; Mutz et al., 2019). Treatment with vagus nerve stimulation applies indirect electrical brain stimulation to the vagus nerve and does not evoke a seizure (Carlson & Birkett, 2017b; Kraus et al., 2019). Transcranial magnetic therapy uses electromagnetic fields to modify the neural activity in relatively focal, superficial areas of the brain, which results in similar benefits as ECT but without inducing the risks that come with it (Carlson & Birkett, 2017b; Mutz et al., 2019). Lastly, deep brain stimulation (DBS) provides direct electrical stimulation of the brain via electrodes at specific neuroanatomical sites. This treatment has very positive results concerning reducing depression symptoms but needs to be further studied (Carlson & Birkett, 2017b; Kennedy et al., 2011). Benefits of brain stimulation therapy have been indicated by literature, however, the underlying mechanisms of this treatment on depression are not always clear and are beyond the scope of this thesis.

In the 1950s and 1960s, more than 1,000 scientific papers and reports were published on the use of classic psychedelics (serotonergic hallucinogens) such as lysergic acid diethylamide (LSD) and 4-phosphoryloxy N,N-dimethyltryptamine (psilocybin) as a psychiatric treatment. However, after a big movement of recreational use of these drugs, they were banned, and supplies for research were constricted by the FDA (Belouin & Henningfield, 2018; Nichols, 2016). Recently scientists are rediscovering the use of psychedelic drugs in the treatment of depression (Tullis, 2021; Vollenweider & Preller, 2020). Studies focused on the use of psilocybin as a treatment to reduce symptoms of depression show promising results, which will be described in chapter 5 (Carhart-Harris et al., 2016, 2018; Davis et al., 2021; Griffiths et al., 2016).

Chapter 3 | The Neurobiological Mechanisms of Depression

As depression results in the coexistence of many symptoms ranging from depressing emotions and decreased energy to eating and sleeping disorders, it is very applicable to imply that depression reflects the changed functioning of different brain parts simultaneously. This reasoning resulted in the traditional focus of research on the neurobiology of depression into the role of the diffuse modulatory systems such as the serotonergic and noradrenergic systems (Bear et al., 2016).

To appreciate the reasoning behind the hypothesised underlying mechanism it is crucial to understand the process of synaptic transmission. Therefore, a brief explanation of the pre-and postsynaptic events will be provided first. Figure 1 schematically depicts a classic neurotransmitter synapse. During the first step of the synthesis, amino acids are conveyed from the blood to the brain. Facilitated by enzymatic processes the precursors are transformed into transmitters. After conversion, these transmitters are stored into synaptic vesicles to eventually be released into the synaptic cleft. This release process is regulated by a before-mentioned depolarization signal which is Ca^{2+}-dependent. The pace at which neurotransmitters are released hinges on the firing rate of the neurons. In the synaptic cleft, the transmitters either react with somatodendritic autoreceptors or specific transporter proteins. Binding to the presynaptic autoreceptors results in a decreased synthesis or further release from the presynapse. Transporter protein binding results in reuptake into the presynapse to induce the termination of the synaptic effects. After reuptake transmitters are re-stored into the vesicles or metabolized by enzymes. As neurotransmitter molecules are not able to pass the postsynaptic membrane they generate a downstream signal transduction cascade via their original binding to post-synaptic surface receptors. These receptors are generally coupled to guanine nucleotide-binding proteins (G-proteins) which are important to the regulation of transmembrane signalling. Disruption of the function of one or more of these stages may be a fundamental mechanism underlying depression. (Bondy, 2002; Carlson & Birkett, 2017c; Jenkins, 2017)

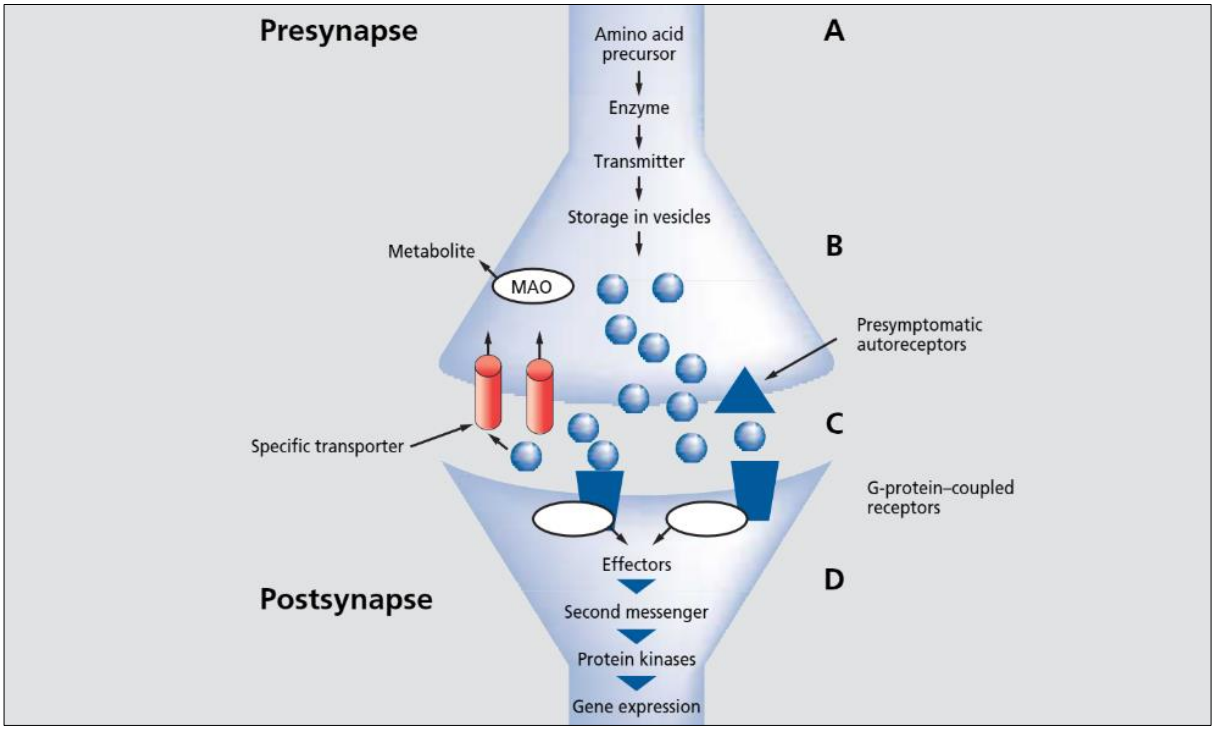

Figure 1. *Schematic depiction of a classic neurotransmitter synapse and its different stages of transmission. A) from the blood, precursors are conveyed into the brain. B) transmission and storage of transmitters. C) Release of transmitters into the synaptic cleft. D) Reaction of transmitters with either presynaptic autoreceptors to control release and synthesis or with postsynaptic receptors to control the downstream cascade. (MAO, monoamine oxidase). (Bondy, 2002)*

Monoamine Hypothesis

About 50 years ago the first major hypothesis of depression was formulated. The monoamine hypotheses proposed that the pathophysiology of depression is an imbalance of the brain's monoaminergic transmitter's 5-HT, NE and DA. Animal experiments and clinical observation provide evidence for this hypothesis in trials with the drugs reserpine and iproniazid. Administration of the antihypertensive drug reserpine leads to a depletion of 5-HT, NE and DA in the presynaptic stores which resulted in the induction of depression-related symptoms. Ipronazid, a drug used for tuberculosis, increases the concentrations of 5-HT and NE in the brain, this caused an antidepressant effect in patients and improved mood in depressed non-tubercular patients (Bear et al., 2016; Bondy, 2002; Carlson & Birkett, 2017b; Delgado, 2000; Yohn et al., 2017). Monoaminergic systems, such as the serotonergic and noradrenergic systems, are accountable for the behaviour of a person and thus the behavioural consequences of depression may originate from disruption of the functioning of one or more stages of these systems. Nonetheless, there is still an ongoing debate on the precise role that insufficiency in monoamine systems plays in depression as intensive research has failed to get convincing results (Carlson & Birkett, 2017b; Delgado, 2000; Ruhé et al., 2007). Despite the evidence that the synthesis of 5-HT may be low in depressed patients, it is suggested that it can be interpreted in multiple ways: depletion in 5-HT synthesis may result in depression, depression may result in a depletion in 5-HT synthesis, or a third factor may be accountable for both a depletion in 5-HT synthases and symptoms of depression (Rosa-Neto et al., 2004; Rot et al., 2009). Despite the debate concerning the precise role of monoaminergic systems, it cannot be denied that these systems play a large role in the mechanisms underlying depression. Other brain interactions and regulation systems must also be taken into consideration, however, the monoamine hypothesis currently remains the basis of the efficiency of antidepressants (Yohn et al., 2017)

Serotonin (5-HT)

5-HT is one of the neurotransmitters that are depleted in depressed patients following the monoamine hypothesis. The effects of antidepressants, especially SSRIs, are primarily based on increasing the levels of 5-HT. Therefore, this thesis will elaborate in more detail on the different 5-HT receptors. 5-HT is as previously mentioned directly connected to the level of mood and is commonly called the hormone of happiness (Jenkins, 2017). Literature implicates that at least five of the fourteen 5-HT receptor subtypes participate in the pathophysiology of depression and depressive-like behaviour. These subtypes are; 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_4 (Yohn et al., 2017). This thesis will elaborate on the first four receptors. Two populations of 5-HT_{1A} receptors are present in the brain of mammals: somatodendritic autoreceptors and postsynaptic heteroreceptors. Somatodendritic autoreceptors are located on the 5-HT neurons in the raphe nuclei. The autoreceptors bind Gi/o-coupled receptors, this results in the correction of potassium channels, which eventually reduces the amount of Ca^{2+} inflow and reduces cyclic adenosine monophosphate (cAMP) levels. Together these mechanisms result in a fast and effective suppression of 5-HT transmission and decrease of 5-HT release (Nautiyal & Hen, 2017; Yohn et al., 2017; Żmudzka et al., 2018). Postsynaptic heteroreceptors can be found on non-serotonergic neurons, mostly in the limbic system (Nautiyal & Hen, 2017; Żmudzka et al., 2018). Animal studies demonstrated that mice with a 5-HT_{1A} receptor knockout, initiated during adolescence, showed less mobility in the forced swim test compared to the controls, which implies that a deficiency in functional 5-HT_{1A} receptors at the beginning of development favours behavioural despair in adulthood(Richardson-Jones et al., 2011). Moreover, in the research of Garcia-Garcia and colleagues, a depression-like behaviour developed from whole-life deletion of the 5-HT_{1A} heteroreceptor expression in adolescence (Garcia-Garcia et al., 2017). In conclusion, 5-HT_{1A} receptors play an essential role in the development and regulation of depressive-like behaviours and targeting these receptors possibly results in antidepressant-like effects (Nautiyal & Hen, 2017; Żmudzka et al., 2018).

5-HT_{1B} receptors are also Gi/o-coupled transmembrane receptors that reduce cAMP levels, mostly in the substantia nigra, striatum, pallidum, nucleus accumbens and ventral tegmental area. The 5-TH_{1B} receptors work both pre-and postsynaptically as inhibitory receptors, which controls the release of other neurotransmitters. Levels of 5-HT_{1B} receptors play a role in the reward pathway and are a key determinant of environmental stress reactivity. Through these mechanisms, 5-HT_{1B} receptors play a role in the development of depression (Nautiyal & Hen, 2017; Żmudzka et al., 2018). Furthermore, lowered

5-HT_{1B} receptor functioning in humans is linked to MD, which emphasizes the correlation of this receptor in depression (Murrough et al., 2011).

Most 5-HT_{2A} receptors can be found in the cerebral, piriform, and entorhinal cortex, several frontal cortices and in all monoaminergic brainstem levels (Guiard & di Giovanni, 2015; Żmudzka et al., 2018). 5-HT_{2A} receptors function by coupling via Gq/11-coupled receptors, to the IP3 (inositol triphosphate)/PKC (protein kinase C)/calcium pathway, which regulates the stimulation of neurotransmission (Guiard & di Giovanni, 2015; Żmudzka et al., 2018). Literature states that 5-HT2A receptors are involved in many disorders concerning the Central Nervous System (CNS), including depression (Żmudzka et al., 2018).

The function of 5-HT_{2B} receptors is similar to the function of 5-HT_{2A} receptors, as both are coupled with Gq/11 proteins (Peng et al., 2018). However, 5-HT_{2B} receptors are found in the septal nuclei, dorsal hypothalamus, and medial amygdala of the CSN and the peripheral tissues (Żmudzka et al., 2018). The study of Diaz and colleagues stipulate that the role of 5-HT_{2B} receptors is essential in depression (Diaz et al., 2012). This can for example be seen in the fact that mice with activated 5-HT_{2B} receptors show a reduced latency to feed when performing a novelty-suppressed feeding test, which can be interpreted as less anxious or depression-like behaviour, and thus an antidepressant-like effect (Diaz et al., 2012; Samuels & Hen, 2011). Moreover, 5-HT2B receptors appeared to be present and active in the dorsal raphe 5-HT neurons where they play a part in the 5-HT release (Diaz et al., 2012). Recent studies indicate similar results as they show that 5-HT2B receptors are positively and directly regulating 5-HT neuron activity (Belmer et al., 2018).

Chapter 4 | Psychedelics

Hallucinogens, also known as psychedelics, are psychoactive substances that alter sensory perception, thought processes, mood, energy levels and affect various cognitive processes. A diverse spectrum of psychoactive molecules is termed hallucinogens such as ecstasy, LSD and Ketamine (Nichols, 2016). However, they are often split into two different categories; classic hallucinogens (such as LSD) and dissociative drugs (such as ketamine) (National Institute on Drug Abuse, 2019). This thesis will focus on the classic serotonergic psychedelics, which exert primary activity as a 5-HT receptor agonist. Agonists are chemicals that bind to a receptor and facilitate a biological response, which in this case is a postsynaptic effect. Antagonists on the other hand block or inhibit this response by binding to the receptor (Carlson & Birkett, 2017a).

History of Psychedelics

Humphrey Osmond was the first to use the term psychedelics, which means "mind-manifesting", as they have the capacity to disclose advantageous properties of the mind (Osmond, 1957). Hallucinogens obtained via the use of plants such as the peyote cactus have been used for centuries in religious practices. The first scientist to produce a synthetic hallucinogen was Albert Hofmann. The Swiss chemist synthesized LSD in 1938. However, it wasn't until April 16, 1943, that he fortuitously came into contact with LSD, during the execution of an experiment, which resulted in "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours" (Hofmann, 2013). LSD appeared on the market under the name Delysid in 1947 and was used as a psychotherapy medication and for experimental studies on the biological basis of psychological disorders. During this period more than 1,000 studies on the psychiatric effects of psychedelics were published (Belouin & Henningfield, 2018; Johnson et al., 2019; Nichols, 2016). In the late 1960s, the reputation of psychedelics crumbles as Harvard psychologist Timothy Leary begins to experiment with psilocybin and LSD on his students. He eventually becomes a polarizing figure by encouraging young people to "turn on, tune in and drop out" with the essential purpose of them to take drugs, discover themselves, and desert convention. In addition, there was an increase in recreational, medically unsupervised use and abuse of psychedelics which was often perceived as the roots of the counter-culture movement. This resulted in political concerns, which initiated the decrease of research with psychedelics and eventually the arrest of research by different laws such as the Controlled Substances Act of 1970. Experimentation with psychedelics eventually moved underground after President Nixon declared the "War on Drugs" (Belouin & Henningfield, 2018; Nichols, 2016). During the past decade, the negative image of psychedelics is slowly recovering and scientists are rediscovering the use of psychedelic drugs in treatment for mental illnesses (Nichols, 2016).

Classic psychedelics

There are different types of classic psychedelics with the most commonly known being LSD, Psilocybin, Peyote (mescaline) and DMT (N,N-dimethyltryptamine). It appears that all the classic hallucinogens affect the brains serotonin systems, elevating the 5-HT levels in the whole brain and reducing levels of 5-hydoxyindole acetic acid, which is the major metabolite of 5-HT (Nichols, 2016). The hallucinogenic effects of psychedelics are mainly due to agonist activity at the 5-HT_{2A} (and perhaps 5-HT_{2C}) receptors. (Johnson et al., 2019). Different types of psychedelics may also have a significant affinity for other types of neurotransmitter receptors, which could explain the qualitative diversity of these drugs (Ray, 2010). There are two general structural categories to which classic psychedelics fall. LSD, psilocybin and DMT fall within the categories that incorporate forms of tryptamine. Peyote falls within the second category which covers forms of the structure phenethylamine (Johnson et al., 2019).

When administering the classic psychedelics an individual is experiencing a so-called "trip", during which psychedelic experiences are evoked, resulting in changes in perception among others. Moreover, a trip on classic psychedelics sometimes provokes a mystical-type experience (Johnson et al., 2019; Nichols, 2016; Reiff et al., 2020). Mystical experiences are sometimes also referred to as religious, conversion, transcendental and transforming experiences. They are a group of experiences that are mainly expressed by a sense of unity of everything combined with a sense of appreciation, and the authoritative truth value of the experience (Johnson et al., 2019). After a mystical-type experience

people sometimes manifest abrupt, significant and maintained changes in perception and behaviour. Research with psychedelics accesses a mystical experience via the MEQ (30-item revised Mystical Experience Questionnaire or MEQ30). The MEQ30 contains a four-factor structure containing: (1) Mystical; including internal and external unity, noetic quality, and sacredness, (2) Positive mood, (3) Transcendence of time and space and (4) Ineffability, which refers to the feeling that the experience cannot be narrated sufficiently in words (Griffiths et al., 2011; MacLean et al., 2012). Moreover, research concerning the effect of psychedelics on depression suggests that mystical-type experiences correlate with positive therapeutic outcomes and improved aspects of mental well-being such as psychological flexibility, personal meaningfulness and decreased anxiety (James et al., 2020; Strassman et al., 2018).

Risks and Addiction

Classic serotonergic psychedelics are commonly seen as dangerous by the general public, however, they are known to be one of the psychologically safest classes of drugs when looking at them from a scientific standpoint. Normal doses of psilocybin, LSD or mescalin do not result in overdose deaths or addiction (Nichols, 2016). Nevertheless, applying classical psychedelics entails risks. These risks can be divided into three different categories. The first category includes the "bad trip" and can apply to everybody that takes classic psychedelics at a significantly high dose. The "bad trip" is a confusing, distressed, anxious and in some cases the delusional state of an individual as an acute reaction to the drugs. In recreational, unsupervised settings these events are more likely to have lasting harmful effects, however, with supervision present, these experiences elapse harmlessly (Carbonaro et al., 2016; Johnson et al., 2019). The second risk is mostly applicable to psychiatrically vulnerable individuals. It is possible to provoke psychotic disorders or initiate a prolonged psychotic reaction with psychedelics. Psychotic vulnerability is suspected if an individual experiences a psychotic reaction within their lifetime subsequent to the administration of the psychedelic drugs, nevertheless, it is impossible to tell if that person would still undergo this reaction without being exposed to the drug (Johnson et al., 2019). The last category of risks contains short-term physiological effects. Vascular muscle contraction, thrombus formation, coronary artery spasms and platelet aggregation are physiological events associated with the 5-HT_{2A} receptor (Nichols, 2016). The use of classic psychedelics can thus result in a moderately raised blood pressure and heart rate but also more severe vascular problems when administered in high doses. Individuals with severe cardiac disease should therefore restrain from administrating classic psychedelics (Griffiths et al., 2011; Johnson et al., 2019). Furthermore, events such as dose-related headaches, nausea and infrequent vomiting are not seen as substantial obstacles for clinical administration but are still unpleasant effects of classic psychedelic drugs (Johnson et al., 2019).

The general public commonly associates drugs with addiction, however, the use of classic serotonergic psychedelics does not lead to addiction nor dependency (Nichols, 2016). Additionally, these substances have not been associated with positive reinforcing, which normally leads to an increase in frequency or duration or a decrease in latency to respond to the drug (Edwards, 2016). It is not surprising that there is no association to addiction when taking into account that these serotonergic psychedelics do not directly affect the dopaminergic system in the brain, which is usually linked to drug dependency (Nichols, 2016). Research with animal models also showed no intracranial self-stimulation behaviour, which is a response to brain-stimulation reward, nor self-administration, which is a model for abuse liability (Nichols, 2016; Schulteis, 2010). In addition, there is even research that shows promising results for the treatment of addiction with these classic psychedelics (Johnson et al., 2019)

Chapter 5 | Psilocybin

Psilocybin is a classic psychedelic that can be found in a variety of mushrooms species, from which the street names "magic mushrooms" and "Shrooms" are derived (National Centre for Biotechnology Information, 2021; Reiff et al., 2020). The history of ritual use of the hallucinogenic mushrooms by native peoples of Central and South America to promote spiritual experiences dates back 3000 years (Reiff et al., 2020; Tylš et al., 2014). Psilocybin is a plant tryptamine alkaloid and is actively metabolized through rapid dephosphorylation into the active compound psilocin. Psilocin is a 5-HT transporter inhibitor and a 5-HT_{2A} receptor partial agonist with <40% activation efficacy, activating these receptors in the CNS and mimicking the effects of 5-HT. Moreover, psilocin is also suggested to bind to the 5-$HT_{2C,}$ 5-HT_{1A}, and 5-HT_{1B} receptors, with their affinity to bind in descending order (National Centre for Biotechnology Information, 2021; Reiff et al., 2020; Tylš et al., 2014). In humans, the effective dosage of oral psilocybin is 0.045-0.429 mg/kg but when taken in high doses (0.3-0.6 mg/kg) psychedelic effects occur. These effects are dependent on dose and result in intense changes in perception such as euphoria, impaired perception of time and space, altered self-perception, sensory illusions, synaesthesia, auditory and visual hallucinations. The onset of these effects is between 20 and 40 minutes and the duration is around 3 to 6 hours after oral intake (Reiff et al., 2020; Tylš et al., 2014). The possibility for unpleasant experiences is also present when administering psilocybin, these can include the beforementioned risks of psychedelics and the feelings of an apparently "unending experience" (Carbonaro et al., 2016; Griffiths et al., 2016; Reiff et al., 2020; Tylš et al., 2014). Analysis of homological scaffolds of the brain when psilocybin is applied showed that there is an expanded integration between cortical regions. The integration is assisted by a scaffold that supports cross modular connectivity when in the psilocybin state. This connectivity is likely established due to 5-HT_{2A} receptor stimulation in the cortex. In figure 2 a simplified visualization of the increase in connectivity between brain networks in a psilocybin influenced brain. The increase in connections is possibly the reason for the changes in perception when on psilocybin (Petri et al., 2014).

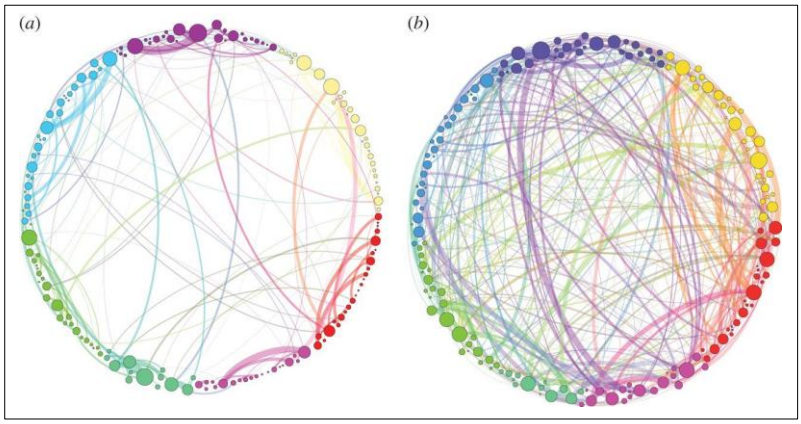

Figure 2. *Simplified presentation of the perseverance homological scaffolds of a) placebo group and b) psilocybin group. Only heavy links are shown and colours depict communities obtained by modularity. The width of the links are corresponding to their weight and the size of the nodes are corresponding to their strength. Take note of the number of heavy links between communities which is much higher in the psilocybin group compared to the placebo group, suggesting more interaction. (Petri et al., 2014)*

Psilocybin is a Schedule I Drug Enforcement Administration (DEA) controlled drug, which means that it is currently not accepted for medical use in the United States. Substances in Schedule I lack accepted safety for use under medical supervision and have a high potential for abuse (Department of Justice & Drug Enforcement Administration, 2020). However, review studies suggest that this scheduling is too restrictive and lowering the schedule category of psilocybin by the DEA to IV would also be acceptable (Johnson et al., 2018). Nevertheless, psilocybin belongs to one of the most used psychedelics in research because of its respective safety, significant absorption after intake and reasonably long duration of action (Tylš et al., 2014). The hallucinogens are already used in human studies and although most are at a somewhat preliminary research state, promising results are reported for major depressive disorder (Davis et al., 2021) and anxiety in patients with life-threatening cancer (Griffiths et al., 2016), as well as in addiction to tobacco (Johnson et al., 2017) and alcohol (Bogenschutz et al., 2015).

Psilocybin as a treatment for depression

Psilocybin thus has a serotonergic action, which can be associated with depression. As the working of established antidepressants is less than satisfactory, new research on the potential of psilocybin and psilocybin-assisted therapy as a treatment for depression is done.

Animal research

In the study of Hibicke and colleagues, psilocybin was administered to Wistar-Kyoto rats which resulted in persistent antidepressant-like effects on the behaviour 5 weeks after administration. Antidepressant-like effects were found in the forced swim test where psilocybin administrated rats were significantly less immobile and had a far greater effect size (d=4.985) (Figure 3) (Hibicke et al., 2020). The same study also looked at the so-called "set and setting" which is dependent on an individual's own experience and future results. Set and setting have an impact on an individual's feeling of comfort and vulnerability during their experience with psychedelics (Hendricks, 2018). An open field test (OFT) was used to have similar effects. Results showed that the repeatedly measured psilocybin rats but not the interval psilocybin rats were significantly longer present in the open arms of the elevated plus mase (EPM) and significantly shorter in the closed arms of the EPM than control rats (figure 4) (Hibicke et al., 2020). The study concluded that even though depression is a uniquely human disease, the robust and long-lasting antidepressant effects of psilocybin in rats will have similar advantage effects to humans. The effect likely results from a combination of both acute neurobiological effects of the psilocybin together with subjective, environmental experiences a subject has during and/or after drug administration (Hibicke et al., 2020).

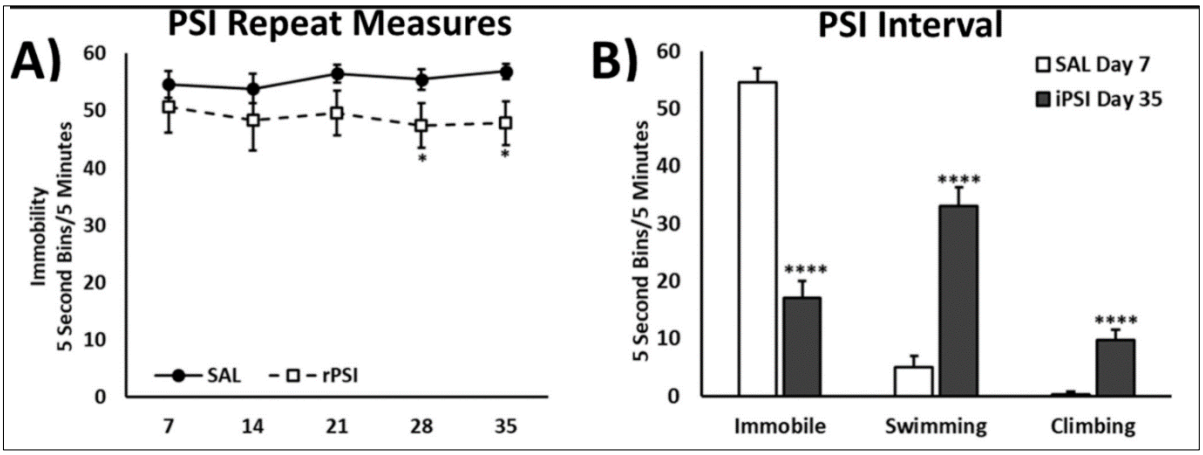

Figure 3*. Forced swim test (FST). A) No significant change over time in immobility in the FST by SAL (n=8) and rPSI (n=8) was found. Nevertheless, in a t-test it was found that rPSI were less immobile compared to SAL rats on day 28 (p<0.05). In the first FST session significant less immobility was found in iPSI (n=8) rats compared to SAL rats (p<0.0001). Moreover, rPSI rats had a significantly higher likeliness to swim (p<0.0001) and climb (p<0.0001)than SAL rats. (SAL, saline group; rPSI, repeated measures psilocybin group; iPSI, interval psilocybin group). (Hibicke et al., 2020)*

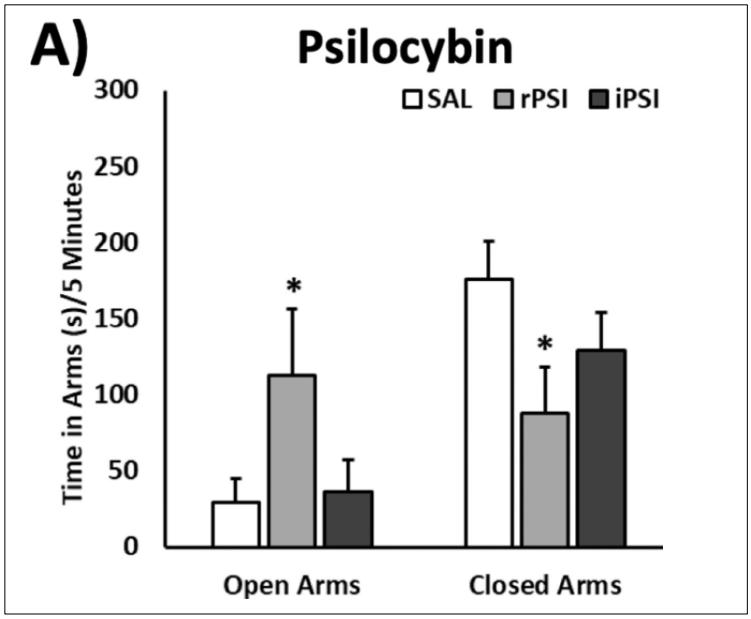

Figure 4. *Elevated plus maze (EPM). rPSI (n=7) rats were significantly longer present in the open arms of the EPM (p<0.05) and significantly shorter present in the closed arms of the EPM (p=0.05) compared to SAL (n=8) rats. No significant difference was observed between iPSI and SAL rats. (SAL, saline group; rPSI, repeated measures psilocybin group; iPSI, interval psilocybin group). (Hibicke et al., 2020)*

On the contrary, research on the antidepressant-like effects of psilocybin on Flinders Sensitive rat Line (FSL) did not show significant results, suggesting that the FST and OFT were not appropriate behavioural tests (Jefsen et al., 2019). This negative result could be explained by the fact that the FSL has extremely low central 5-HT_{2A} mRNA expression which abolishes the 5-HT_{2A} related antidepressant-like effects of psilocybin (Hibicke et al., 2020).

Literature commonly attributes the behavioural effects of psilocybin in animals to activation of 5-HT_{2A} receptors (Halberstadt & Geyer, 2018). However, after researching the mechanisms of action of psilocybin Hesselgrave and colleges indicate the importance of 5-HT_{2A} independent mechanisms for the antidepressant-like working of psilocybin, which includes restoration of synaptic strength in the cortico-mesolimbic reward circuits (Hesselgrave et al., 2021).

Human research

Controlled clinical trials using psilocybin are increasing in the past few years, they report rapid and abiding improvements in depression symptoms (Carhart-Harris et al., 2016; Davis et al., 2021; Griffiths et al., 2016). In fact, studies on healthy individuals that received a single dose of psilocybin showed results of improvements in wellbeing (Amsterdam et al., 2011). Coming back to depression, the study of Griffiths and colleagues used a two-session, random, double-blind, cross-over trial on cancer patients with symptoms of depression and anxiety. Two groups were established, the Low-Dose-1st Group were administered a low dose (1 or 3 mg/70kg) of psilocybin on the first session and a high dose (22 or 30 mg/70 kg) during the second session, and the High-Dose-1st Group which received a high dose during the first session and a low dose during the second session. A remaining decrease in depressive symptoms was documented after receiving a high dose of psilocybin (figure 5). A lower dose showed non-significant trends for the positive effects of psilocybin. A mystical experience did significantly associate with most of the abiding changes in therapeutic results which is similar to previous findings that show that such events during a session predict long term positive therapeutic outcomes (Griffiths et al., 2016) (James et al., 2020). Taken together this study showed the efficacy of taking psilocybin of a high dose under supportive circumstances in decreasing depression-like symptoms in life-threatening cancer patients (Griffiths et al., 2016).

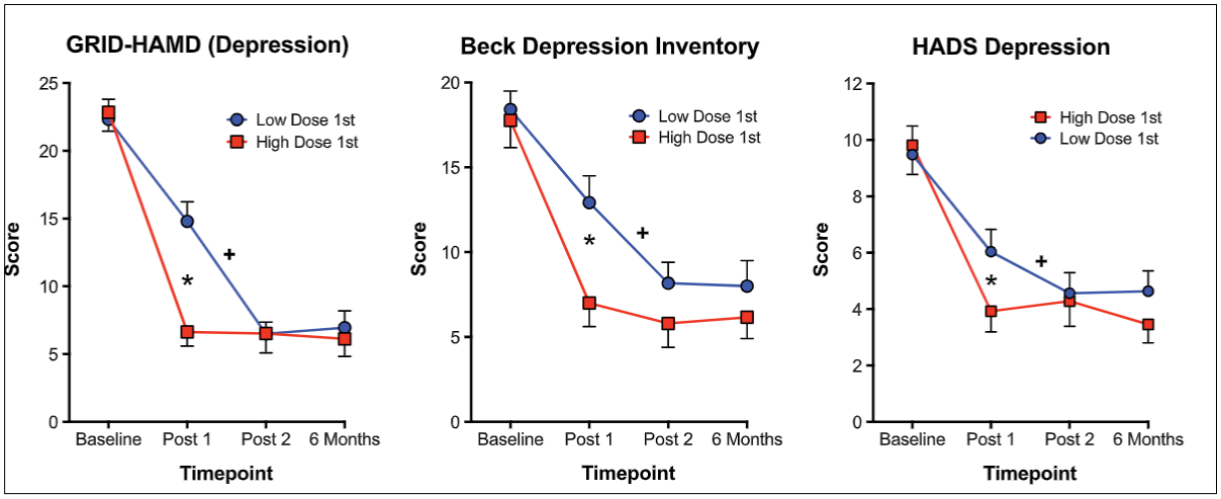

Figure 5. *The effect of psilocybin on GRID-HAMD, BDI and HADS scores. Measures were evaluated at Baseline, Post-session 1 (5 weeks after session 1), Post-session 2 (5 weeks after session 2), and 6-month follow-up. (Data points display means; Error bars are SEM; Star symbol stipulates a significant difference between the groups at Post-1($p<0.05$); Cross symbol stipulates a significant difference between Post 1 and Post 2 in Low-Dose-1st group ($p<0.05$); GRID_HAMD is a clinician-rated measure for depression; BDI, Beck Depression inventory is a self-rated measure for depression; HADS is a self-rated measure for depression and anxiety). (Griffiths et al., 2016)*

In response to the previous study, the study of Carhart-Harris et all (2016), looked at the feasibility of medical use of psilocybin in TRD patients. In this open-label, single-arm pilot study a low dose during the first session (10 mg) and a high dose of psilocybin at the second session (25 mg) together with psychological support before, during and after administration resulted in decreased depressive symptoms. The patients showed a 67% response rate at 1 week and a rate of 58% after 3 months, 42% remained in remission. This study presents preliminary evidence for the effectiveness and safety of treatment with psilocybin for TRD patients (Carhart-Harris et al., 2016). In a follow-up study, the number of patients was increased and the follow-up period was extended. Similar results to the previous studies were observed, with fast and sustained response to psilocybin treatment. All 19 patients that completed the study showed a decrease in depression scores (Carhart-Harris et al., 2018).

The John Hopkins University in Baltimore established a centre for psychedelic and consciousness research which acquired the first regulatory approval to study the effects of psychedelics in healthy volunteers in 2000 (Lewis, 2020). Davis and colleagues looked at the effects of psilocybin-assisted therapy on MD in 2021 (Davis et al., 2021). During this randomized, waiting list-controlled clinical trial 20mg/70kg was administered in the first session and 30 mg/70kg in the second together with supportive psychotherapy. The research showed results of a fast and enduring antidepressant effect of psilocybin-assisted therapy among the MD patients (figure 6). Results showed that 71% of the patients had a clinically significant response to the treatment at week 1 and also at week 4 of follow-up post psilocybin sessions. Furthermore, 58% of the patients met the norm for the remission of depression at week 1 and 54% at week 4 of follow-up post psilocybin sessions. Effect sizes (week 1, d=2.3; week 4, d=2.3) of this study are greater than effect sizes found in psychotherapy (approx. 2.5 times) and psychopharmacological (more than 4 times) depression treatment studies (Davis et al., 2021).

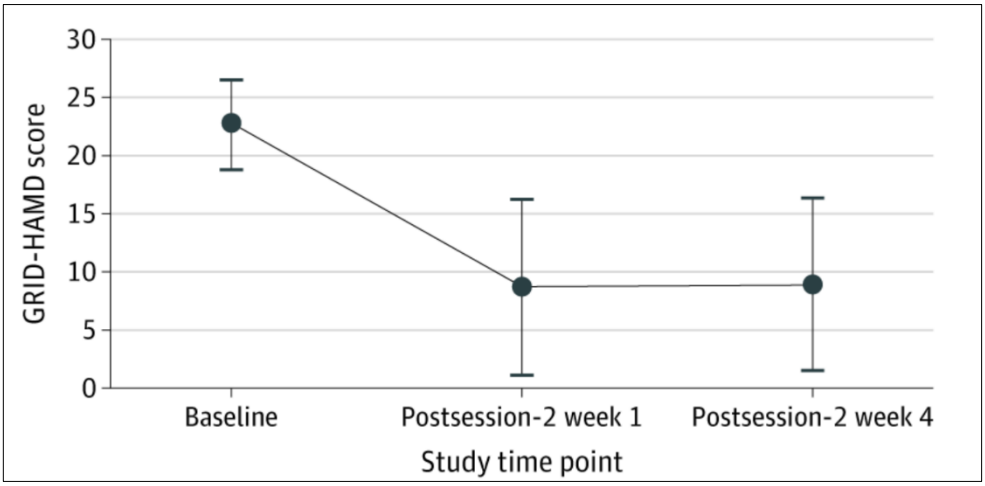

Figure 6. *GRID-HAMD scores at Baseline, Week 1 and Week 4 Postsession-2 Follow-up. Mean (SD) at baseline was 22.8, at week 1 it was 8.7 and at week 4 it was 8.9. (Davis et al., 2021)*

Psilocybin vs. SSRIs

There are speculations that treatment with psilocybin may be more tolerable to patients with depression than the commonly prescribed antidepressants, such as SSRIs, as these come with more severe and higher numbers of side effects. Moreover, treatment with psilocybin seems to give faster results compared to SSRIs, which have a delay in the onset of their effects. (Carhart-Harris et al., 2016, 2018; Davis et al., 2021; Griffiths et al., 2016) In 2021 Carhart-Harris and colleges published one of the first studies to research direct comparisons between psilocybin and Escitalopram, an established SSRI. In this phase 2, double-blind, randomized, controlled trial, no significant difference in scores for depression between the trial groups was found (Figure 7a). Psilocybin was favoured in secondary outcomes, however, statistical analysis was not executed correctly, making it impossible to draw conclusions from this data (Figure 7b). Nevertheless, no patients stopped treatment with psilocybin compared to 4 patients that stopped and 1 patient that halved the dose in the escitalopram group. Furthermore, adverse and/or side effects were less severe in the psilocybin group. Taken together, the study cannot favour one treatment over another, however, psilocybin seems to be slightly more tolerable (Carhart-Harris et al., 2021).

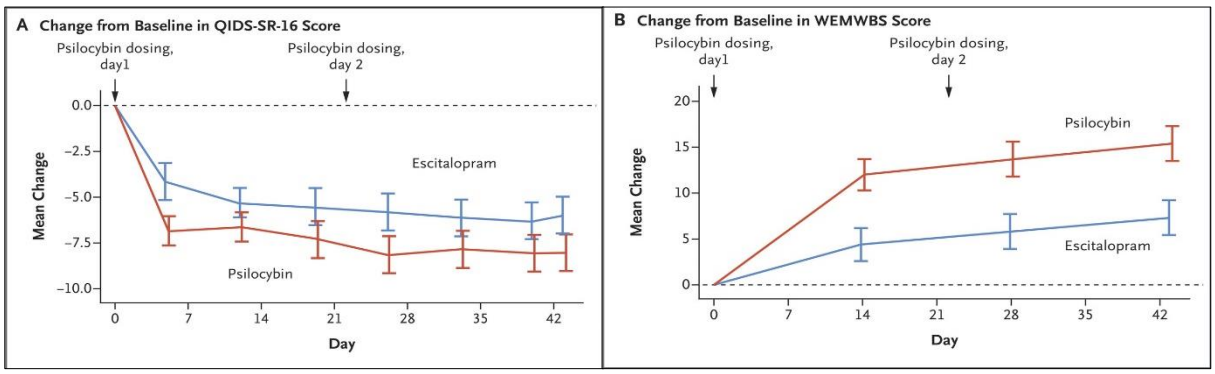

Figure 7. *Change in A) Depression Severity (Primary measurement) and B) Well-Being (Secondary measurement) over 6 weeks. Data points resemble mean change; Bars indicate standard error; QIDS-SR-16, Quick Inventory of Depressive Symptomatology – Self Report (higher scored indicate greater depression; WEMWBS, Warwick-Edinburgh Mental Wellbeing Scale (higher scores indicate greater mental well-being); No p-values are shown due to lack of correction for multiple comparisons in the analyses of the WEMWBS). (Carhart-Harris et al., 2021)*

Discussion

Recent research shows the fast and enduring antidepressant effects of psilocybin, however, most of these studies in addition treat their patients with psychotherapy. Even though the precise role of psychotherapy in combination with psychedelic is still unknown, it is speculated that set and setting, mystical experiences and induced neuroplasticity can be leveraged in psychotherapy to guide depressed patients towards symptom reducing results (Reiff et al., 2020; Vollenweider & Preller, 2020). Furthermore, it is not clear whether the results of change in the patients can be attributed to psilocybin itself, the psilocybin-assisted psychotherapy experience, or psilocybin-facilitated improvements in the therapeutic alliance (Reiff et al., 2020). More research could be done on the specific role of psychotherapy during the treatment of depression with psilocybin and vice versa.

The before mentioned human studies come with some limitations. Firstly, they all have a relatively small sample size and lack ethnic diversity in participants (predominately white). Moreover, most of the participants were highly educated which could have influenced the experiences of the patients. Secondly, some patients were excluded from the studies such as patients with bipolar disorder and patients with preexisting psychiatric conditions. The exclusion was necessary because these patients are prone to exhibit a prolonged psychotic reaction when administering psilocybin. This means that treatment is only feasible for patients with MD like symptoms and no psychiatric history. It is also important to mention that the research was mostly done on self-referring patients and as psychedelics are known to assist suggestibility the results could be more positive compared to research done on patients that are not actively seeking this treatment. It can thus also be that the results of their research are suggestive of an expectancy bias. (Carhart-Harris et al., 2016, 2018, 2021; Davis et al., 2021; Griffiths et al., 2016)

To look at the relative effects of the different factors during psychedelics-assisted psychotherapy and also to reduce the expectancy bias a placebo-controlled double-blind randomized trial would be best. However, this would be unsuccessful with psychedelics as patients could straightforwardly discern the active from the control condition as psychedelics affect personal perception. Active placebos should be considered for use in the control condition as it makes it harder to discriminate between the effects (Carhart-Harris et al., 2016). Therefore, future research should focus on this matter to strengthen the conclusion made during their studies.

In this thesis, the monoamine hypothesis has been of the main interest considering the working of psilocybin and its effect on depression as most studies suspect this to be one of the underlying neurobiological mechanisms for the antidepressant-like effects. Nevertheless, the glutaminergic hypothesis is recently gaining interest. This hypothesis states that depression may be linked to atypical or dysfunctional glutamatergic neurotransmission (Moriguchi et al., 2019). Recent research has found that psilocybin, besides its serotonergic action, also has a glutaminergic action (Mason et al., 2020). Further details concerning this hypothesis and its relationship to the antidepressant working of psilocybin are beyond the scope of this thesis. Despite that, more research certainly needs to be done on the activation of the glutamate networks and their relationship to depression as well as on other possible underlying mechanisms.

Psilocybin might be a viable and promising option for treating patients with depression as multiple studies show the antidepressant-like effects on humans and animal models (Carhart-Harris et al., 2016, 2018; Davis et al., 2021; Griffiths et al., 2016; Hibicke et al., 2020). Furthermore, fewer adverse side effects, as well as a faster onset of the effects, gives the impression that treatment with psilocybin would be more favourable as studies suggest it to be more tolerable than antidepressants (Carhart-Harris et al., 2021). These insights give an option for developing new antidepressant drugs. However, further research with larger and longer trials and a more credible study design is necessary. Such research will establish if treatment with psilocybin is more effective and tolerable compared to established treatments such as antidepressants.

Conclusion

In summary, depression is a worldwide problem affecting people of all ages. Depression is characterized by a depressed mood and loss of interest or pleasure in activities and negatively affects the quality of a person's life. Established treatments such as psychotherapy and antidepressant do provide some relief from the symptoms of depression, however, these are still highly unsatisfactory. Antidepressants, especially, come with many common side effects. Moreover, treatment-resistant depression is also a problem. Treatment with psilocybin could be a new and good option for patients suffering from depression. A few studies confirmed this careful assumption with significant results, indicating that psilocybin has fast and enduring antidepressant effects on depressed patients. Moreover, these same studies show results that suggest that treatment with psilocybin would very tolerable, as no severe side effects were encountered. These outcomes are important for improving the treatment of patients with depression. Despite the assumptions that treatment with psilocybin could be better and more tolerable than treatment used nowadays, not enough studies compared them with established treatments to confirm this assumption. The one that did compare treatment with psilocybin to an established treatment with antidepressants, could not draw a conclusion as no significant difference was found and wrong statistical analysis was done. Coming back to the main question stated at the beginning of this thesis, which reads as follows: "Is the use of psilocybin as a treatment for depression better than the currently used treatments?". Despite the hopeful results. that cannot be ignored, it is not possible to confirm nor reject that treatment with psilocybin is better than the currently used treatments for depression. More research is necessary to be able to make such assumptions and to find the mechanisms that underlie the antidepressant effects of psilocybin.

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Epilogue

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