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Psychoplastogens Without the Trip?

Psychoplastogenic Mechanisms: The Role of the Altered State of Consciousness in Depression, Anhedonia, and Reward Sensitivity

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Introduction

1 Psychoplastogens in Therapeutic Context

Psychoplastogens induce profound changes in mood, cognition, and perception. The most well-known compounds for their therapeutic effects include *lysergic acid diethylamide* (LSD), *psilocybin* (the active ingredient in so-called “magic mushrooms”), *N,N-dimethyltryptamine* (DMT, the main psychoactive compound in ayahuasca), *ketamine* (a dissociative hallucinogen), and *3,4-methylenedioxymethamphetamine* (MDMA, also known as ecstasy).

While LSD, psilocybin, and DMT are classified as *classic psychedelics* primarily acting on serotonin receptors, ketamine is a dissociative anaesthetic that mainly targets the glutamatergic system. Subanaesthetic ketamine predominantly functions as a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor, a subtype of the glutamate receptor (Anis et al., 1983; Lodge & Mercier, 2015). MDMA is considered an entactogen with a distinctive pharmacological profile, characterised by promoting the release and inhibiting the reuptake of serotonin, dopamine, and norepinephrine (Nichols, 2016; Vollenweider et al., 2007; Passie et al., 2008; Vollenweider & Kometer, 2010; Kyzar et al., 2017).

Despite these differences, a common characteristic of these substances is that they rapidly promote both structural and functional neural plasticity, including dendritic growth, synaptogenesis, and changes in whole-brain connectivity (Ly et al., 2018; Olson, 2021).

Historically, these substances have followed different paths of use and regulation. LSD, synthesised in the 1930s, and psilocybin, naturally occurring in mushrooms, became the subject of psychiatric research in the 1950s. Although early trials indicated promising clinical benefits, their growing popularity as recreational drugs and the War on Drugs under Nixon led to prohibition in the mid-1960s, which halted research despite positive evidence (Carhart-Harris & Goodwin, 2017). DMT, long used in traditional Amazonian rituals in the form of ayahuasca, has been associated with healing and spiritual practices across cultures (Tófoli & de Araujo, 2016). Classic psychedelics such as LSD, psilocybin, and DMT have shown potential in treating depression and addiction, partly by modulating functional brain connectivity and boosting emotional well-being (Nichols, 2016; Psiuk et al., 2021; Muttoni et al., 2019; Nutt et al., 2020; Carhart-Harris et al., 2016a, 2017).

Ketamine, initially synthesised in the 1960s as an anaesthetic, was later restricted in the 1990s due to misuse, but has recently gained attention for its rapid antidepressant effects (Kumar & Amit, 2021; Delray Center for Healing, 2022). In 2019, the U.S. Food and Drug Administration (2019) approved esketamine nasal spray as the first ketamine-based therapy for treatment-resistant depression (TRD). MDMA, synthesised in the early 20th century, gained popularity for its empathogenic effects and is currently under investigation mainly for treating post-traumatic stress disorder (Kyzar et al., 2017).

In recent years, these substances have re-emerged as promising tools in psychiatry.

However, it should be noted that in modern clinical practice, these drugs are rarely administered in isolation. Instead, they are usually combined with psychotherapy (psychedelic-assisted therapy, PAT). Nonetheless, PAT is neither a standard nor is it routinely applied. Psilocybin and most other psychoplastogens are not approved by the FDA or EMA. With Switzerland being an exception in Europe, most psychoplastogens are only supplied under clinical exemptions and for research purposes. The combined approach with psychotherapy makes it difficult to distinguish the effects of the substances from those of the therapeutic environment (Goodwin et al., 2024). Scientifically, their mechanisms have been investigated across various fields: pharmacological research has examined receptor-level interactions, neuroimaging studies have mapped changes in connectivity and brain activity, and phenomenological research has documented the subjective “trips” that seem to play a central role in therapeutic outcomes. This work reviews the most significant findings in psychedelic research, with particular focus on psilocybin, refining the understanding of the role of altered states of consciousness in therapeutic and well-being outcomes.

2 Altered States of Consciousness

As mentioned, psychedelics have the potential to profoundly alter human consciousness. While their immediate effects on functional connectivity, cognition, memory, and emotion are well documented, these changes do not fully capture the complexity of the subjective *psychedelic experience*.

The psychedelic experience is often described as an altered state of consciousness characterised by significant changes in perception, self-experience, and the perception of space and time. As Studerus et al. (2022) explain, it involves “changes in perception of the external world, of one’s own feelings, sensations, and thoughts,

an altered sense of space and time, the disintegration of self-consciousness (ego dissolution), hallucinations or the experience of unity" (p. 2). Building on these descriptions, the psychedelic state can be viewed as a form of consciousness where the scope and intensity of sensory and cognitive contents are broadened, the usual boundaries of the self may dissolve, and external stimuli often seem unusually salient and personally meaningful. For example, a long-term follow-up study found that 58% of participants rated the psychedelic experience as one of the five most personally meaningful, and 67% rated it as one of the most spiritually significant experiences of their lives. Additionally, 64% reported increased well-being and life satisfaction (Griffiths et al., 2008). But what makes this altered state of consciousness so uniquely transformative, and how can it be connected to measurable changes in brain activity?

To address this, theoretical models have emerged that aim to bridge the gap between subjective experience and neurobiological mechanisms. Nevertheless, the field of psychedelic research cannot agree on a single measure of entropy, which can lead to many inconsistent findings.

One particularly influential framework is the *Entropic Brain Hypothesis* (EBH, Carhart-Harris et al. 2014), which offers a compelling explanation for how psychedelics like psilocybin affect large-scale brain dynamics in ways that may enable psychological flexibility and insights commonly reported during psychedelic experiences. According to the EBH, psychoplastogens, especially psychedelics, increase *brain entropy*. Brain entropy refers to the randomness or unpredictability of neural signalling. When brain activity is highly ordered and predictable, entropy is low; it increases when it becomes less predictable. However, more randomness does not automatically mean more complexity. As Toker et al. (2022) demonstrated, complexity and randomness follow an inverted U-shaped relationship: the brain reaches its highest complexity at the point of *criticality*, where activity is balanced between stability and instability. If the system becomes too ordered or too chaotic, both complexity and information processing decline. Generally, systems in this critical state are believed to be more capable of integrating information and exhibiting response flexibility (Atasoy et al., 2017), a key trait of the human brain.

Under psilocybin, the brain explores a broader range of functional network states, which has been described as an increase in global entropy (Tagliazucchi et al., 2014). These distinctive changes in brain dynamics may underpin the altered

perception of time, self, and space often reported under psilocybin, leading to a very unique experience, often described as mystical-type experiences that could account for the life-changing effects of psychoplastogens.

Mystical experiences represent a central element of the psychedelic state. These are characterised by a profound sense of unity, reverence, and a perceived encounter with ultimate reality (Stace, 1960a). Stace's framework outlines several key dimensions of mystical experience: unity (both internal and external), sacredness, noetic quality (a sense of profound truth), positive mood, transcendence of time and space, ineffability, and paradoxicality. The latter refers to the coexistence of seemingly contradictory states, such as feeling deeply connected yet dissolved as an individual.

Mystical experiences and the psychedelic state can induce *quantum change*, further highlighting the transformative power of mystical-type experiences by emphasising their enduring effects. Quantum change is a concept linked to mystical experiences but focuses more specifically on the lasting transformation that follows. These sudden, profound, and benevolent experiences fundamentally reshape an individual's emotions, thoughts, and behaviours (Baka & Miller, 2001; Miller, 2004). Unlike gradual behavioural change, quantum change occurs in a single, impactful moment (James, 1902), such as during a psychedelic experience. Ross and colleagues (2016) suggested that the mystical experience might act as a mediator for the therapeutic effects of psilocybin, particularly in relieving anxiety and depression.

The mystical experience, observed on a subjective level of effects caused by psychoplastogens, likely underpins the therapeutic potential of psychedelics and may explain why a single experience can lead to lasting psychological growth. Therefore, the subjective quality of the altered state of consciousness may play a crucial role in therapeutic outcomes.

2.1 Psychological and Therapeutic Effects of the Psychedelic State

Psychedelic research still lacks a single behavioural operationalisation of altered states of consciousness. A deeper understanding of this field in psychometry is provided by Fort and collegues (2024) as well as Studerus and collegues (2010). Nevertheless, the *Five-Dimensional Altered States of Consciousness Questionnaire* (5D-ASC, Dittrich, 1975, 1998; Studerus et al., 2010) is commonly used in psychedelic research. Along with the *Mystical Experience Questionnaire* (MEQ, MacLean et al., 2012; Barrett et al., 2015), these two psychometric scales aim to

depict the complex behavioural and cognitive dimensions of psychedelic experiences during alteration of consciousness. A more detailed description of the 5D-ASC is provided in the methods section of this master's thesis.

Under the influence of psilocybin (25mg), especially the *oceanic boundlessness* (OBN, also referred to as *oceanic self-expansion*, OSE) component of the 5D-ASC, which closely resembles mystical experiences, a notable interaction effect was observed in decreasing depressive symptoms (Roseman et al., 2018) in cases of TRD.

In clinical studies, the degree of mystical experience, as measured by the MEQ, increased significantly with psilocybin dose (Johnson et al., 2019). Participants who experienced more intense mystical experiences also showed stronger therapeutic outcomes, including reductions in depression and anxiety (Griffiths et al., 2016; Ross et al., 2016).

Psychoplastogens appear to be a powerful treatment for various psychological conditions, including substance use disorder (DiVito and Leger, 2020) and PTSD (Krediet et al., 2020). Research on their therapeutic benefits mainly focuses on the psychoplastogens psilocybin and ketamine, especially regarding their effects on depression symptoms in major depressive disorder (MDD), particularly TRD. Unlike traditional antidepressants, which usually require daily doses, psilocybin has produced strong, lasting improvements in mood after only one or two sessions. Remarkably, 71% of participants showed a clinically significant response at both week 1 and week 4, with over half reaching remission (Davis et al., 2021). Clinical trials have reported considerable effect sizes for reducing depressive symptoms, as shown in a recent meta-analysis of 524 adult patients (Fang et al., 2024). In another study, psilocybin combined with supportive psychotherapy yielded even more pronounced effects than standard psychotherapy or pharmacological treatments (Rubin & Yu, 2017; Fournier et al., 2010). Nayak and colleagues (2023) observed significant decreases in depressive symptoms at both 2-4 weeks and 2-3 months, also indicating that the intensity of the mystical experience influenced these improvements. They further revealed that these enhancements were related to altered cognitive reappraisal.

Psilocybin has been shown to reduce recognition and processing of predominantly negative emotions and to shift attention towards positive stimuli (Kometer et al., 2012). This shift is supported by evidence indicating that psilocybin decreases

reactivity in the amygdala, a brain area strongly associated with emotional responses, with this reduced reactivity being linked to an increase in positive mood (Kraehenmann et al., 2015). Similar findings have been reported across various psychedelic compounds (Kraehenmann et al., 2015; Grimm et al., 2018). Barrett et al. (2020) also noted decreased negative affect, increased positive affect, and suppression of amygdala responses, suggesting a general shift in emotional salience. One week after a second psilocybin session, participants also showed significant improvements in recognising emotions (Stroud et al., 2018).

Another effect of psilocybin on emotional processing is its capacity to facilitate the processing of difficult autobiographical material, as it appears to assist individuals in accessing and processing emotionally intense memories that are typically repressed or avoided (Healy, 2021). Psilocybin also altered integration of sensory information, which may disrupt rigid or ruminative thinking patterns often seen in psychiatric conditions (De Gregorio et al., 2021).

In cancer patients, Ross et al. (2016) found that a single dose of psilocybin caused lasting reductions in depression, anxiety, and existential distress over 6.5 months; the intensity of the psilocybin-induced mystical experience drove the therapeutic effect.

The subjective experience caused by psychoplastogens is intense and can sometimes include unpleasant effects. However, psilocybin's appeal in clinical settings is bolstered by its favourable safety profile: it has low physiological toxicity (Passie et al., 2002), minimal risk of dependence (Nichols, 2016), and generally produces only temporary and reversible adverse effects (Mithoefer et al., 2016; Todorović Vukotić et al., 2021; Wang et al., 2018). These adverse effects are often highly challenging psychological experiences (Carbonaro et al., 2016) or the potential to trigger psychotic symptoms in vulnerable individuals (Johnson, Richards, & Griffiths, 2008), though they tend to be short-lived. Another concern is hallucinogen persisting perception disorder (HPPD), which involves flashbacks or ongoing visual disturbances. Although most often associated with LSD, only one case of HPPD has been reported following psilocybin use (Halpern et al., 2016; Martinotti et al., 2018). Additionally, symptoms from the dissociative spectrum, such as depersonalisation and derealisation, have been observed, and may overlap with or resemble HPPD (Simeon et al., 2009).

LSD, along with psilocybin as a classic psychedelic substance, has a limited number of studies examining its therapeutic effects. In a small sample (n = 9, Gasser et al.,

2014), LSD was observed to reduce anxiety associated with life-threatening diagnoses.

DMT in the form of Ayahuasca demonstrates significant effects in alleviating symptoms of MDD and TRD (Sanches et al., 2016; Palhano-Fontes et al., 2019). Both DMT and LSD have similar adverse effects to psilocybin, with early-phase DMT trials indicating a favourable safety profile across different doses (Swieczkowski et al., 2025).

Treatment with MDMA led to reductions in anxiety (Amorose, 2015) and improvements in emotion regulation and other self-capacities (van der Kolk et al., 2024). In patients with MDD, MDMA significantly decreased symptoms of depression (Kvam et al., 2025). MDMA has moderate abuse potential and is approved as a safe substance for clinical trials (Feduccia et al., 2019).

Post-ketamine infusion, both patients and control group showed notable improvements in symptoms of anhedonia, anxiety, post-traumatic stress disorder (PTSD), suicidality, and quality of life (Nugent et al., 2021, Xiong et al., 2021). Ketamine, as a subanaesthetic dissociative, can induce unpleasant dissociative experiences accompanied by anxiety and the induction of psychosis, especially in vulnerable individuals (Ceban et al., 2021). Naturally, its effects on the cardiovascular system must be monitored by medical professionals.

When discussing therapeutic outcomes, psychedelic research mainly focuses on disorders. This master's thesis provides a brief overview of both the effects on mental illness and mental well-being, offering a clearer understanding of the potential of psychoplastogens. Mental well-being, unlike disorders and symptoms, is described as a positive and resilient state of emotional, psychological, and social functioning, characterised by the ability to cope with everyday challenges, maintain meaningful relationships, and experience contentment (Gautam et al., 2024). Psilocybin is of particular interest for research on well-being. In naturalistic settings, users report improvements in overall mental health, psychological functioning, and interpersonal relationships after using psilocybin (Nayak et al., 2023). Higher MEQ scores predicted greater personal meaning, well-being, and behaviour change at both one-month and 14-month follow-ups (Griffiths et al., 2008; 2011). The acute altered state of consciousness does not account for the observed long-term therapeutic effects of psychoplastogens. A significant finding by Barrett and colleagues (2020) is that modifications in brain connectivity and emotional processing persisted and remained

detectable long after the metabolism of psilocybin, which occurs approximately three hours post-ingestion (Passie et al., 2002; Brown et al., 2017).

To explore this potential, a more detailed examination of neurobiological mechanisms and altered brain dynamics enhances understanding of the connection between the altered state of consciousness during the psychedelic experience and its long-term therapeutic benefits. Altered signalling and information integration, as well as changes in the brain's functional connectivity, can provide further insights into the therapeutic mechanisms of psychoplastogens. We will assess the effects on a neurobiological and neuropsychological level by examining various perspectives, from neurochemical to system-wide.

2.2 Neurobiological Correlates of the Psychedelic State

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a tryptamine compound that primarily acts on the serotonergic system by interacting with various *serotonin* (5-hydroxytryptamine, 5-HT) *receptors*. These receptors play a central role in perception, emotion regulation, and attention. Psilocybin mainly binds to the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptor subtypes, with particularly high affinity for 5-HT_{2A} receptors (Ki = 6 nM), compared to lower affinity (Ki = 190 nM) for 5-HT_{1A} receptors (McKenna et al., 1990). The subjective effects of psilocybin are thought to arise primarily through activation of 5-HT_{2A} receptors. This receptor activation leads to glutamate release and subsequent stimulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in increased cortical excitability and enhanced information processing (Uthaug et al., 2018; Dos Santos et al., 2016; Marek, 2018; Murnane, 2018). Suggesting a connection between the receptor and the psychedelic state, this relationship is not yet clarified. Therapeutic effects may also occur independently of 5-HT_{2A} receptor activation (e.g. Hesselgrave et al., 2021).

LSD mainly targets the 5-HT_{2a} receptor as well, indicating effects similar to psilocybin, but it also shows moderate affinity for dopamine receptors (de Vos et al., 2021). DMT also interacts with 5-HT_{2A} receptors and additionally with σ1 receptors as an agonist. In the mixture ayahuasca, β-carbolines (tetrahydroharmine, harmaline, and harmine) are added which are reversible monoamine oxidase inhibitors blocking DMT´s first-pass metabolism by monoamine oxidase. It is not yet certain whether 5-HT_{2A} receptor agonism exclusively mediates the effects of Ayahuasca/DMT (Egger et al., 2024). The pharmacodynamic and pharmacokinetic characteristics of DMT might

offer advantages over psilocybin: Inhalation or intravenous (IV) administration results in a rapid onset, usually within about 2 minutes, and the psychedelic effects completely dissipate after approximately 30 minutes (Holze et al., 2024).
MDMA inhibits the norepinephrine transporter, the dopamine transporter, and the 5-HT transporter, resulting in the release of supraphysiological levels of 5-HT, dopamine, and norepinephrine (Green et al., 2003; Rothman and Baumann, 2002). Studies have demonstrated that blocking the 5-HT_{2A} receptor with antagonists such as ketanserin eliminates the subjective effects of 5-HT_{2a}-interacting substances (e.g. Preller et al., 2017).
Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. The blockade of the NMDA receptor triggers a cascade of downstream effects, including increased AMPA receptor activity and increased release of *brain-derived neurotrophic factor* (BDNF), which are believed to mediate its rapid antidepressant properties (Li et al., 2010; Duman & Aghajanian, 2012). The NMDAr is a physiologically complex receptor that initiates a cascade of effects. NMDAr-mediated glutamate neurotransmission provides a plausible neurobiological basis for new interventions for depression (Pilc et al., 2013). Interestingly, other NMDA antagonists, including ion channel blockers such as lanicemine, memantine, and N_2O, which bind to the same site on the receptor as ketamine, have not demonstrated the same evidence of antidepressant efficacy (Newport et al., 2015).

5-HT_{2a} agonism and NMDA antagonism have been shown to trigger a cascade of neurobiological events, including neuronal plasticity.

2.2.1 Findings on neuronal plasticity

Disruptions in neuroplasticity are seen in many mood disorders (Ray et al., 2014), especially in depression, where they are characterised by reduced cortical neuroplasticity (e.g., Player et al., 2013). Usually, changes in neuroplasticity are triggered by experiences and activities to adapt to a changing environment (Cramer et al., 2011).
Psychoplastogens such as ketamine and psychedelics rapidly induce a period of heightened neuroplasticity, alongside lasting neuroplastic changes (Hasler, 2020; Olson, 2018). For instance, in cortical cultures, psychedelics have been shown to increase dendritic growth cone size, promote the growth of new neurites, raise dendritic spine density, and alter spine morphology (Ly et al., 2018; Jones et al., 2009; Mi et al., 2017; Yoshida et al., 2011; Ohtani et al., 2014; Cameron et al., 2023),

with even brief stimulation periods causing long-lasting changes in cortical neuron growth (Ly et al., 2021). Furthermore, ketamine administration has been found to increase spine density and the population of mushroom (large-diameter) spines (Li et al., 2010). Studies indicate that dendritic spine formation three days after psilocybin treatment exceeds the rate observed just one day after treatment (Ly et al., 2018; Shao et al., 2021), highlighting long-term therapeutic effects beyond the acute and subjective alteration of consciousness.

The consequences of enhanced neuroplasticity include that, in chronically stressed mice, psilocybin both strengthened cortico-hippocampal synapses, reducing anhedonia, potentially due to improved synaptic efficacy within reward circuits (Hesselgrave et al., 2021). Additionally, the increased spinogenesis caused by ketamine has been linked to reductions in depression-related behaviours (Moda-Sava et al., 2019; Wu et al., 2021). It is important to note, however, that unwanted neuroplastic changes in sensory regions of the brain may cause more severe HPPD (Müller et al., 2021).

The plastogenic effects depend on multiple interconnected molecular mechanisms, including the activation of tropomyosin receptor kinase B (TrkB), the mammalian target of rapamycin (mTOR) pathway, AMPA receptor signalling (Ly et al., 2018; Vargas et al., 2023). Proteomic analyses show that LSD treatment upregulates the mTOR pathway in human brain organoids, indicating that psychedelics affect intracellular signalling networks linked to neuronal growth and synaptic remodelling (Dakic et al., 2017). Moreover, mTOR activation in excitatory pyramidal neurons of the cortex is essential for the prosocial effects observed after repeated LSD administration, demonstrating a causal connection between this pathway and behavioural outcomes (de la Fuente Revenga et al., 2021).
Since mTOR functions downstream of TrkB in canonical neurotrophic signalling, these findings further support BDNF - TrkB - mTOR signalling as a crucial mechanism through which psychedelics affect structural neuroplasticity. Interestingly, recent evidence indicates that LSD and psilocin can act as positive allosteric modulators of BDNF signalling by directly binding to TrkB, thereby boosting neurotrophic processes (Casarotto et al., 2021).
Studies in animals (e.g., de la Fuente Revenga et al., 2021; Desouza et al., 2021) have shown that LSD, psilocybin, and DMT can increase the expression of genes associated with synaptic plasticity, including immediate-early genes (IEGs). A more

detailed understanding of the biological mechanisms underlying neuroplasticity can be found elsewhere (e.g., De Vos et al., 2021).

Psychedelics seem to boost neuroplasticity through the 5-HT_{2A} receptor (Vollenweider & Preller, 2020), although other studies report that selective 5-HT_{2A} receptor antagonists do not fully prevent psychedelic-induced neuroplasticity (Shao et al., 2021; Hesselgrave et al., 2021). Increased neuroplasticity may make individuals more receptive to key therapeutic targets (Calder & Hasler, 2023).

The mechanisms behind the effects of psychoplastogens are more complex than simply acting on a single receptor type or specific neuroplasticity pathways. To fully grasp the multifaceted impacts of psychoplastogens, it is essential to consider system-wide changes in brain function, particularly alterations in functional connectivity across large-scale neural networks.

2.2.2 Findings on functional connectivity

When focusing on the functional connectivity of neuropsychological functions and brain areas, serotonergic psychedelics such as psilocybin appear to alter the hierarchical neural organisation by reducing top-down control and increasing bottom-up information flow (Dos Santos & Hallak, 2020)**.** Examining more specific changes in activity and connectivity within key brain regions involved in information integration, both factors were elevated within the claustrum, the thalamus, the posterior cingulate cortex (PCC), and the medial prefrontal cortex (mPFC) under the influence of psilocybin (Carhart-Harris et al., 2012; McCulloch et al., 2022). More recently, whole-brain averaged connectivity was found to significantly increase under the influence of psilocybin (Mortaheb et al., 2024), indicating globally hyperconnected functioning patterns. Dynamic analyses of connectivity patterns after psilocybin have demonstrated that the brain repeatedly reconfigures itself into short-lived functional states with low stability (Lord et al., 2019). When comparing the functional connectivity analysis with subjective aspects of brain-state alterations (Mortaheb et al., 2024), 5D-ASC ratings suggest that hyperconnectivity correlates most strongly with the OSE and the visionary restructuralisation (VRS) factor of the 5D-ASC, with OSE being particularly notable due to its proximity to the mystical experience. Various psychoplastogens have been shown to modify the brain's functional organisation, thereby promoting increased global integration through both short-range and long-range functional connections (Tagliazucchi et al., 2016; Timmermann et al., 2023). The resulting altered integration of sensory input is believed to facilitate

a novel experience of the self and the surrounding environment (De Gregorio et al., 2021).

To better address the alteration of more complex, dynamic systems, the concept of entropy, originating from the EBH, can enhance the classification of findings related to changes in brain activity, providing a more multidimensional approach to the data. While studies on functional connectivity are widespread across various areas of cognitive neuroscience, entropy remains a notably distinct aspect within the psychedelic neuroimaging literature (Shinozuka et al., 2024). Furthermore, the meta-analysis by Shinozuka and colleagues shows that the data on blood-oxygenation-level-dependent (BOLD) activity across studies are highly variable, making it difficult to interpret results.

The Dynamic Mean-Field Model, developed by Deco and colleagues (2014), can simulate whole-brain activity. When simulating stimulation of the 5-HT_{2a} receptor through psychedelics, the activation of the receptor causes a heterogeneous, linear increase in entropy, defined here as the diversity of neural activity (Herzog et al., 2023). The observed increase in entropy was more nuanced, suggesting a spatially heterogeneous reconfiguration of brain activity and connectivity, rather than a globally uniform increase in entropy. This study did not yield consistent findings regarding the relationship between these observations and the density of 5-HT_{2a} receptors. They conclude that 5-HT_{2A} agonists do not have a simple, localised effect on brain activity, but instead amplify the collective properties of the brain as a complex system of interacting elements, requiring an even more dimensional operationalisation of entropy.

Yeo networks, system-relevant networks of which there are 7 in the brain (differentiable into 17 sub-networks), can summarise changes in the overall entropy of the active brain. Based on intrinsic functional connectivity, Yeo and colleagues (2011) identified seven canonical large-scale networks: the *Visual Network* (Vis), the *somatomotor network* (SMN), the *dorsal attention network* (DAN), the *ventral attention and salience network* (VAN), the *limbic network* (Limbic), the *frontoparietal control network* (FPN), and the *default mode network (DMN)*. These structured functional networks provide a robust organisational framework for studying cognition, emotion and, of particular interest, the processing of rewards and hedonic responses: The DMN, which includes the ventromedial prefrontal cortex (vmPFC), the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC), is involved in

representing the value of rewards, as well as in self-referential processing and the integration of sensory inputs (Gorwood, 2008). These regions are central nodes within valuation processes, which involve interactions between cortical regions (e.g., vmPFC/OFC) and subcortical structures, particularly the ventral striatum (Camara et al., 2009; Zald & Treadway, 2017). As activity within the DMN decreases, it could enable less rigid self-referential processing and allow for a new valuation of rewards. Under psychedelics, the DMN is more functionally connected to the FPN (Shinozuka et al., 2024).

The FPN, including the dorsolateral prefrontal cortex (dlPFC) and the medial prefrontal cortex (mPFC), further improves cognitive flexibility by integrating cognitive control for responses to rewards (Gorwood, 2008). These prefrontal regions are essential in modulating valuation and decision-making signals through top-down control, affecting activity in the ventral striatum and other valuation regions (Camara et al., 2009; Zald & Treadway, 2017). Both the functional connectivity of the DMN and FPN to the VAN is increased under psychedelics (Shinozuka et al., 2024).

The VAN includes the amygdala, the insula, and the ACC, and is responsible for recognising emotional and motivational salience (Gorwood, 2008). This network has been implicated in detecting salient reward cues and switching between internally focused (DMN) and externally oriented (FPN/DAN) networks, thereby influencing reward-related attention and motivation (Camara et al., 2009; Zald & Treadway, 2017).

Together with the enhanced within-DAN functional connectivity under psychedelics (Shinozuka et al., 2024), especially between the parietal cortex and the striatum, the allocation of attention on reward-relevant stimuli may enable the more flexible processing of more salient appearing rewards. This finding is consistent with research indicating that the dorsal attention network interacts with striatal structures to allocate attention toward motivationally relevant stimuli, thereby supporting the anticipatory and attentional components of reward processing (Camara et al., 2009; Zald & Treadway, 2017).

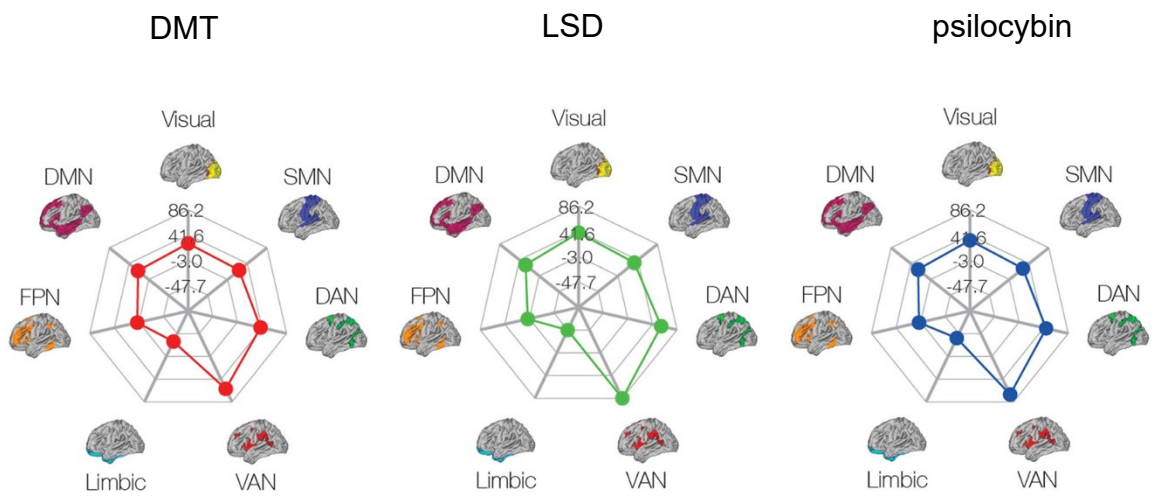

Figure 1. *Phenomenology profiles of the psychedelics demonstrate broad similarity between the neural correlates of their subjective effects (Shinozuka et al., 2024).*

Another approach to whole brain dynamics involves information theory, a framework that conceptualises the brain as a multivariate information processing system. This approach enables the study of how higher-order information processing is integrated within brain multivariate dynamics. The integration of information can be classified into synergy and redundancy (Luppi et al., 2024). Synergy describes information that arises solely from the combined activity of multiple regions and cannot be found in any single region alone. This property may facilitate more efficient information processing (Rassouli, Rosas & Gündüz, 2020). However, because it depends on the coordinated input of these regions, synergistic information is fragile and can be easily lost if even one contributing region is disrupted. Conversely, redundancy refers to information duplicated across regions, ensuring a reliable representation of critical information. Finding the right balance between synergy and redundancy is essential in the brain's strategies for information integration, balancing the flexibility of emergent processing with the dependability of robust information representation (Rassouli et al., 2020; Varley et al., 2023).

Engagement with a complex stimulus shifts the brain's dynamic organisation toward greater synergy, reducing redundancy (Kathofer et al., 2025). This shift becomes even more pronounced during intense music-evoked hedonic experiences, suggesting that hedonic processing relies on the synergistic interaction of many widely distributed cortical and subcortical areas.

Ketamine induces subtle and subacute shifts in resting brain dynamics towards increased redundancy, improving the brain's capacity to access critical internal representations reliably. This may enhance access to vital internal information,

fostering a neural state that supports more intense hedonic experiences as a reaction to rewards (Kathofer et al., 2025). Interestingly, the greater this shift towards redundancy, the more intense the hedonic experiences become. Both the increase in redundancy and the decrease in synergy indicate that the brain prioritises redundancy under ketamine to safeguard the transmission of essential internal information, making it less vulnerable to errors and disruptive influences, thereby ensuring reliable and stable downstream processing (Kathofer et al., 2025).

Besides their impact on the neurobiological tissue, psychoplastogens may improve handling of more complex rewards than sex and food in psychiatric conditions by altering and flexibly activating brain networks and information processing. The connection between psychiatric conditions with impaired reward processing and its potential as a target for new treatments is discussed in the following section.

3 Anhedonia and Rewards

Anhedonia is a core symptom of various psychiatric disorders (e.g., depression and schizophrenia) and a common feature of many others (American Psychiatric Association (APA), 2013; Lambert et al., 2018). The DSM-5 (APA, 2013) describes anhedonia as a diminished ability to experience interest or pleasure from stimuli that were previously regarded as rewarding. According to the DSM-5, a diagnosis of Major Depressive Disorder requires the presence of at least five symptoms during the same two-week period, including either depressed mood or markedly diminished interest or pleasure (anhedonia) as one of the core symptoms. Anhedonia has been associated with notably negative mental health and treatment outcomes (e.g., Pizzagalli et al., 2022; Vrieze et al., 2014), and even after accounting for overall depression severity, more severe anhedonia predicts greater psychosocial impairment (Vinckier et al., 2017). Anhedonia can be particularly resistant, responding poorly to pharmacological (McMakin et al., 2012; Uher et al., 2012), psychological (Craske et al., 2016), and neurostimulation therapies (Siddiqi et al., 2022). Therefore, anhedonia and its related features continue to be a central focus for healthcare providers and patients due to their substantial impact on self-care, daily routines, and interpersonal relationships (Chevance et al., 2020; Treadway & Zald, 2011).

As the definition indicates, anhedonia is linked to brain deficits in processing and responding to rewards (e.g., Keedwell et al., 2015; Pizzagalli et al., 2022). Changes in reward processing are arguably among the most common symptoms of psychopathology (Zald & Treadway, 2017). Conversely, appropriately enhanced reward processing is associated with better mental health-related quality of life, increased enjoyment and satisfaction in life, and greater improvements in physical health-related quality of life over time (Whitton et al., 2023). However, specific brain functions such as reward processing under psychoplastogens remain underexplored, exposing a significant gap in the assessment of therapeutic treatment targets.
The National Institute of Mental Health's (NIMH) Research Domain Criteria aims to characterise psychopathology through functional domains. It defines reward-related processes as part of the positive valence system (PVS) of anhedonia and as one of five overarching substrates for psychopathology (Insel et al., 2010), emphasising the importance of rewards in therapeutic outcomes. Reward sensitivity refers to responses that evoke hedonic reactions to current or anticipated rewarding stimuli (NIMH, n.d.).

First-line pharmacotherapies (e.g., SSRIs, TCAs, and bupropion) do not effectively or sufficiently treat or alleviate symptoms of anhedonia, nor do they address the nuanced and multidimensional aspects of depression, such as reward-processing and consequently reward-sensitivity deficits (Belujon & Grace, 2017; Perna et al., 2020; Treadway & Zald, 2011; Walsh et al., 2018). Psychoplastogens appear to address this gap, even though research with psychedelics in this specific area remains in its early stages, particularly regarding human data.
Dopaminergic neurons originating from the ventral tegmental area (VTA) and projecting to the ventral striatum (VS) via the mesolimbic pathway encode important and fundamental aspects of reward processing (Camara, 2009). A more detailed understanding of the underlying biological and network-level mechanisms of reward processing is provided elsewhere (e.g., Haber & Knutson, 2010; Osugo et al., 2025; Xu et al., 2025). The administration of psilocybin in rats caused a rapid increase in dopamine release in the PFC (Wojtas et al., 2022), indicating enhanced dopamine signalling for reward circuits. Furthermore, psilocybin influences positive valence encoding both in the short and long term (Pouyan et al., 2022), as does LSD (Pouyan et al., 2023). LSD showed reward-related brain activity even at low (13-26µg) doses (Glazer et al., 2023).

Ketamine reverses reward-related deficits and relieves anhedonia-like symptoms in both humans and preclinical studies (Nogo et al., 2022). It also counteracts stress-induced modifications in excitatory synapses within the nucleus accumbens (Lucantonio et al., 2025). Ketamine reduces hypoactivity in the striatum (a brain area involved in reward processing), leading to anti-anhedonic effects (Kotoula et al., 2022).

Humans are capable of experiencing complex rewards, including social, musical, artistic, altruistic, and intellectual pleasures (Rømer Thomsen et al., 2015). Social rewards are of special interest for therapeutic outcomes as impairments in social cognition and social motivation are a diagnostic criterion for various psychiatric disorders (Kennedy & Adolphs, 2012). Psychedelics appear to reopen the critical period of social reward learning (Nardou et al., 2023), indicating a fundamental rewiring of social reward processing. MDMA (1-2 mg/kg) increased ratings of feeling “sociable,” “friendly,” “talkative,” “close to others,” and “loving” (Regan et al., 2021), and also heightened social seeking behaviour (Bershad et al., 2019).

Listening to enjoyable or preferred music is often described as a pleasurable experience (Dubé & Le Bel, 2003). Music activates the reward system, emotions, memory, and various cognitive functions (Vusst et al., 2022; Kaiser & Berntsen, 2023; Kölsch, 2014; Blood & Zatorre, 2001), indicating a valid way to explore responses to complex rewards. Exposure to chill-evoking music had a significant impact on reward learning in individuals with anhedonia (Jain et al., 2025).

Peak hedonic experiences are most robustly predicted by changes in redundant information processing (Kathofer et al., 2025). Ketamine has been shown to facilitate the emergence of hedonic experiences through altered information processing, enhancing all facets of hedonic experiences, especially when listening to music (Kathofer et al., 2025).

These findings highlight the significance of anhedonia as a transdiagnostic and currently hard-to-treat factor in psychiatric disorders. Because anhedonia is closely associated with impaired reward processing, responses to complex rewards are valid indicators for antidepressant outcomes. Psychoplastogens tend to influence not only plasticity and functional connectivity but also the processing of these effects rewards.

4 Objectives and Hypotheses

The common belief is that the subjective, altered state of consciousness caused by psychoplastogens is essential for achieving clinical benefits (Nutt et al., 2020; Roseman et al., 2018; Yaden & Griffiths, 2020).

Addressing the noted inconsistency in highly heterogeneous methodological studies, this master's thesis provides an initial investigation of the role and necessity of the subjective altered state of consciousness.

A more precise understanding of the necessity and role of specific factors in the subjective altered state of consciousness has implications for safer and effective therapeutic use of psychoplastogens, by also increasing public and clinical acceptance (Rosenblat et al., 2023; Burke & Blumberger, 2021; Husain et al., 2023; Hesselgrave et al., 2021).

To address the research question of whether and how the subjective altered state of consciousness under psychoplastogens influences reward sensitivity as well as depression symptoms and well-being, a mechanistic study on psilocybin was designed, employing multi-level measurements of the subjective psychedelic experience and clinically relevant outcomes for both healthy and anhedonic populations.

Regrettably, the planned data collection on the altered state of consciousness under psilocybin and its interaction with therapeutic outcomes was not completed within the timeframe set for this thesis. An outline of the experimental design for the intended investigation into psilocybin is included in the discussion of this thesis.

Instead, data from a recent project on ketamine was used. Ketamine was selected due to its partially overlapping properties with classic psychedelics (e.g., rapid-acting antidepressant effects, psychoplastogenic properties, and the potential to induce the altered states of consciousness), making it a suitable alternative for investigating the necessity, intensity, and quality of subjective altered states of consciousness under psychoplastogens.

To explore therapeutic outcomes within this healthy population dataset, reward sensitivity - a component of the positive valence system of anhedonia - has been utilised. To assess the importance of the subjective sensation, along with the influence of the intensity and quality of the altered state of consciousness, the following hypotheses have been formulated.

H1: Compared to placebo, ketamine is expected to produce greater within-subject improvements in reward sensitivity, as measured by DARS total and domain scores, while controlling for baseline scores, period effects (within-subject), and sequence effects (between-subject, to account for potential carry-over effects) in the two-period crossover design.

H2: The effect of ketamine on ΔDARS is mediated by distinct facets of the subjective altered state of consciousness (5D-ASC).

> ***H2a:*** When the 5D-ASC components are entered simultaneously as mediators, the direct ketamine effect on ΔDARS becomes statistically negligible. This pattern would indicate that 5D-ASC facets are necessary for reward improvements.
>
> ***H2b:*** Across all measured 5D-ASC components, the 5D-ASC component OSE exerts the largest unique contribution to ΔDARS total score.
> (Special focus on OSE is due to its theoretical proximity to mystical experience.)

Methods

Experimental Design

The data was collected in a randomised, single-blind, crossover, placebo-controlled study. The study features two experimental manipulations:

0. Placebo (0.9% NaCl)
1. Ketamine (0.5mg/kg, diluted in 0.9% NaCl)

The solutions are provided over a 40-minute period, four hours before administering the questionnaires. All participants experience both pharmacological conditions (placebo and ketamine). A two-week washout period is enforced between sessions to prevent short-term carryover effects.

Power analysis

An a priori power analysis was conducted in G*Power (Version 3.1.9.6, Faul et al., 2009) for the primary within-subject contrast (ketamine vs. placebo) on ΔDARS. Recent systematic and narrative reviews since 2019 report small-to-moderate improvements in anhedonia after ketamine or esketamine, including effects partly decoupled from global depression severity (Kwaśny et al., 2024; Almeida et al., 2024; Johnston et al., 2023). Converging human neuroimaging work shows rapid modulation of reward circuitry and associated improvements on anhedonia scales after ketamine (Kotoula et al., 2022; Alexander et al., 2023). Because our sample is non-depressed (minimising baseline symptom variance), a conservative within-subject effect size of dz = 0.40 for ΔDARS was adopted. Using a two-tailed paired-samples t-test (α = .05, power = .90), the required sample size is n = 66 completers; with power = .80, n = 50 suffices. This a priori plan targets the primary treatment effect; mediation tests involving 5D-ASC facets (OSE, AIA, VIS, AVE, VUS) will be analysed, but their power is not estimated via GPower and typically requires larger samples.

Population

Participants were recruited via local advertisements, electronic media, postings at public places at the General Hospital of Vienna (AKH) and local supermarkets. Two participants were excluded due to technical issues, resulting in a final sample of N = 38. The sample consisted of 16 male and 22 female participants. The mean age of male participants was 24.38 years (SD = 4.08), while female participants had a mean age of 23.18 years (SD = 3.47). The age range was 19 to 32 years for males and 20 to 37 years for females.

Physical health was assessed through medical examinations, including electrocardiogram, blood, urine, pregnancy, and drug tests. Mental health was evaluated using the Structured Clinical Interview (Lobbestael, Leurgans & Arntz, 2011). Exclusion criteria included history of neurological and psychiatric disorders, any current pharmacological treatment, pregnancy, breastfeeding, current or former substance abuse and prior experience with ketamine (in context of recreational or therapeutic use).

Measuring Instruments

The following questionnaires have been used to assess the role of subjective altered states of consciousness in changes to reward sensitivity.

Altered States of Consciousness Scale (5D-ASC)

The 5D-ASC is a widely used tool for quantifying altered states of consciousness (ASC) caused by psychedelics. It is based on Dittrich's earlier work (APZ and OAV questionnaires) and was developed into a five-dimensional model through extensive psychometric studies (Dittrich, 1998; Studerus et al., 2010). It includes 94 items rated on 100-mm visual analogue scales, anchored from "no, not more than usual" to "yes, much more than usual." The questionnaire comprises five dimensions:

1. Oceanic Self-Expansion (OSE): experiences of positive ego-dissolution, feelings of unity, bliss, transcendence, and spirituality.
2. Anxious Identity Attenuation (AIA): anxiety, loss of control, and experiences of self-disintegration or identity instability.
3. Visual Intensification and Synesthesia (VIS): vivid visual hallucinations, synesthetic experiences, and alterations in perceptual organization.
4. Auditory Variability and Enhancement (AVE): distortions, amplifications, or heightened sensitivity to sounds and music.
5. Vigilance and Understanding Shifts (VUS): reduced alertness, sedation, and dreamlike or confused states of consciousness.

The 5D-ASC demonstrates high internal consistency across dimensions ($\alpha > .80$ in most studies) and robust validity in psychedelic research.

Dimensional Anhedonia Rating Scale (DARS)

The Dimensional Anhedonia Rating Scale (DARS, Rizvi et al., 2015) measures anhedonia across various reward domains. Unlike previous unidimensional assessments, the DARS reflects the complexity of anhedonia by assessing desire, motivation, effort, and consummatory pleasure.

The DARS contains 17 items and requires participants to generate examples of rewarding activities in four domains, which are then rated according to their rewarding value:

1. Hobbies/Interests
2. Food/Drink
3. Social Activities
4. Sensory Experiences

Psychometric analyses identified a solid four-factor structure and high internal consistency (α = .75 - .92), exhibiting superior validity compared to the commonly used Snaith-Hamilton Pleasure Scale (Rizvi et al., 2015). A recent study also confirmed content validity in patients with major depressive disorder (Bean et al., 2025).

Procedure

All participants provided written informed consent after being thoroughly briefed on the study's purpose, procedures, risks, and potential implications. They were explicitly informed that participation was voluntary and that they could withdraw at any time without affecting their medical care. In addition to the investigator's verbal explanation, each participant received a written information sheet summarising the study in clear language. Consent also included agreement to the possible disclosure of study-related data to authorised regulatory bodies. This study was conducted in full accordance with the principles of the "Declaration of Helsinki" (as amended at the 64th WMA General Assembly, Fortaleza, Brazil, 2013) and with the laws and regulations of Austria.

Before and after each session, participants completed measures of reward sensitivity (DARS). Participants spent most of the time inside an fMRI scanner during each session. The altered state of consciousness questionnaire (5D-ASC) was administered during the ketamine session to assess acute experiential effects.

Four hours before the session, participants received either a saline solution (0.9% NaCl) or 0.5 mg/kg of racemic ketamine (50 mg/ml ampoules; Hameln Pharma

Plus GmbH), diluted in 0.9% NaCl, infused over 40 minutes. Medication was prepared, stored, and supplied by the hospital pharmacy of the AKH Vienna.
To reduce risk, blood pressure, heart rate, and blood oxygenation were continuously monitored during ketamine infusion. A physician was always present, and participants were monitored for three hours after ketamine administration. Subjects were assessed for any psychotomimetic effects, and vital parameters (blood pressure, heart rate) were measured before each session day. Additionally, subjects were required to be accompanied home after the study day by a trusted friend or relative.

Statistical Analysis

All statistical analyses were conducted using RStudio (Version 2024.09.0+375R, Posit Software, 2024) and JASP (version 0.95.3; JASP Team, 2025). Prior to analysis, data will be screened for accuracy, missing values, and outliers. Normality of residuals will be assessed using the Shapiro-Wilk tests and visual inspection of Q-Q plots. Homogeneity of variances and sphericity will be checked where applicable. Where assumptions of normality are violated, nonparametric equivalents will be applied. Confidence intervals will be set at 95%, and bootstrapped estimates will be used in mediation and moderation models to ensure robust inference. Descriptive statistics and data visualisation will be conducted in RStudio using the packages *dplyr* and *tidyr* for data preparation.

H1: A linear mixed-effects model (LMM) was fitted to test the primary hypothesis. The model predicted post-treatment reward sensitivity (DARS Total) from baseline DARS scores, drug condition (ketamine vs. placebo), period (first vs. second treatment period), and sequence, with a random intercept for subjects to account for the non-independence of repeated measures within participants. Model selection was guided by the Bayesian Information Criterion (BIC) to balance model fit and parsimony, and the best-fitting model was refitted using restricted maximum likelihood (REML) estimation for inference.
Linear mixed-effects models were fitted with *lme4* (Bates et al., 2015) and *lmerTest* (Kuznetsova et al., 2017); estimated marginal means and contrasts were obtained using *emmeans* (Lenth, 2024). Model diagnostics and effect size estimation relied on *performance* (Lüdecke et al., 2021) and *effectsize* (Ben-Shachar et al., 2020). Nonparametric comparisons were conducted with the base R *stats* package (*wilcox.test*).

The utilised theoretical model before model selection can be described as:

$$DARS_{ij}^{post} = \beta_0 0 + \beta_1 1 DARS_{ij}^{pre} + \beta_2 Drug_{ij} + \beta_3 Period_{ij} + \beta_4 Sequence_{ij} + u_{0j} + \varepsilon_{ij}$$

With:

i = measurement occasion (within-subject level)

j = participant (between-subject level)

β_0 = fixed intercept

β_1-β_4 = fixed-effect coefficients for the respective predictors

$u_{0j} \sim N(0, \sigma_u^2)$ = subject-specific random intercept (accounts for within-subject correlation)

$\varepsilon_{ij} \sim N(0, \sigma^2)$ = residual error term

H2a: To examine whether the effect of ketamine on changes in reward sensitivity (ΔDARS) is mediated by intensity of the altered state of consciousness, a parallel multiple mediation model within the ketamine condition will be tested using the *lavaan*, *semTools*, *boot*, and *relimpo* packages in R. The model can be formally expressed as follows:

$$M_1 = a_1 X + eM_1$$
$$M_2 = a_2 X + eM_2$$
$$M_3 = a_3 X + eM_3$$
$$M_4 = a_4 X + eM_4$$
$$M_5 = a_5 X + eM_5$$
$$Y = c'X + b_1 M_1 + b_2 M_2 + b_3 M_3 + b_4 M_4 + b_5 M_5 + eY$$

Where:

X = drug condition (ketamine = 1, placebo = 0)

M_1-M_5 = the five 5D-ASC components (OSE, AIA, VUS, AVE, VIS)

Y = change in DARS score (ΔDARS Total or ΔDARS Social)

a_i = effect of ketamine on mediator M_i

b_i = effect of mediator M_i on outcome Y, controlling for other mediators

c' = direct effect of ketamine on Y controlling for all M_i

$a_i b_i$ = specific indirect effect through M_i

$\Sigma a_i b_i$ = total indirect effect

$c' + \Sigma a_i b_i$ = total effect of ketamine on ΔDARS

All indirect effects were estimated using nonparametric bootstrapping (5,000 resamples) with percentile confidence intervals.

H2b: A relative importance analysis was conducted to determine the unique variance contribution of each 5D-ASC component to ΔDARS, allowing direct evaluation of whether OSE accounted for the largest unique proportion of explained variance. A multiple linear regression was calculated using *relimpo*, *lavaan*, *semTools*, and *boot* packages in R. The formal model was:

$$Y = b_1 M_{OSE} + b_2 M_{AIA} + b_3 M_{VUS} + b_4 M_{AVE} + b_5 M_{VIS} + e_Y$$

Where: *Y* = change in DARS score (ΔDARS Total).

Additionally, a standardised model was utilised:

$$Z_Y = \beta_1 Z_{OSE} + \beta_2 Z_{AIA} + \beta_3 Z_{VUS} + \beta_4 Z_{AVE} + \beta_5 Z_{VIS} + e_Y$$

Results

Preliminary Analyses

Descriptive analyses have been performed on the variables of interest (see Appendix for tables). A visual examination of 5D-ASC total scores (weighted through PCA) suggests the data is normally distributed. The OSE subscale showed a normal distribution, whereas the other components did not.

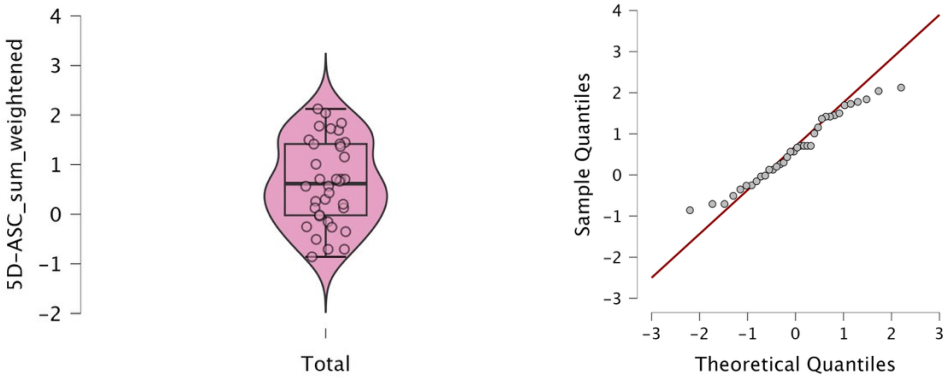

Figure 2. *Violin plot and QQ plot for 5D-ASC total.*

Inspection of prae- and post-DARS scores for ketamine session indicated normality of data for post_DARS (after session) but not for prae_DARS. Difference in DARS (ΔDARS) was not normally distributed.

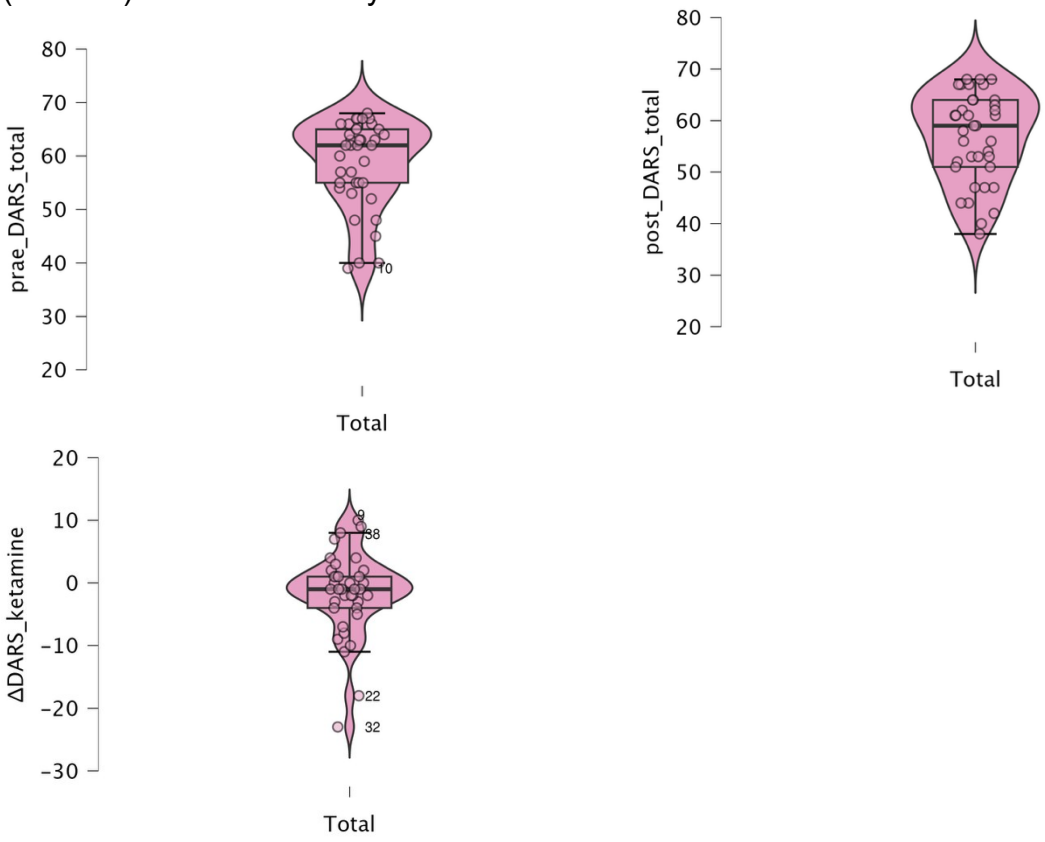

Figure 3. *Violin plots for prae-, post- and Δ-DARS scores for ketamine session.*

Effects of Ketamine on Reward Sensitivity

To approach the question of whether ketamine influences reward sensitivity, the model selection prioritised the Bayesian Information Criterion (BIC) to obtain the most parsimonious model. Ties within ΔBIC ≤ 2 were resolved by selecting the model with fewer parameters, with the lower AIC serving as a secondary criterion. According to this procedure, the model without the sequence factor (no_sequence) provided the best fit to the data (BIC = 485.68), with only minimal differences compared to the other reduced models. Likelihood-ratio tests against the full model confirmed that excluding *drug*, *period*, or *sequence* did not significantly worsen model fit.
The selected mixed-effects model included *baseline DARS (pre)*, *drug condition*, and *period* as fixed effects, with a random intercept for participants to account for within-subject dependence:

$$DARS_{ij}^{post} = \beta_o + \beta_1 DARS_{ij}^{pre} + \beta_2 Drug_{ij} + \beta_3 Period_{ij} + u_{oj} + \varepsilon_{ij}$$

Baseline DARS significantly predicted post-treatment scores, *b* = 0.86, *SE* = 0.09, *t*(69) = 9.92, *p* < .001, indicating strong baseline-outcome continuity. However, the effect of ketamine vs. placebo was not significant, *b* = -0.62, *SE* = 1.19, *t*(69) = -0.52, *p* = .61, 95% CI [-3.00, 1.77], and neither was the period effect (Table 3). Estimated marginal means (adjusted for baseline) were 57.38 (SD = 0.87) for placebo and 56.76 (SD = 0.88) for ketamine, yielding a non-significant contrast, Estimate = -0.62, *SE* = 1.19, *t*(36) = -0.52, *p* = .61, 95% CI [-3.04, 1.81].

Table 1. *Candidate models (ML): k, logLik, AIC, BIC, ΔAIC, ΔBIC.*

Model	k	logLik	AIC	BIC	dAIC	dBIC
no_sequence	6	-229.89	471.77	485.68	0.00	0.00
no_drug	6	-229.96	471.91	485.82	0.14	0.14
no_period	6	-230.23	472.45	486.36	0.68	0.68
full	7	-229.81	473.63	489.85	1.86	4.17

Table 2. *Likelihood-ratio tests versus the full model (χ^2, df, p).*

Comparison	Chisq	p
no_drug vs full	0.29	0.592
no_period vs full	0.83	0.364
no_sequence vs full	0.14	0.704

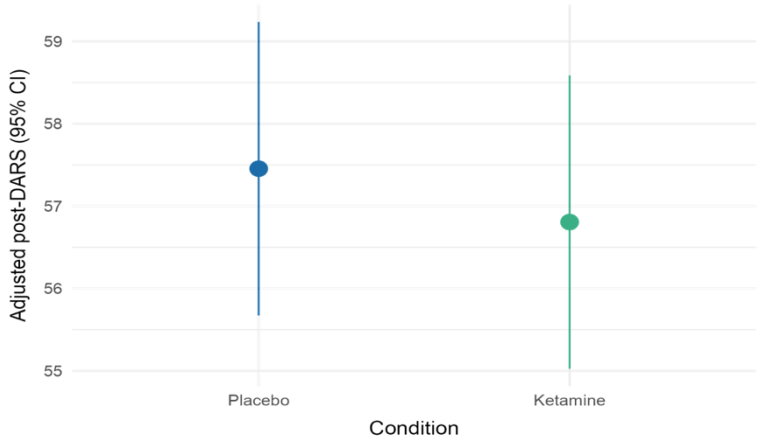

Figure 4. *Adjusted post-DARS means by condition.*

Table 3. *Estimated marginal means for adjusted post-DARS by condition (95% CI).*

Predictor	b	SE	t	df	p	CI_low	CI_high
pre	0.86	0.09	9.92	69	< .001	0.68	1.03
drug/ketamine	-0.62	1.19	-0.52	69	0.607	-3.00	1.77
sequence/period	1.05	1.20	0.88	69	0.382	-1.33	3.44

Table 4. *Estimated marginal means for adjusted post-DARS by condition (95% CI).*

Condition	Mean_adj	SE	df	CI_low	CI_high
placebo	57.38	0.87	71	55.65	59.10
ketamine	56.76	0.88	71	55.01	58.51

Table 5. *Contrast (ketamine - placebo) on adjusted post-DARS (95% CI).*

Contrast	Estimate	SE	df	t	p	CI_low	CI_high
ketamine - placebo	-0.62	1.19	36	-0.52	0.609	-3.04	1.81

To validate the robustness of the primary mixed-effects model results, a nonparametric Wilcoxon signed-rank test was conducted on within-subject change scores in reward sensitivity (ΔDARS; post-pre) between the ketamine and placebo conditions. The median paired difference (Hodges-Lehmann estimate) was 0.50, 95% CI [3.00, 2.00], $W = 242.5$, $p = .694$. This indicates no significant difference in

median improvement between ketamine and placebo sessions, consistent with the mixed-model results.

For exploratory purposes, dimension-specific change scores from the DARS subscales (Motivation, Effort, Desire, Consummatory, and Total) were standardised and compared between the ketamine and placebo conditions using paired Wilcoxon signed-rank tests (Table 7). Standardisation (z-transformation) was applied to allow comparability across domains with different response ranges and variance levels. Across all DARS dimensions, no significant within-subject differences were found between ketamine and placebo sessions (all *ps* > .40). Median standardised change scores did not differ systematically, suggesting that no specific aspect of reward functioning showed selective enhancement under ketamine. This pattern aligns with the main model-based result, which indicated no overall improvement in reward sensitivity relative to placebo.

Table 6. *Wilcoxon Signed-Rank Tests on Residualised Change Scores (Ketamine vs. Placebo), Two-Period Crossover.*

Outcome	n_pairs	med_ket	med_pla	med_diff	HL	ci_low	ci_high	W	z	r	p
DARS Consummatory Pleasure	37	0.074	0.376	-0.301	-0.000	-0.699	0.500	335.5	-0.241	-0.040	0.814
DARS Desire	37	-0.046	0.329	-0.441	-0.000	-0.941	0.559	328.5	-0.347	-0.057	0.734
DARS Effort	37	-0.294	0.556	-0.150	-0.150	-0.650	0.500	297.5	-0.815	-0.134	0.419
DARS Motivation	37	0.088	0.291	-0.224	-0.224	-0.724	0.276	291.5	-0.905	-0.149	0.369
DARS Total	37	0.617	0.733	-0.883	-0.500	-2.500	1.617	323.0	-0.430	-0.071	0.673

These findings provide no evidence that ketamine enhanced overall reward responsiveness relative to placebo in this non-depressed sample. Period and sequence effects were negligible, indicating that treatment order and session number did not systematically influence outcomes.

Path Analyses: The Role of the Subjective Altered State of Consciousness and its Components

A mediation model was estimated to examine whether the intensity of the altered state experience (ASC_PC1, derived from a PCA of the five 5D-ASC dimensions) mediated the relationship between perceived ketamine strength (*X_strength*) and changes in reward sensitivity (ΔDARS_total).

The PCA supported a one-component solution (KMO = .76; Bartlett's $\chi^2(10) = 112.20$, $p < .001$) with strong and consistent loadings across 5D-ASC dimensions (range = .71- .91), indicating that the first principal component (ASC_PC1) adequately captured the global intensity of the altered state experience.

In the mediation model ($N = 37$, 5000 bootstrap samples, BCa confidence intervals), the path from perceived strength to ASC intensity was not significant ($a = 0.007$, $SE = 0.020$, 95% CI [-0.029, 0.052], $p = .744$, $\beta = .06$).

ASC intensity did not significantly predict changes in reward sensitivity ($b = 0.910$, $SE = 1.258$, 95% CI [-1.660, 3.268], $p = .470$, $\beta = .14$).

The direct effect of perceived strength on ΔDARS was negligible ($c' = 0.002$, $SE = 0.119$, 95% CI [-0.236, 0.237], $p = .986$, $\beta = .00$).

The indirect effect via ASC intensity was also non-significant ($a \times b = 0.006$, $SE = 0.035$, 95% CI [-0.032, 0.142], $p = .862$), and the total effect was similarly small and non-significant ($b = 0.008$, $SE = 0.112$, 95% CI [-0.203, 0.237], $p = .942$).

A true mediation analysis cannot be performed: In the present dataset, 5D-ASC scores were collected only during the ketamine session, which precludes estimation of the path linking drug condition to the mediators. Consequently, a full mediation model (drug → 5D-ASC → ΔDARS) is not identifiable. The analyses conducted within the ketamine condition should therefore be regarded as exploratory path models assessing within-condition associations between the subjective components of the psychedelic experience and changes in reward responsiveness, rather than as causal mediation effects.

Table 8. *Within-Ketamine Mediation with PCA (BCa 5000 bootstraps).*

Effect	b_unstd	SE	CI	p	beta
a: ASC_PC1 ~ X_strength	0.007	0.020	[-0.029, 0.052]	0.744	0.056
b: ΔDARS ~ ASC_PC1	0.910	1.258	[-1.660, 3.268]	0.470	0.137
c′: ΔDARS ~ X_strength	0.002	0.119	[-0.236, 0.237]	0.986	0.003
Indirect (a*b)	0.006	0.035	[-0.032, 0.142]	0.862	
Total	0.008	0.112	[-0.203, 0.237]	0.942	

A multiple regression analysis was conducted within the ketamine condition to examine whether the Oceanic Boundlessness (OSE) dimension of the 5D-ASC uniquely predicted changes in reward sensitivity (ΔDARS_total) when controlling for other experiential domains (AIA, VUS, AVE, VIS).

The overall model was not statistically significant, $F(5, 31) = 1.72$, $p = .16$, $R^2 = .22$. Among the predictors, only VUS (Vigilance Reduction) showed a significant negative association with ΔDARS_total (β = -0.56, 95% BCa CI [-1.19, -0.03], $p = .025$).

In contrast, OSE exhibited a small, non-significant positive effect (β = 0.33, 95% BCa CI [-0.18, 0.87], $p = .20$).

Bayesian model comparisons corroborated these findings, with inclusion Bayes factors below 1 for all predictors (OSE: $BF_{10} = 0.49$; AIA: 0.41; VUS: 0.86; AVE: 0.36; VIS: 0.35), indicating that the data are about twice as likely under the null hypothesis as under the alternative, providing anecdotal to moderate evidence for the absence of an OSE effect.

Robustness checks across *rscaleCont* values (0.5-1.5) confirmed that OSE's inclusion Bayes factor remained consistently below 1 (0.72-0.36).

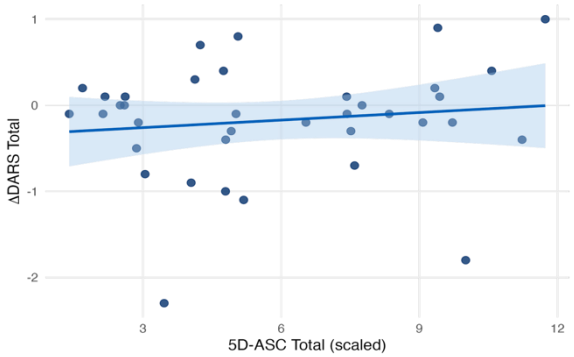

Figure. 5. *Within Ketamine linear regression of 5D-ASC total on ΔDARS outcomes*

Table 9. Within-Ketamine regression predicting ΔDARS_total from 5D-ASC dimensions. Standardised betas (z), HC3-robust SEs, BCa 95% CIs (B=5000), and inclusion Bayes factors (rscaleCont=1.0).

Predictor	beta	SE_HC3	CI	p	BF10_inclusion
OSE	0.326	0.248	[-0.182, 0.869]	0.197	0.494
AIA	0.175	0.287	[-0.317, 0.846]	0.546	0.412
VUS	-0.560	0.239	[-1.192, -0.032]	0.025	0.864
AVE	0.169	0.227	[-0.339, 0.619]	0.462	0.358
VIS	0.120	0.279	[-0.444, 0.630]	0.672	0.346

Discussion

Discussion of Results

This master's thesis explored how subjective alterations of consciousness under ketamine relate to changes in reward sensitivity. Across all analyses, ketamine did not enhance reward sensitivity compared to placebo. Information criteria (AIC/BIC) were marginally lower for models that excluded period and sequence, indicating that more parsimonious models described the data equally well.

The results of Hypotheses 2a and 2b consistently show that the intensity or phenomenological qualities of the altered state experience do not directly account for changes in reward sensitivity under ketamine. The multiple mediation model (H2a) demonstrated that none of the 5D-ASC dimensions, nor their overall intensity, significantly mediated the relationship between ketamine and improvement in reward sensitivity.

Similarly, the within-ketamine regression analysis showed that Oceanic Boundlessness (OSE) - the mystical experience proxy - did not uniquely predict increases in DARS scores when controlling for other 5D-ASC domains. Bayesian analyses further supported these null results. Interestingly, the only significant association was a negative link between Vigilance Reduction (VUS) and ΔDARS, suggesting that intense perceptual alterations might even impede reward-related recovery.

A main strength of this study is its two-period crossover design, which effectively controls for interindividual differences and improves internal validity.
The integration of the 5D-ASC framework provides another methodological advantage, as it includes subjective aspects relevant to contemporary theories of consciousness and therapeutic benefits. The clarity of null results also improves the reproducibility and transparency of research in this emerging field.
However, this dataset did not include key variables of therapeutic outcome, which restricts its clinical interpretability. Additionally, the subjective intensity of the ASC may be too coarse a measure to capture mechanistic variations in reward sensitivity. Also, the modest sample size and observed heterogeneity of residual variance reduce power to detect small effects. The mediation framework applied in this study was conceptually motivated but statistically limited. Because 5D-ASC scores were obtained only during the ketamine session, the indirect pathway from drug condition to outcome could not be formally estimated. Consequently, the present model does not demonstrate a causal mediation of the ketamine effect through altered states of consciousness but rather identifies which experiential components of the ketamine state covary with improvements in reward responsiveness. This distinction is critical for interpretation: the observed associations are informative for understanding potential psychological mechanisms of ketamine's action, but cannot establish mediation in the strict statistical sense.

Conclusion and Future Outlook for Psilocybin

The results indicate that the intensity or phenomenological qualities of the subjective altered state do not directly account for changes in reward sensitivity. This indicates that the subjective experience might not be necessary for the beneficial effects of psychoplastogens, instead highlighting different neurobiological or integrative mechanisms beyond conscious awareness.
Although ketamine and psilocybin share certain phenomenological and therapeutic features, their pharmacological mechanisms differ substantially. Consequently, findings of this thesis cannot be directly generalised to psilocybin or other psychoplastogens. Ketamine-induced ASCs differ qualitatively from classic psychedelic states such as those produced by psilocybin. While both substances can evoke perceptual and affective alterations, psilocybin more consistently elicits mystical or positive self-transcendent experiences associated with therapeutic outcomes (Carhart-Harris et al., 2021; Yaden & Griffiths, 2021). In contrast, the

ketamine state may involve different neural and phenomenological processes - potentially more dissociative than emotionally integrative. A more precise evaluation of the quantum change evoking compound of the subjective altered state of consciousness can be achieved using both MEQ30 and 5D-ASC questionnaires. Therapeutic outcomes for psychoplastogens should be more multidimensional to assess various beneficial mechanisms. Although reward sensitivity is conceptually linked to anhedonia within the *positive valence system*, it indirectly measures anhedonia. Since anhedonia is absent in this healthy sample, comparing patients with healthy controls can yield more robust findings on therapeutic outcomes. Using the DARS, alongside depression assessments such as MADRS and BDI-II, allows for a more detailed understanding of clinically relevant outcomes, including reward processing of complex social and musical rewards. To explore possibilities beyond disorders, the use of WEMWBS can incorporate well-being measurements. Furthermore, using a placebo as a control group cannot distinguish between different psychopharmacological mechanisms of psychoplastogens. Blocking the 5-HT_{2a} receptor with an antagonist such as risperidone should significantly reduce the subjective altered state of consciousness. Changes in outcome measurements after suppressing the psychedelic state could offer clues to mechanisms beyond consciousness.

To investigate the role of the subjective altered state of consciousness more precise, a mechanistic study with psilocybin can effectively answer the research question of this thesis. In a monocentric, randomised, open-label, cross-over, fMRI trial, participants are randomly assigned to one of two groups with different sequences of pharmacological conditions (psilocybin alone, psilocybin + risperidone) to enable counterbalancing. Over approximately 13 weeks, starting with screening and baseline assessments, participants undergo two treatment days combined with assessment days one day after each treatment and a follow-up six weeks later. A washout period of six weeks is observed between the two treatment days. Subconscious changes in reward and emotion processing can be observed through an fMRI study design, which also systematically assesses BDNF levels at various time points to identify active windows of neuroplasticity.

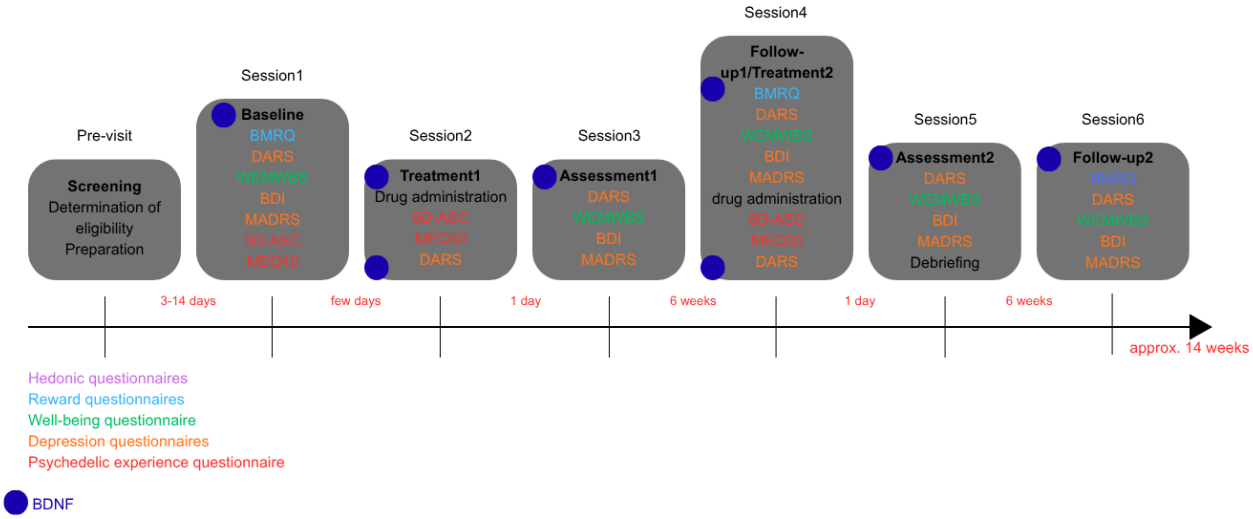

Figure 6. *Schematic illustration of the procedure for patients and healthy participants.*

To clarify the question of whether specific components of the altered state of consciousness - particularly mystical *or* emotionally integrative experiences - mediate therapeutic outcomes in healthy and patient populations, the outlined study on psilocybin addresses this demand with multi-level measures of outcomes and psychedelic state components. Combined with the investigation of biological markers and fMRI imaging, specific mechanisms of psychoplastogens and their individual contributions to therapeutic effects can be identified.

Further research into the therapeutic mechanisms of psychoplastogens could help identify the most effective psychological and neurobiological windows for intervention. Clarifying the conscious and unconscious mechanisms behind the therapeutic benefits of psychoplastogens allows for optimising the safety and acceptability of psychoplastogen-assisted treatments.

Literature

Aday, J. S., Davis, A. K., Mitzkovitz, C. M., Bloesch, E. K., & Davoli, C. C. (2021). Predicting reactions to psychedelic drugs: A systematic review of states and traits related to acute drug effects. *ACS Pharmacology & Translational Science, 4*(2), 424-435. https://doi.org/10.1021/acsptsci.1c00014

Alexander, L., Speckens, A., Carson, A., Anderson, I. M., Nathan, P. J., McCabe, C., & Cowen, P. (2023). Preliminary evidence that ketamine alters anterior cingulate connectivity in relation to improvements in anhedonia. *Translational Psychiatry, 13*, 272.

Almeida, T. M., et al. (2024). The anti-anhedonic effects of ketamine in the treatment of mood disorders: A review. *Neuroscience & Biobehavioral Reviews*. Advance online publication.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Publishing.

Amoroso, T. (2015). The psychopharmacology of ±3,4-methylenedioxymethamphetamine and its role in the treatment of posttraumatic stress disorder. *Journal of Psychoactive Drugs, 47*(5), 337-344. https://doi.org/10.1080/02791072.2015.1078550

Anis, N. A., Berry, S. C., Burton, N. R., & Lodge, D. (1983). The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology, 79*(2), 565-575. https://doi.org/10.1111/j.1476-5381.1983.tb11031.x

Arrua-Duarte, E., Migoya-Borja, M., Barrigón, M. L., Barahona, I., Delgado-Gómez, D., Courtet, P., … Delgado, C. (2019). Spanish adaptation of the Dimensional Anhedonia Rating Scale (DARS). *Journal of Affective Disorders, 245,*702-707. https://doi.org/10.1016/j.jad.2018.11.040

Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. *Psychopharmacology, 232*(21-22), 3603-3611. https://doi.org/10.1007/s00213-015-3357-9

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using *lme4. Journal of Statistical Software, 67*(1), 1-48.

Bayne, T., Hohwy, J., & Owen, A. M. (2018). Are there levels of consciousness? *Neuroscience of Consciousness, 2018*(1), 1-11. https://doi.org/10.1093/nc/niy008

Bean, S., Dhanda, R., Graham, C. A., & Rizvi, S. J. (2025). Establishing content validity of the Dimensional Anhedonia Rating Scale (DARS). *Journal of Patient-Reported Outcomes.* https://doi.org/10.1186/s41687-025-00847-6

Belouin, S. J., & Henningfield, J. E. (2018). Psychedelics: Where we are now, why we got here, what we must do. *Neuropharmacology, 142,* 7-19. https://doi.org/10.1016/j.neuropharm.2018.02.018

Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. *International Journal of Neuropsychopharmacology, 20*(12), 1036-1046. https://doi.org/10.1093/ijnp/pyx056

Ben-Shachar, M. S., Lüdecke, D., & Makowski, D. (2020). *effectsize: Estimation of effect size indices and standardized parameters. Journal of Open Source Software, 5*(56), 2815.

Bershad, A. K., Mayo, L. M., Van Hedger, K., McGlone, F., Walker, S. C., & de Wit, H. (2019). Effects of MDMA on attention to positive social cues and pleasantness of affective touch. *Neuropsychopharmacology, 44*(10), 1698-1705. https://doi.org/10.1038/s41386-019-0377-9

Calder, A., & Hasler, G. (2023). Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacology, 48*(1), 174-190. https://doi.org/10.1038/s41386-022-01497-0

Cameron, L. P., Patel, S. D., Vargas, M. V., Barragan, E. V., Saeger, H. N., Kumar, A., … Olson, D. E. (2023). 5-HT2ARs mediate therapeutic behavioral effects of psychedelic tryptamines. *ACS Chemical Neuroscience, 14*(3), 351-358. https://doi.org/10.1021/acschemneuro.2c00528

Carhart-Harris, R. L., & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: Past, present, and future. *Neuropsychopharmacology, 42*(11), 2105-2113. https://doi.org/10.1038/npp.2017.84

Carhart-Harris, R. L., & Goodwin, G. M. (2022). The therapeutic potential of psychedelic drugs: Past, present, and future. *Neuropsychopharmacology, 47*, 2110-2123. https://doi.org/10.1038/s41386-022-01310-3

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., … Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-

measured brain mechanisms. *Scientific Reports, 7*(1), 13187. https://doi.org/10.1038/s41598-017-13282-7

Carhart-Harris, R. L., Erritzoe, D., Haijen, E., et al. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology*, 32(7), 725-731. https://doi.org/10.1177/0269881118754710

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., … Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences of the United States of America, 109*(6), 2138-2143. https://doi.org/10.1073/pnas.1119598109

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., & Nutt, D. (2014). The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience, 8,* Article 20.

Carhart-Harris, R. L., Murphy, K., Leech, R., Erritzoe, D., Wall, M. B., Ferguson, B., Williams, L. T., Roseman, L., Brugger, S., De Meer, I., Tanner, M., Tyacke, R., Wolff, K., Sethi, A., Bloomfield, M. A. P., Williams, T. M., Bolstridge, M., Stewart, L., Morgan, C., … Nutt, D. J. (2016). The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biological Psychiatry, 78*(8), 554-562. https://doi.org/10.1016/j.biopsych.2015.08.003

Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E. E., Nest, T., Orban, C., Leech, R., Williams, L. T., Williams, T. M., Bolstridge, M., Sessa, B., McGonigle, J., Sereno, M. I., Nichols, D., Hellyer, P. J., … Nutt, D. J. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences of the United States of America, 113*(17), 4853-4858. https://doi.org/10.1073/pnas.1518377113

Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., & Branchi, I. (2018). Psychedelics and the essential importance of context. *Journal of*

Psychopharmacology, 32(7), 725-731. https://doi.org/10.1177/0269881118754710

Casarotto, P. C., Girych, M., Fred, S. M., Kovaleva, V., Moliner, R., Enkavi, G., … Castrén, E. (2021). Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. *Cell, 184*(5), 1299-1313.e19. https://doi.org/10.1016/j.cell.2021.01.034

Chevance, A., Ravaud, P., Tomlinson, A., Le Berre, C., Teufer, B., Touboul, S., … Tran, V. T. (2020). Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: Qualitative content analysis of a large international online survey. *The Lancet Psychiatry, 7*(8), 692-702. https://doi.org/10.1016/S2215-0366(20)30191-7

Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., … Chen, R. (2011). Harnessing neuroplasticity for clinical applications. *Brain, 134*(6), 1591-1609. https://doi.org/10.1093/brain/awr039

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., & Dour, H. J. (2016). Treatment for anhedonia: A neuroscience driven approach. *Depression and Anxiety, 33*(11), 927-938. https://doi.org/10.1002/da.22490

Dakic, V., Minardi Nascimento, J., Costa Sartore, R., Maciel, R. M., de Araujo, D. B., Ribeiro, S., & Martins-de-Souza, D. (2017). Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. *Scientific Reports, 7,* 12863. https://doi.org/10.1038/s41598-017-12779-5

de Almeida, R. N., Galvão, A. C. M., da Silva, F. S., Silva, E., Palhano-Fontes, F., Maia-de-Oliveira, J. P., … Hallak, J. E. C. (2019). Modulation of serum brain-derived neurotrophic factor by a single dose of ayahuasca: Observation from a randomized controlled trial. *Frontiers in Psychology, 10,* 1234. https://doi.org/10.3389/fpsyg.2019.01234

de la Fuente Revenga, M., Zhu, B., Guevara, C. A., Naler, L. B., Saunders, J. M., Zhou, Z., & Olson, D. E. (2021). Prolonged psychoplastogenic effects of psychedelics involving mTOR signaling in the prefrontal cortex. *iScience, 24*(2), 102139. https://doi.org/10.1016/j.isci.2021.102139

Deco, G., Hagmann, P., Romani, G. L., Mantini, D., & Corbetta, M. (2014). How local excitation-inhibition ratio impacts the whole brain dynamics. *Journal of Neuroscience, 34*(23), 7886-7898. https://doi.org/10.1523/JNEUROSCI.5068-13.2014

Delray Center for Healing. (2022, September 2). *A brief history of ketamine.* https://www.delraycenter.com/a-brief-history-of-ketamine/

Desouza, L. A., Benekareddy, M., Fanibunda, S. E., Mohammad, F., Janakiraman, B., Ghai, U., … Vaidya, V. A. (2021). The hallucinogenic serotonin2A receptor agonist 2,5-dimethoxy-4-iodoamphetamine promotes cAMP response element binding protein-dependent gene expression of specific plasticity-associated genes in the rodent neocortex. *Frontiers in Molecular Neuroscience, 14,* 790213. https://doi.org/10.3389/fnmol.2021.790213

Dittrich, A. (1975). Zusammenstellung eines Fragebogens (APZ) zur Erfassung abnormer psychischer Zustände [Construction of a questionnaire (APZ) for assessing abnormal mental states]. *Zeitschrift für Klinische Psychologie, Psychiatrie und Psychotherapie, 23,* 12-20.

Dittrich, A. (1998). The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry, 31*(Suppl 2), 80-84. https://doi.org/10.1055/s-2007-979351

DiVito, A. J., & Leger, R. F. (2020). Psychedelics as an emerging novel intervention in the treatment of substance use disorder: A review. *Molecular Biology Reports, 47*(12), 9791-9799. https://doi.org/10.1007/s11033-020-05955-6

Dubé, L., & Le Bel, J. (2003). The content and structure of laypeople's concept of pleasure. *Cognition and Emotion, 17*(2), 263-295. https://doi.org/10.1080/02699930302295

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160.

Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2019). Breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Frontiers in Psychiatry, 10,* 650. https://doi.org/10.3389/fpsyt.2019.00650

Garcia, A. C. M., & Maia, L. de O. (2022). The therapeutic potential of psychedelic substances in hospice and palliative care. *Progress in Palliative Care, 30*(1), 1-3. https://doi.org/10.1080/09699260.2022.2059736

Glennon, R. A., Titeler, M., & McKenney, J. D. (1984). Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. *Life Sciences, 35*(25), 2505-2511. https://doi.org/10.1016/0024-3205(84)90436-3

González-Maeso, J., Weisstaub, N. V., Zhou, M., Chan, P., Ivic, L., Ang, R., … Sealfon, S. C. (2007). Hallucinogens recruit specific cortical 5-HT_2A receptor-mediated signaling pathways to affect behavior. *Neuron, 53*(3), 439-452. https://doi.org/10.1016/j.neuron.2007.01.008

Goodwin, G. M., Malievskaia, E., Fonzo, G. A., & Nemeroff, C. B. (2024). Must psilocybin always "assist psychotherapy"? *The American Journal of Psychiatry, 181*(1), 20-25. https://doi.org/10.1176/appi.ajp.20230262

Gorwood, P. (2008). Neurobiological mechanisms of anhedonia. *Dialogues in Clinical Neuroscience, 10*(3), 291-299. https://doi.org/10.31887/DCNS.2008.10.3/pgorwood

Green, A. R., Mechan, A. O., Elliott, J. M., O'Shea, E., & Colado, M. I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacological Reviews, 55*(3), 463-508. https://doi.org/10.1124/pr.55.3.463

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology, 30*(12), 1181-1197. https://doi.org/10.1177/0269881116675513

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology, 187*(3), 268-283. https://doi.org/10.1007/s00213-006-0457-5

Gu, X., Su, Y.-A., Lin, J., Si, T., & Zhang, L. (2025). Quantitative validation of the Dimensional Anhedonia Rating Scale (DARS) in Chinese patients with major depressive disorder. *Psychology Test and Assessment Modeling, 67*(1), 45-60.

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4-26. https://doi.org/10.1038/npp.2009.129

Hasler, G. (2020). Toward specific ways to combine ketamine and psychotherapy in treating depression. *CNS Spectrums, 25*(4), 445-447. https://doi.org/10.1017/S1092852920000157

Hesselgrave, N., Troppoli, T. A., Wulff, A. B., Cole, A. B., & Thompson, S. M. (2021). Harnessing psilocybin: Antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. *Proceedings of the National Academy of Sciences of the United States of America, 118,* e2022489118. https://doi.org/10.1073/pnas.2022489118

Holze, F., Vizeli, P., Müller, F., Ley, L., Duerig, R., Varghese, N., … Liechti, M. E. (2020). Distinct acute effects of LSD, MDMA, and d-amphetamine in healthy subjects. *Neuropsychopharmacology, 45*(3), 462-471. https://doi.org/10.1038/s41386-019-0569-3

JASP Team (2025). JASP (Version 0.95.3) [Computer software].

Johnston, J. N., & Duman, R. S. (2023). Ketamine in neuropsychiatric disorders: An update. *Frontiers in Psychiatry, 14*, 1211573.

Jones, G. M., & Nock, M. K. (2022). Lifetime use of MDMA/ecstasy and psilocybin is associated with reduced odds of major depressive episodes. *Journal of Psychopharmacology, 36*(1), 57-65. https://doi.org/10.1177/02698811211066714

Jones, K. A., Srivastava, D. P., Allen, J. A., Strachan, R. T., Roth, B. L., & Penzes, P. (2009). Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. *Proceedings of the National Academy of Sciences of the United States of America, 106*(46), 19575-19580. https://doi.org/10.1073/pnas.0905889106

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences, 16*(11), 559-572. https://doi.org/10.1016/j.tics.2012.09.006

Khan, A., & Brown, W. A. (2015). Antidepressants versus placebo in major depression: An overview. *World Psychiatry, 14*(3), 294-300. https://doi.org/10.1002/wps.20241

Ko, K., Knight, G., Rucker, J., Cleare, A. J. (2022). Psychedelics, mystical experience, and therapeutic efficacy: A systematic review. *Frontiers in Psychiatry*, 13, 917199. https://doi.org/10.3389/fpsyt.2022.917199

Koelsch, S. (2014). Brain correlates of music-evoked emotions. *Nature Reviews Neuroscience, 15*(3), 170-180. https://doi.org/10.1038/nrn3666

Kotoula, V., Argyropoulos, S. V., et al. (2022). Ketamine modulates the neural correlates of reward processing in depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 7*(12), 1262-1272.

Krediet, E., Bostoen, T., Breeksema, J., van Schagen, A., Passie, T., & Vermetten, E. (2020). Reviewing the potential of psychedelics for the treatment of PTSD. *International Journal of Neuropsychopharmacology, 23*(6), 385-400. https://doi.org/10.1093/ijnp/pyaa018

Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews Neuroscience, 6*(9), 691-702. https://doi.org/10.1038/nrn1747

Kringelbach, M. L., & Berridge, K. C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends in Cognitive Sciences, 13*(11), 479-487. https://doi.org/10.1016/j.tics.2009.08.006

Kumar, A., & Amit, K. (2021). Comeback of ketamine: Resurfacing facts and dispelling myths. *Korean Journal of Anesthesiology, 74*(2), 103-114. https://doi.org/10.4097/kja.20550

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). *lmerTest package: Tests in linear mixed effects models.Journal of Statistical Software, 82*(13), 1-26.

Kwaśny, A., et al. (2024). Ketamine treatment for anhedonia in unipolar and bipolar depression: A systematic review. *Journal of Affective Disorders Reports, 8*, 100497.

Kyzar, E. J., Nichols, C. D., Gainetdinov, R. R., Nichols, D. E., & Kalueff, A. V. (2017). Psychedelic drugs in biomedicine. *Trends in Pharmacological Sciences, 38*(11), 992-1005. https://doi.org/10.1016/j.tips.2017.08.003

Lambert, C., Da Silva, S., Ceniti, A. K., Rizvi, S. J., Foussias, G., & Kennedy, S. H. (2018). Anhedonia in depression and schizophrenia: A transdiagnostic challenge. *CNS Neuroscience & Therapeutics, 24*(7), 615-623. https://doi.org/10.1111/cns.12854

Lenth, R. V. (2024). *emmeans: Estimated marginal means, aka least-squares means* (R package version 1.10.x).

Lippolis, M., Stage, M., Vuust, P., & Kringelbach, M. L. (2024). Validation of the Danish Barcelona Music Reward Questionnaire. *Frontiers in Psychology, 15,* 1424579. https://doi.org/10.3389/fpsyg.2024.1424579

Lobbestael, J., Leurgans, M., and Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother 18, 75-79. https://doi.org/10.1002/cpp.693.

Lobbestael, J., Leurgans, M., and Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother 18, 75-79. https://doi.org/10.1002/cpp.693.

Lodge, D., & Mercier, M. S. (2015). Ketamine and phencyclidine: The good, the bad and the unexpected. *British Journal of Pharmacology, 172*(17), 4254-4276. https://doi.org/10.1111/bph.13222

López-Giménez, J. F., & González-Maeso, J. (2018). Hallucinogens and serotonin 5-HT2A receptor-mediated signaling pathways. *Current Topics in Behavioral Neurosciences, 36,* 45-73. https://doi.org/10.1007/7854_2017_478

Lord, L. D., Expert, P., Atasoy, S., Roseman, L., Rapuano, K., Lambiotte, R., … Kringelbach, M. L. (2019). Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. *NeuroImage, 199,* 127-142. https://doi.org/10.1016/j.neuroimage.2019.05.060

Lucantonio, F., Roeglin, J., Li, S., Lu, J., Shi, A., Czerpaniak, K., Fiocchi, F. R., Bontempi, L., Shields, B. C., Zarate, C. A., Tadross, M. R., & Pignatelli, M. (2025). Ketamine rescues anhedonia by cell-type- and input-specific adaptations in the nucleus accumbens. *Neuron, 113*(9), 1398-1412.e4. https://doi.org/10.1016/j.neuron.2025.02.021

Lüdecke, D., Ben-Shachar, M. S., Patil, I., Waggoner, P., & Makowski, D. (2021). *performance: An R package for assessment, comparison and testing of statistical models. Journal of Open Source Software, 6*(60), 3139.

Luppi, A.I., Rosas, F.E., Mediano, P.A.M., Menon, D.K., and Stamatakis, E.A. (2024). Information decomposition and the informational architecture of the brain. Trends in Cognitive Sciences 28, 352-368. https://doi.org/10.1016/j.tics.2023.11.005.

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., … Olson, D. E. (2018). Psychedelics promote structural and functional neural plasticity. *Cell Reports, 23*(11), 3170-3182. https://doi.org/10.1016/j.celrep.2018.05.022

Ly, C., Greb, A. C., Vargas, M. V., Duim, W. C., Grodzki, A. C. G., Lein, P. J., … Olson, D. E. (2021). Transient stimulation with psychoplastogens is sufficient to initiate neuronal growth. *ACS Pharmacology & Translational Science, 4*(2), 452-460. https://doi.org/10.1021/acsptsci.0c00197

Madsen, M. K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., … Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology, 44*(7), 1328-1334. https://doi.org/10.1038/s41386-019-0324-9

Mas-Herrero, E., Marco-Pallares, J., Lorenzo-Seva, U., Zatorre, R. J., & Rodriguez-Fornells, A. (2013). Individual differences in music reward experiences. *Music Perception, 31*(2), 118-138. https://doi.org/10.1525/mp.2013.31.2.118

Mas-Herrero, E., Zatorre, R. J., Rodriguez-Fornells, A., & Marco-Pallares, J. (2014). Dissociation between musical and monetary reward responses in specific musical anhedonia. *Current Biology, 24*(6), 699-704. https://doi.org/10.1016/j.cub.2014.01.068

McCulloch, D. E., Madsen, M. K., Stenbæk, D. S., Kristiansen, S., Ozenne, B., Jensen, P. S., … Knudsen, G. M. (2022). Lasting effects of a single psilocybin dose on resting-state functional connectivity in healthy individuals. *Journal of Psychopharmacology, 36*(1), 74-84. https://doi.org/10.1177/02698811211069157

McMakin, D. L., Olino, T. M., Porta, G., Dietz, L. J., Emslie, G., Clarke, G., … Brent, D. A. (2012). Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(4), 404-411. https://doi.org/10.1016/j.jaac.2012.01.011

Mi, Z., Si, T., Kapadia, K., Li, Q., & Muma, N. A. (2017). Receptor-stimulated transamidation induces activation of Rac1 and Cdc42 and the regulation of

dendritic spines. *Neuropharmacology, 117,* 93-105. https://doi.org/10.1016/j.neuropharm.2017.01.021

Moda-Sava, R. N., Murdock, M. H., Parekh, P. K., Fetcho, R. N., Huang, B. S., Huynh, T. N., … Liston, C. (2019). Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science, 364,* eaat8078. https://doi.org/10.1126/science.aat8078

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry, 134*(4), 382-389. https://doi.org/10.1192/bjp.134.4.382

Müller, F., Kraus, E., Holze, F., Becker, A., Ley, L., Schmid, Y., … Liechti, M. E. (2022). Flashback phenomena after administration of LSD and psilocybin in controlled studies with healthy participants. *Psychopharmacology, 239*(6), 1933-1943. https://doi.org/10.1007/s00213-022-06106-2

Muttoni, S., Ardissino, M., & John, C. (2019). Classical psychedelics for the treatment of depression and anxiety: A systematic review. *Journal of Affective Disorders, 258,* 11-24. https://doi.org/10.1016/j.jad.2019.07.076

Nardou, R., Lewis, E. M., & Dölen, G. (2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature, 569*(7754), 116-120. https://doi.org/10.1038/s41586-019-1075-9

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews, 68*(2), 264-355. https://doi.org/10.1124/pr.115.011478

Nutt, D., Erritzoe, D., & Carhart-Harris, R. (2020). Psychedelic psychiatry's brave new world. *Cell, 181*(1), 24-28. https://doi.org/10.1016/j.cell.2020.03.020

Ohtani, A., Kozono, N., Senzaki, K., & Shiga, T. (2014). Serotonin 2A receptor regulates microtubule assembly and induces dynamics of dendritic growth cones in rat cortical neurons in vitro. *Neuroscience Research, 81-82,* 11-20. https://doi.org/10.1016/j.neures.2014.01.003

Olson, D. E. (2021). Psychoplastogens: A promising class of plasticity-promoting neurotherapeutics. *Journal of Experimental Neuroscience, 15,* 11790695211029099. https://doi.org/10.1177/11790695211029099

Osugo, M., Wall, M. B., Selvaggi, P., Zahid, U., Finelli, V., Chapman, G. E., Whitehurst, T., Onwordi, E. C., Statton, B., McCutcheon, R. A., Murray, R. M., Marques, T. R., Mehta, M. A., & Howes, O. D. (2025). Striatal dopamine D2/D3 receptor regulation of human reward processing and

behaviour. *Nature Communications, 16*(1), 1852. https://doi.org/10.1038/s41467-025-56663-7

Passie, T., Halpern, J. H., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: A review. *CNS Neuroscience & Therapeutics, 14*(4), 295-314. https://doi.org/10.1111/j.1755-5949.2008.00059.x

Perna, G., Alciati, A., Daccò, S., Grassi, M., & Caldirola, D. (2020). Personalized psychiatry and depression: The role of sociodemographic and clinical variables. *Psychiatry Investigation, 17*(3), 193-202. https://doi.org/10.30773/pi.2019.0289

Pilc, A., Wieronska, J. M., & Skolnick, P. (2013). Glutamate-based antidepressants: Preclinical psychopharmacology. *Biological Psychiatry, 73*(12), 1125-1132. https://doi.org/10.1016/j.biopsych.2012.11.004

Pizzagalli, D. A. (2022). *Anhedonia: Preclinical, translational, and clinical integration.* Springer Nature Switzerland.

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P., Martin, D., … Loo, C. K. (2013). Neuroplasticity in depressed individuals compared with healthy controls. *Neuropsychopharmacology, 38*(11), 2101-2108. https://doi.org/10.1038/npp.2013.126

Posit Software, PBC. (2024). *RStudio (Version 2024.09.0+375R)* [Computer software].

Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., … Vollenweider, F. X. (2017). The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Current Biology, 27*(3), 451-457. https://doi.org/10.1016/j.cub.2016.12.030

Psiuk, D., Nowak, E., Cholewa, K., Łopuszańska, U., & Samardakiewicz, M. (2021). The potential role of serotonergic hallucinogens in depression treatment. *Life, 11*(8), 765. https://doi.org/10.3390/life11080765

Rassouli, B., Rosas, F.E., and Gündüz, D. (2020). Data Disclosure Under Perfect Sample Privacy. IEEE Transactions on Information Forensics and Security 15, 2012-2025. https://doi.org/10.1109/TIFS.2019.2954652.

Ray, M. T., Shannon Weickert, C., & Webster, M. J. (2014). Decreased BDNF and TrkB mRNA expression in multiple cortical areas of patients with

schizophrenia and mood disorders. *Translational Psychiatry, 4,* e389. https://doi.org/10.1038/tp.2014.17

Regan, A., Margolis, S., de Wit, H., & Lyubomirsky, S. (2021). Does ±3,4-methylenedioxymethamphetamine (ecstasy) induce subjective feelings of social connection in humans? A multilevel meta-analysis. *PLOS ONE, 16*(11), e0258849. https://doi.org/10.1371/journal.pone.0258849

Rizvi, S. J., Quilty, L. C., Sproule, B. A., Cyriac, A., Bagby, R. M., & Kennedy, S. H. (2015). Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research, 229*(1-2), 109-119. https://doi.org/10.1016/j.psychres.2015.07.062

Rocha, J. M., Rossi, G. N., de Lima Osório, F., Bouso, J. C., de Oliveira Silveira, G., Yonamine, M., … Hallak, J. E. C. (2021). Effects of ayahuasca on the recognition of facial expressions of emotions in naive healthy volunteers: A pilot, proof-of-concept, randomized controlled trial. *Journal of Clinical Psychopharmacology, 41*(3), 267-274. https://doi.org/10.1097/JCP.0000000000001362

Roseman, L., Preller, K. H., Fotiou, E., & Winkelman, M. J. (2022). Editorial: Psychedelic sociality: Pharmacological and extrapharmacological perspectives. *Frontiers in Pharmacology, 13*, 1-4. https://doi.org/10.3389/fphar.2022.950258

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., … Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology, 30*(12), 1165-1180. https://doi.org/10.1177/0269881116675512

Rothberg, R. L., Azhari, N., Haug, N. A., & Dakwar, E. (2021). Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *Journal of Psychopharmacology, 35*(12), 1508-1517. https://doi.org/10.1177/0269881120970879

Rothman, R. B., & Baumann, M. H. (2002). Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacology & Therapeutics, 95*(1), 73-88. https://doi.org/10.1016/S0163-7258(02)00245-6

Saliba, J., Lippi, S., & Ceccato, E. (2016). Validation of the French Barcelona Music Reward Questionnaire. *Frontiers in Human Neuroscience, 10,* 502. https://doi.org/10.3389/fnhum.2016.00502

Schartner, M. M., Carhart-Harris, R. L., Barrett, A. B., Seth, A. K., & Muthukumaraswamy, S. D. (2017). Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. *Scientific Reports, 7,*46421. https://doi.org/10.1038/srep46421

Shao, L. X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., … Xu, X. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron, 109*(16), 2535-2544.e4. https://doi.org/10.1016/j.neuron.2021.06.008

Siddiqi, S. H., Haddad, N., & Fox, M. D. (2022). Circuit-targeted neuromodulation for anhedonia. *Current Topics in Behavioral Neurosciences, 61,* 277-297. https://doi.org/10.1007/7854_2022_1350

Stewart-Brown, S., Tennant, A., Tennant, R., Platt, S., Parkinson, J., & Weich, S. (2009). Internal construct validity of the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS): A Rasch analysis using data from the Scottish Health Education Population Survey. *Health and Quality of Life Outcomes, 7,* 15. https://doi.org/10.1186/1477-7525-7-15

Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric evaluation of the Altered States of Consciousness Rating Scale (OAV). *Psychopharmacology, 212*(4), 1-13. https://doi.org/10.1007/s00213-010-2008-7

Studerus, E., Gamma, A., Kometer, M., & Vollenweider, F. X. (2022). The altered states of consciousness rating scale (OAV/5D-ASC): Psychometric evaluation of a short form in healthy volunteers. *Scientific Data, 9*(1), 468. https://doi.org/10.1038/s41597-022-01822-4

Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., … Carhart-Harris, R. L. (2016). Increased global functional connectivity correlates with LSD-induced ego dissolution. *Current Biology, 26*(8), 1043-1050. https://doi.org/10.1016/j.cub.2016.02.010

Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., Parkinson, J., Secker, J., & Stewart-Brown, S. (2007). The Warwick-Edinburgh Mental Well-

Being Scale (WEMWBS): Development and UK validation. *Health and Quality of Life Outcomes, 5,* 63. https://doi.org/10.1186/1477-7525-5-63

Timmermann, C., Roseman, L., Haridas, S., Rosas, F. E., Luan, L., Kettner, H., … Carhart-Harris, R. L. (2023). Human brain effects of DMT assessed via EEG-fMRI. *Proceedings of the National Academy of Sciences of the United States of America, 120,* e2218949120. https://doi.org/10.1073/pnas.2218949120

Timmermann, C., Roseman, L., Schartner, M., Milliere, R., Williams, L. T., Erritzoe, D., Muthukumaraswamy, S., Ashton, M., Bendrioua, A., Kaur, O., Turton, S., Nour, M. M., Day, C. M., Leech, R., Nutt, D. J., & Carhart-Harris, R. L. (2019). Neural correlates of the DMT experience assessed with multivariate EEG. *Scientific Reports, 9,* 16324. https://doi.org/10.1038/s41598-019-51974-4

Tófoli, L. F., & de Araujo, D. B. (2016). Treating addiction: Perspectives from EEG and imaging studies on psychedelics. *International Review of Neurobiology, 129,* 157-185. https://doi.org/10.1016/bs.irn.2016.04.001

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience & Biobehavioral Reviews, 35*(3), 537-555. https://doi.org/10.1016/j.neubiorev.2010.06.006

Tupper, K. W., Wood, E., Yensen, R., & Johnson, M. W. (2015). Psychedelic medicine: A re-emerging therapeutic paradigm. *Canadian Medical Association Journal, 187*(14), 1054-1059. https://doi.org/10.1503/cmaj.141124

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273-289. https://doi.org/10.1006/nimg.2001.0978

U.S. Food and Drug Administration. (2019, March 5). *FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic.* https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

Uher, R., Perlis, R. H., Henigsberg, N., Zobel, A., Rietschel, M., Mors, O., … McGuffin, P. (2012). Depression symptom dimensions as predictors of

antidepressant treatment outcome: Replicable evidence for interest-activity symptoms. *Psychological Medicine, 42*(5), 967-980. https://doi.org/10.1017/S0033291711001905

van der Kolk, B. A., Wang, J. B., Yehuda, R., Bedrosian, L., Coker, A. R., Harrison, C., … Mithoefer, M. C. (2024). Effects of MDMA-assisted therapy for PTSD on self-experience. *PLOS ONE.* Advance online publication. https://doi.org/10.1371/journal.pone.0307676

Vargas, M. V., Dunlap, L. E., Dong, C., Carter, S. J., Tombari, R. J., Jiao, H., … Olson, D. E. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science, 379*(6633), 700-706. https://doi.org/10.1126/science.adf2791

Varley, T.F., Sporns, O., Schaffelhofer, S., Scherberger, H., and Dann, B. (2023). Informationprocessing dynamics in neural networks of macaque cerebral cortex reflect cognitive state and behavior. Proceedings of the National Academy of Sciences 120, e2207677120. https://doi.org/10.1073/pnas.2207677120.

Vinckier, F., Gourion, D., & Mouchabac, S. (2017). Anhedonia predicts poor psychosocial functioning: Results from a large cohort of patients treated for major depressive disorder by general practitioners. *European Psychiatry, 44,* 1-8. https://doi.org/10.1016/j.eurpsy.2017.03.001

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews Neuroscience, 11*(9), 642-651. https://doi.org/10.1038/nrn2884

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews Neuroscience, 11*(9), 642-651. https://doi.org/10.1038/nrn2884

Vollenweider, F. X., Csomor, P. A., Knappe, B., Geyer, M. A., & Quednow, B. B. (2007). The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. *Neuropsychopharmacology, 32*(9), 1876-1887. https://doi.org/10.1038/sj.npp.1301324 PubMed

Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans

via a serotonin-2 agonist action. *NeuroReport, 9*(17), 3897-3902. https://doi.org/10.1097/00001756-199812010-00024

Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D. A., Sienaert, P., … Claes, S. (2014). Dimensions in major depressive disorder and their relevance for treatment outcome. *Journal of Affective Disorders, 155,* 35-41. https://doi.org/10.1016/j.jad.2013.10.020

Vuust, P., Heggli, O. A., Friston, K. J., & Kringelbach, M. L. (2022). Music in the brain. *Nature Reviews Neuroscience, 23*(5), 287-305. https://doi.org/10.1038/s41583-022-00578-5

Walsh, A. E. L., Huneke, N. T. M., Brown, R., Browning, M., Cowen, P., & Harmer, C. J. (2018). A dissociation of the acute effects of bupropion on positive emotional processing and reward processing in healthy volunteers. *Frontiers in Psychiatry, 9,* 482. https://doi.org/10.3389/fpsyt.2018.00482

Watts, V. J., Lawler, C. P., Neve, K. A., Nichols, D. E., & Mailman, R. B. (1995). LSD and structural analogs: Pharmacological evaluation at D1 dopamine receptors. *Psychopharmacology, 118*(4), 401-409. https://doi.org/10.1007/BF02245943

Wickham, H. (2016). *ggplot2: Elegant graphics for data analysis.* Springer.

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T. L., Miller, E., Bache, S. M., Müller, K., Ooms, J., Robinson, D., Seidel, D. P., Spinu, V., ... Yutani, H. (2019). Welcome to the tidyverse. *Journal of Open Source Software, 4*(43), 1686.

Williams, J. B. W., Kobak, K. A., Bech, P., Engelhardt, N., Evans, K., Lipsitz, J., Olin, J., Pearson, J., & Kalali, A. (2008). The Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA): Development and reliability. *The British Journal of Psychiatry, 192*(1), 52-58. https://doi.org/10.1192/bjp.bp.106.032532

Willner, P. (2016). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiology of Stress, 6,* 78-93. https://doi.org/10.1016/j.ynstr.2016.08.002

Wojtas, A., Bysiek, A., Wawrzczak-Bargiela, A., Szych, Z., Majcher-Maślanka, I., … Wierońska, J. M. (2022). Effect of psilocybin and ketamine on brain neurotransmitters, glutamate receptors, DNA and rat behavior. *International*

Journal of Molecular Sciences, 23(12), 6713. https://doi.org/10.3390/ijms23126713

Wu, M., Minkowicz, S., Dumrongprechachan, V., Hamilton, P., & Kozorovitskiy, Y. (2021). Ketamine rapidly enhances glutamate-evoked dendritic spinogenesis in medial prefrontal cortex through dopaminergic mechanisms. *Biological Psychiatry, 89*(11), 1096-1105. https://doi.org/10.1016/j.biopsych.2020.12.019

Xiong, J., Lipsitz, O., Chen-Li, D., Rosenblat, J. D., Rodrigues, N. B., Carvalho, I., Lui, L. M. W., Gill, H., Nasri, F., Subramaniapillai, M., Lee, Y., McIntyre, R. S., … Carvalho, A. F. (2021). The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: A systematic review and meta-analysis. *Journal of Psychiatric Research, 134,* 57-68. https://doi.org/10.1016/j.jpsychires.2020.12.038

Xu, Y., Lin, Y., Yu, M., & Zhou, K. (2024). The nucleus accumbens in reward and aversion processing: Insights and implications. *Frontiers in Behavioral Neuroscience, 18,* 1420028. https://doi.org/10.3389/fnbeh.2024.1420028

Yaden, D. B., & Griffiths, R. R. (2020). The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science*, 3(2), 563-570. https://doi.org/10.1021/acsptsci.0c00194

Yoshida, H., Kanamaru, C., Ohtani, A., Li, F., Senzaki, K., & Shiga, T. (2011). Subtype specific roles of serotonin receptors in the spine formation of cortical neurons in vitro. *Neuroscience Research, 71*(3), 311-314. https://doi.org/10.1016/j.neures.2011.08.008

Appendix

English Abstract

Psychoplastogens have increasingly attracted attention in psychopharmacological research due to their antidepressant properties. They modulate complex alterations in the brain's functional connectivity and promote more flexible patterns of information processing while maintaining stable internal representations, a mechanism relevant to many psychiatric disorders. These compounds profoundly alter consciousness (Altered State of Consciousness, ASC). Among the various facets of the ASC, the mystical component - conceptually related to *Oceanic Self-Expansion* - has been directly associated with therapeutic effects in several studies. However, it remains unclear whether such intense and sometimes challenging subjective experiences are truly necessary to achieve the observed symptom improvements.

This master's thesis examined whether the intensity and quality of a ketamine-induced ASC influence changes in reward sensitivity - a central aspect of the positive valence system and a core feature of anhedonia. In a randomised two-period crossover design, 38 healthy participants received subanesthetic doses of ketamine and placebo in separate sessions. Reward sensitivity was assessed using the *Dimensional Anhedonia Rating Scale (DARS)*, and subjective alterations in consciousness were measured with the *Five-Dimensional Altered States of Consciousness Questionnaire (5D-ASC)*. Analyses revealed no significant differences in reward sensitivity between ketamine and placebo ($b = -.62$, $p = .61$; Wilcoxon $p = .694$). None of the 5D-ASC dimensions mediated this relationship, and Bayesian model comparisons supported the null hypothesis. These findings suggest that ketamine-induced alterations in consciousness do not directly affect reward sensitivity. This challenges the prevailing assumption that subjective experiences are an essential prerequisite for the antidepressant effects of psychoplastogenic substances. Neurobiological and neuropsychological mechanisms may instead play a more prominent role. Future studies using psilocybin should investigate the impact of specific alterations in consciousness on clinically relevant outcomes to define therapeutic windows with greater precision and safety.

German Abstract

Psychoplastogene rücken zunehmend aufgrund ihrer antidepressiven Wirkung in den Fokus der psychopharmakologischen Forschung. Sie modulieren komplexe Veränderungen der funktionellen Konnektivität des Gehirns und fördern eine flexiblere Informationsverarbeitung bei gleichzeitiger Stabilität interner Repräsentationen - ein Mechanismus, der für viele psychische Störungen relevant ist. Diese Substanzen verändern das Bewusstsein stark (Altered State of Consciousness, ASC). Besonders die mystische Komponente, konzeptuell eng verwandt mit der ozeanischen Selbstentgrenzung (OSE), wurde in mehreren Studien direkt mit therapeutischen Effekten in Verbindung gebracht. Unklar bleibt jedoch, ob solche intensiven, teils auch belastenden Erfahrungen tatsächlich notwendig sind, um die beobachteten Symptomverbesserungen zu erzielen.

Diese Masterarbeit untersuchte, ob Intensität und Qualität eines Ketamin-induzierten ASCs Veränderungen der Belohnungssensitivität hervorrufen - einem zentralen Aspekt des positiven Valenzsystems und Kernmerkmal der Anhedonie. In einem randomisierten Zwei-Perioden-Crossover-Design erhielten 38 gesunde Teilnehmende subanästhetisches Ketamin und Placebo in getrennten Sitzungen. Die Belohnungssensitivität wurde mit der *Dimensional Anhedonia Rating Scale (DARS)*, der subjektive Bewusstseinszustand mit dem *Five-Dimensional Altered States of Consciousness Questionnaire (5D-ASC)* erfasst.

Die Analysen ergaben keine signifikanten Unterschiede in der Belohnungssensitivität zwischen Ketamin und Placebo (b = -.62, p = .61; Wilcoxon p = .694). Keine der 5D-ASC-Dimensionen vermittelte diesen Zusammenhang, und Bayes'sche Modellvergleiche stützten die Nullhypothese. Die Ergebnisse deuten darauf hin, dass Ketamin-induzierte Bewusstseinsveränderungen keinen direkten Einfluss auf die Belohnungssensitivität haben. Damit muss die verbreitete Annahme infrage gestellt werden, dass subjektive Bewusstseinsveränderungen grundsätzlich Voraussetzung für die antidepressive Wirkung psychoplastogener Substanzen sind. Möglicherweise spielen neurobiologische und neuropsychologische Mechanismen eine größere Rolle. Zukünftige Studien mit Psilocybin sollten den Einfluss spezifischer Bewusstseinsveränderungen auf klinisch relevante Outcomes untersuchen, um therapeutische Wirkfenster präziser und sicherer bestimmen zu können.

List of Abbreviations

5D-ASC - Five-Dimensional Altered States of Consciousness Questionnaire
ACC - Anterior Cingulate Cortex
AIA - Auditory Alterations (subscale of 5D-ASC)
AKH - Allgemeines Krankenhaus (General Hospital of Vienna)
AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASC - Altered State of Consciousness
AVE - Audio-Visual Synesthesia (subscale of 5D-ASC)
BDI-II - Beck Depression Inventory-II
BDNF - Brain-Derived Neurotrophic Factor
BIC - Bayesian Information
BMRQ - Barcelona Music Reward Questionnaire
DAN - Dorsal Attention Network
DARS - Dimensional Anhedonia Rating Scale
DMT - N,N-Dimethyltryptamine
DMN - Default Mode Network
dlPFC - Dorsolateral Prefrontal Cortex
DSM-5 - Diagnostic and Statistical Manual of Mental Disorders
FPN - Frontoparietal Control Network
fMRI - Functional Magnetic Resonance Imaging
HPPD - Hallucinogen Persisting Perception Disorder
LSD - Lysergic Acid Diethylamide
MADRS - Montgomery-Åsberg Depression Rating Scale
MDMA - 3,4-Methylenedioxymethamphetamine
mPFC - Medial Prefrontal Cortex
mTOR - Mechanistic Target of Rapamycin
NMDA - N-Methyl-D-Aspartate (receptor)
OFC - Orbitofrontal Cortex
OSE - Oceanic Boundlessness (subscale of 5D-ASC)
PTSD - Post-Traumatic Stress Disorder
SMN - Somatomotor Network
TRD - Treatment-Resistant Depression
TrkB - Tropomyosin Receptor Kinase B
VAN - Ventral Attention and Salience Network

VIS - Visionary Restructuralization (subscale of 5D-ASC)

vmPFC - Ventromedial Prefrontal Cortex

VUS - Vigilance Reduction (subscale of 5D-ASC)

Erklärung zur Verwendung von Künstlicher Intelligenz (KI)

Hiermit erkläre ich, dass ich die folgenden KI-Hilfsmittel zur Erstellung meiner Masterarbeit mit dem Titel „Psychoplastogens Without The Trip?“ verwendet habe. Ich versichere, dass die Kennzeichnung der verwendeten KI-Hilfsmittel vollständig ist, inkl. Verwendungszweck, Produktname, als auch ggfs. Prompts und Outputs des KI-Hilfsmittels. Ich verantworte die Auswahl und die Übernahme sämtlicher Ergebnisse der von mir verwendeten KI-Hilfsmittel vollumfänglich selbst.

Verwendungszweck*	**Produktname des KI-Hilfsmittels**	**Ggfs. Prompt (Input) und Output des KI-Hilfsmittels**
Literaturverzeichnis kontrollieren	ChatGPT 5, OpenAI	Input: Analysiere dieses Dokument (Masterarbeit) auf die enthaltenen in-text Zitationen. Überprüfe das zweite Dokument (Literaturverzeichnis) und berichte, ob alle in-text Zitationen in der Masterarbeit auch im Literaturverzeichnis aufgelistet sind. Berichte fehlende Quellen mit Seitenanzahl und Formfehler der Zitationen (in-text und Verzeichnis) mit Seitenanzahl.
Fehlercodes aus R (Studio) erklären und Verbessern	ChatGPT5, OpenAI	Input: Ich habe beim Rechnen einer Analyse X/Y diese Fehlermeldung in R Studio erhalten. Waran kann das liegen und wie behebe ich es?

* Hilfsmittel zur Überprüfung von Grammatik und Rechtschreibung oder der automatisierten Erstellung des Literaturverzeichnisses sind von dieser Erklärung ausgenommen.