The Ramifications of Psilocybin on Synaptic Plasticity

Om Patel[1], **Darnell K. Adrian Williams**[2]

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Psilocybin, a natural psychedelic compound found in Mexico, Central America, and the United States, has created research interest in its ability to have potential therapeutic results in treating mental health disorders (e.g. depression, anxiety, and post-traumatic stress disorder). This paper examines psilocybin's effects on synaptic plasticity, neurotransmission, and functional connectivity in the prefrontal cortex, amygdala, and hippocampus, crucial brain areas for cognitive and emotional control and regulation. Findings support that psilocybin treatment amplifies dendritic spine density and excitatory neurotransmission in the, promoting cognitive flexibility and emotional processing. In the amygdala, psilocybin modifies emotional sensitivity by reducing reactions to negative stimuli, possibly facilitating therapeutic effects for anxiety and mood disorders. Additionally, psilocybin improves functional connectivity between the amygdala, visual, and cognitive regions, which may improve emotional regulation and threat assessment. In the hippocampus, psilocybin stimulates neurogenesis, modifies functional connectivity, and alters neurotransmitter levels, which play a role in enhanced cognitive and emotional resilience. These results collected and analyzed from various studies underscore psilocybin's role in stimulating neuroplasticity across the brain, displaying its possibilities as a therapeutic agent for neuropsychiatric conditions. Despite promising evidence, further evidence is needed to clarify the long-term effects, optimal dosages, and methods by which psilocybin causes these impacts on brain function and behavior.

Introduction

Introduction to Psilocybin

Psilocybin is an organic psychedelic found in specific variations of mushrooms, often popularized as "magic mushrooms." It has been used for many centuries in many cultural and religious traditions, specifically in indigenous civilizations in Central and South America. Although the use of psilocybin historically dates back to ancient times, when it was used in ritualistic practices to create altered states of consciousness and spiritual experiences, psilocybin was first isolated and discovered by Swiss chemist Albert Hofmann in 1958[1,2].

In chemistry, psilocybin is a latent drug, meaning it is changed into its active form, psilocin, after consumption. Psilocin (the active metabolite of psilocybin) acts mainly on the mind's serotonin receptors, specifically the 5-hydroxytryptamine receptor 2A (5-HT2A) receptor, which is acknowledged to play a significant role in the moderation of cognition, moods, and perception[3]. Activating these receptors by psilocin leads to changes in awareness, mood, and thought processes. Studies have displayed that psilocybin can considerably impact synaptic plasticity, strengthening the brain's ability to create new connections and reorganize synaptic networks[4].

Psilocybin is found explicitly in around 200 types of mushrooms that belong to the genus psilocybe, among others. These mushrooms grow in many habitats, including forests, grasslands, and tropical regions. The most common variations include psilocybe cubensis, psilocybe semilanceata, and psilocybe cyanescens[5]. The significance of analyzing psilocybin lies in its potential uses in therapeutics. Dysfunctional neural circuitry and impaired synaptic plasticity often distinguish these, suggesting that psilocybin's capacity to strengthen plasticity could underlie its therapeutic effects[6].

Regardless of psilocybin's illegal status in multiple major countries worldwide, such as the United States, the increasing amount of evidence from new studies backing its benefits underscores the necessity for continued research and a reevaluation of its legality[6].

Despite the increasing evidence of psilocybin's abilities to modulate synaptic plasticity and its subsequent impact on the brain and disease, substantial gaps remain in comprehending its precise mechanisms. This paper reviews studies that examen how psilocybin affects synaptic plasticity in the prefrontal cortex, amygdala, and hippocampus.

Why Psilocybin?

There are a grand variety psychedelic compounds and other treatment options that can be utilized for psychiatric and medical treatments, however, there are documented cases of common psychedelics used for treatment inducing schizophrenia-spectrum disorders, affective disorders, anxiety, and depersonalization, even after a single use. The duration of these adverse effects varies, with some lasting for years. Some individuals experience recurrent, distressing visual disturbances after us-

ing psychedelics, known as flashbacks or HPPD. While these symptoms often resolve within a year, they can persist longer in certain cases[7].

Psilocybin had been utilized in indigenous and traditional practices for centuries before most recently it was used by members of the "hippie" movement and counterculture in the 1960s. However, it was later banned by former United States president Richard Nixon in the 1970 Controlled Substances Act. It was believed to possess a high potential for abuse as well as no possible uses in medical treatments. However, advocates for psilocybin claim that modern research, which recently spiked, in psilocybin's potential use as a psychedelic as shown the drug to be nonaddictive, as well as a reduced number of side effects, disorders, and other unpredicted symptoms. This would make Psilocybin a better alternative to other psychedelic compounds currently used in treatments for conditions such as treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD).

This review focuses on psilocybin because if the data from the compiled collection of scientific studies surrounding psilocybin support the claims that advocates for psilocybin make about modern studies on psilocybin, then psilocybin could be a much better alternative to current psychedelics used in psychiatric and medical treatments.

Why These Brain Regions?

Prefrontal Cortex

The prefrontal cortex was chosen due to its relevance for important for higher-order cosyngnitive tasks such as decision-making, emotion control, and executive control, making it significant to analyze the effects of psilocybin. Psilocybin's impact on the prefrontal cortex may display data on how it modifies thought patterns, emotional processing, and self-perception, which are critical for comprehending its therapeutic potential. Additionally, modifications in prefrontal cortex connections under psilocybin are connected to its antidepressant and consciousness-altering possibilities, making it important to study its effect on mental health.

In previous studies conducted on psylocibin's impact on the prefrontal cortex, it was seen that pigs exposed to a hallucinogenic dose of psilocybin showed increased presynaptic density in the prefrontal cortex. It was also noticed that there was a significant increase in dendritic spine density by tracing psilocybin administration in rodents. This review will focus on how studies on these effects may impact on psychiatric treatments for conditions like depression based on these previously seen effects of psilocybin in the prefrontal cortex.

Amygdala

The amygdala plays a critical part in emotional comprehension, reactions to fear, and memory, making it an important part of the brain to study with psilocybin. Psilocybin's impact on the amygdala can inform us of how it modifies emotional reactivity, specifically in reaction to negative stimuli, which is crucial for knowing its possibilities in treating anxiety and depression. Additionally, modifications in amygdala activity and connections under psilocybin are connected to decreases in fear and amplified emotional regulation, making it a key focus in research on its therapeutic effects.

In studies conducted to investigate the effect of psylocibin on the Amygdala, amplified amygdala reactions to emotional faces one day post-psilocybin administration was related to favorable clinical results in patients with TRD seven days later. It was also noticed that post-psilocybin administration amplified functional connectivity was analyzed amongst the amygdala as well as an significantly amplification of Fos protein expression in the amygdala, specifically in the central amygdala of male rats. This review will analyze these results in greater depth and specifically how they can relate to psychiatric and medical treatments.

Hippocampus

The hippocampus is one of the most significant parts of the brain for memory formation, learning, and spatial navigation, making it a critical part of the brain to study with psilocybin. Psilocybin's effects on the hippocampus can shed light on how it affects memory operations and cognitive flexibility, which are applicable for comprehending its capabilities in addressing disorders like major depressive disorder and PTSD. Moreover, modifications in hippocampal plasticity are associated with amplified neuroplasticity, hinting at a system for its therapeutic effects on mood and cognition.

Recent studies conducted on psilocybin's effects on the Hippocampus region highlight how Psilocybin at administrations of 2 and 10 mg/kg amplified dopamine levels in the hippocampus, these effects as well as more provides a look into the detailed pharmacological profile of psilocybin but also hints at new routes for investigating its therapeutic effects in the environment of stress-related mood conditions that will be analyzed in this review.

Introducing Synaptic Plasticity

Synaptic plasticity, also known as neural plasticity, is the capacity of synapses, the junctions where neurons communicate with each other or with other target cells, to modify their strength in response to activity. This intricate process is significant to our ability to learn and memorize and the brain's capacity to adapt to new environments and scenarios. Synaptic plasticity includes long-term potentiation (LTP) and long-term depression (LTD),

strengthening and weakening neural connections between the synapses. The alterations are moderated by many molecular processes, such as modifying neurotransmitter receptors, alterations in synaptic morphology, and more [8].

The discovery of neural plasticity took place in the early 20th century, with many contributions from neuroscientists and neurologists such as Santiago Ramón y Cajal, who proposed the idea of synaptic plasticity based on observations of the changes in structure that took place in neurons [9]. However, Donald Hebb's theory in 1949 set the base for our modern understanding that synaptic strength increases when presynaptic and postsynaptic neurons function together—a principle often summarized as "cells that fire together wire together" [10]. Research in the 1970s by Terje Lømo and Timothy Bliss showed evidence of the hippocampus utilizing LTP [11]. Since then, many studies have increased our knowledge of synaptic plasticity [12].

Synaptic plasticity affects nearly every part of our lives and brain functions. It is necessary for cognitive processes such as learning and memory, enabling the brain to collect and save information. During growth, neural plasticity allows for the refinement of neural circuits and the collection of information and skills. In adulthood, it plays a role in the brain's ability to adapt to new experiences and recover from injuries. For example, post-stroke, neural plasticity can reorganize synaptic networks to compensate for lost functions [13]. On top of this, plasticity is a key part of many neurological and psychiatric conditions, such as Alzheimer's and schizophrenia, where dysregulation of neural plasticity may contribute to mental deficits [14,15].

Neural plasticity is crucial for learning languages, mastering musical instruments, and adapting to change. It also plays an essential role in the brain's reaction to stress and in creating resilience. For example, exposure to chronic stress can lead to maladaptive changes in synaptic plasticity, particularly in regions such as the prefrontal cortex and hippocampus, which are involved in executive function and emotional regulation [16].

Why Synaptic Plasticity? & How Can We Measure It?

Synaptic plasticity became this literature review's primary focus because of its significant role in our brain's ability to learn, remember, and adapt. Synaptic plasticity is the primary factor in cognitive functions and behavior changes. It is a critical area of research for knowing how the brain understands data and how these processes can be moderated. This is specifically relevant when analyzing the outcome of substances like psilocybin, which have displayed capabilities in changing synaptic plasticity and, as a result, cognitive and emotional outcomes. Furthermore, neural plasticity is at the center of many neurological and psychiatric disorders, including PTSD, major depressive disorder, psychosis, and anxiety disorders. Knowing how and why neural plasticity occurs and how it can be affected by pharmaceutical factors is extremely important for developing new therapeutic strategies for these conditions [8,17].

Many strategies are there to measure synaptic plasticity, giving special insights into the mechanisms and outcomes of synaptic changes. Electrophysiological methods, like patch-clamp recordings and field potential recordings, are often utilized to measure alterations in synaptic strength by analyzing synaptic currents and potentials in response to specific stimuli [18]. Imaging methods, including two-photon microscopy and calcium imaging, enable the analysis of synaptic structures and activity in living tissues, providing specific data about the interactions of synaptic changes [19]. Molecular methods, such as Western immunohistochemistry, can be utilized to count the expression levels of synaptic proteins and receptors, offering knowledge of the biochemical routes involved in synaptic plasticity [20]. Furthermore, behavioral assays, such as education and memory tests, can be applied to examine the functional outcomes of neural plasticity in animal models [21]. Synaptic plasticity is specifically applicable in the setting of diseases such as PTSD, depression, and anxiety. In PTSD, abnormal synaptic plasticity in regions like the amygdala and hippocampus can lead to the determination of traumatic memories and increased fear reactions [22]. Likewise, in depression, shortcomings in neural plasticity, especially in the prefrontal cortex and hippocampus, are structured with impaired cognitive function and emotional regulation [23]. Anxiety disorders also incorporate disruption of synaptic plasticity, resulting in extreme and inappropriate fear responses [24].

Methodology

The studies reviewed in this paper were collected through a comprehensive database search to identify relevant studies on the effects of psilocybin on synaptic plasticity in the prefrontal cortex, amygdala, and hippocampus. The databases used for the search included PubMed, Google Scholar, JSTOR, and EBSCOhost.

Specific keywords and search terms were used to locate relevant studies, including "Psilocybin," "Psilocybin Mushrooms," "Synaptic plasticity," "Neural plasticity," "Prefrontal cortex," "Amygdala," "Hippocampus," "Psychedelics and brain," and "Psilocybin and Synaptic Plasticity." Boolean operators (AND, OR) were employed to refine the search results, combining terms such as "Psilocybin AND Synaptic Plasticity" and "Psilocybin AND Prefrontal Cortex" to narrow down the studies to those of particular interest.

The inclusion criteria for the review required that studies be peer-reviewed articles published in academic journals, conducted on human or animal models that investigated the effects of psilocybin on synaptic plasticity, and published in English. Additionally, the research had to focus specifically on the prefrontal cortex, amygdala, and hippocampus and employ methodologies such as electrophysiological recordings, neuroimaging techniques, or biochemical assays to measure synaptic plasticity.

Conversely, articles that were not peer-reviewed did not address the effects of psilocybin on synaptic plasticity, focused solely on behavioral or psychological effects without examining neural mechanisms, or were non-English publications excluded.

The screening process involved an initial review of titles and abstracts to identify potentially relevant studies, followed by a full-text review of selected articles to ensure they met the inclusion criteria. The bibliographies of these articles were also cross-referenced to identify additional relevant studies. Key information, such as study design, sample size, methodologies used, and key findings, was then extracted from each included study. The extracted data were synthesized to identify common themes, trends, and gaps in the existing research.

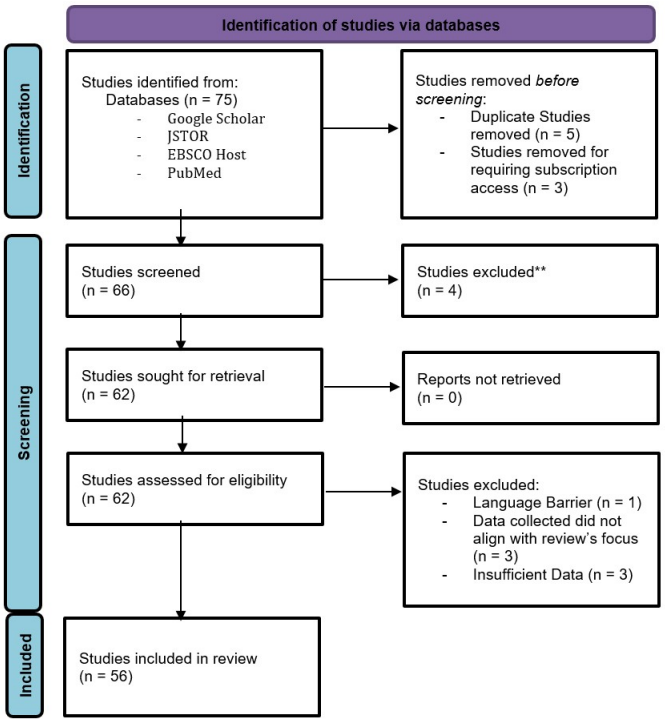

Fig. 1 Flow Diagram for the Identification of Studies via Databases

Results

Prefrontal Cortex

Psilocybin, a serotonin 2A receptor activator found in certain mushrooms, has gained attention for its significant impact on neural plasticity in the prefrontal cortex, which is necessary for emotional regulation and executive decisions. Here, we integrate results from many investigations to thoroughly examine the methods through which psilocybin influences structural, molecular, and functional features of synaptic plasticity in the prefrontal cortex.

Rapid and Persistent Growth of Dendritic Spines

Psilocybin triggers substantial structural alterations in the dendritic structure within the prefrontal cortex. Ling-Xiao Shao et al., showed a significantly increased dendritic spine density by tracing psilocybin administration in rodents [25]. This increase persisted over time, predicting a lasting effect on neural plasticity. Dendritic spines are vital areas for neural transmission and plasticity, and their expansion under psilocybin may bolster the cognitive and perceptual alterations witnessed during psychedelic experiences. A single dose of psilocybin induces rapid and long-lasting dendritic remodeling in layer 5 pyramidal neurons in the mouse medial frontal cortex [25].

Psilocybin elevates excitatory neurotransmission in the frontal cortex

Shao et al. (2021) also performed whole-cell recordings in brain slices to measure miniature excitatory postsynaptic currents (mEPSCs) [25]. Studies showed an increase in mEPSC frequency in psilocybin-treated animals compared to saline controls.

In Calder et al. (2022) Pigs exposed to a hallucinogenic dose of psilocybin showed increased presynaptic density in the prefrontal cortex. In humans, positron emission tomography (PET) imaging has shown that psilocybin increases glutamate (GLU) signaling in the prefrontal cortex, which is theorized to be essential for psychedelic-enhanced plasticity [26].

An earlier study by Mertens et al. (2020) studied functional connectivity changes in the prefrontal cortex while performing face-processing tasks post-psilocybin treatment, focusing on the ventromedial prefrontal cortex (vmPFC). Following treatment, the vmPFC displayed amplified connectivity with visual and parietal areas, specifically the left occipital and parietal lobes, and reduced connection with the right amygdala. These modifications were expression-specific, with remarkable amplifications in connectivity for fearful and happy faces in different brain regions. Although there are significant reductions in depression and rumination following treatment, edits in vmPFC-amygdala connections were not substantially related to clinical outcomes. Despite this, decreased connectivity following treatment was associated with decreased rumination rates. In total, psilocybin emerged to increase visual processing and alter vmPFC-amygdala connections during emotional face processing [27].

Additionally, Davoudian et al. (2023) investigated the concept that psilocybin has been seen to increase synaptic plasticity, with its effect on gene expression in the prefrontal cortex being of specific interest. This study used cutting-edge imaging methods to map c-Fos expression and saw that psilocybin and ketamine both substantially elevated c-Fos

levels in multiple brain areas, including the anterior cingulate cortex. The analysis displayed that cortical sensitivity to these drugs was related to the endogenous levels of glutamatergic receptors, hinting at a basic pathway for their therapeutic effects[28].

Functional Magnetic Resonance Imaging (fMRI)-Measured Psilocybin Reactivity

To get a more visual perception of what was occurring, Carhart Harris et al. (2017) tested nineteen patients with diagnoses of treatment-resistant major depressive disorder and completed pre-treatment and one-day post-psilocybin treatment fMRI scanning. Psilocybin treatment led to quick and lasting antidepressant outcomes, with average depression scores (QIDS-SR16) reducing from 16.9 ± 5.1 before treatment to 8.8 ± 6.2 following treatment (change = -8.1 ± 6, t = -5.2, p ¡ 0.001) and from 18.9 ± 3 at the initial level to 10.9 ± 4.8 at 5 weeks (change = -8 ± 5.1, t = -6.3, p ¡ 0.001). Following treatment, substantial reductions in cerebral blood flow (CBF) were analyzed in areas including the left amygdala, with decreases in amygdala CBF substantially related to decreases in symptoms of depression (r = 0.59; p = 0.01). However, no significant impact in CBF changes was noticed between responsive and non-responsive participants at 5 weeks (t = 0.11; p = 0.46)[29].

Psilocybin Effect Comparison Between Rat Prefrontal Cortex and Hippocampus

Rather than looking at the regions of the brain individually, Jefsen et al. (2021) compared the rat prefrontal cortex and hippocampus. The study found psilocybin stimulates quick transcriptional regulation in the prefrontal cortex and hippocampus. In the prefrontal cortex, acute provision of psilocybin considerably enhanced the expression of multiple genes, which includes CCAAT/enhancer-binding protein beta (Cebpb), FBJ murine osteosarcoma viral oncogene homolog (c-Fos), Dual specificity phosphatase 1 (Dusp1), Jun B proto-oncogene (Junb), Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (I$\kappa\beta$-α), Nuclear receptor subfamily 4 group A member 1 (Nr4a1), and Serum and glucocorticoid-induced kinase 1 (Sgk1), depending on the psilocybin dosage. FBJ murine osteosarcoma viral oncogene homolog B (Fosb), Protein S100-A10 (P11), and Postsynaptic density protein 95 (Psd95) also showed amplified expression at specific doses of psilocybin, while Clk1 activation was reduced in a dose-dependent manner. Most monitored genes exhibited profound pairwise relations. In the hippocampus, psilocybin similarly amplified the expression of Dusp1, I$\kappa\beta$-α, and Sgk1. It reduced Casein kinase 1 epsilon (Clk1) expression but also led to small modifications in Activity-regulated cytoskeleton-associated protein (Arc), early growth response 2 (Egr2), Prostaglandin-endoperoxide synthase 2 (Ptgs2), and Interleukin 6 (Il6) transcripts while leaving Cebpb, c-Fos, Fosb, I$\kappa\beta$-α, Junb, Nr4a1, P11, and Psd95 unmodified. Protein levels of commonly regulated genes (Sgk1, Dual specificity phosphatase 1 (Dusp1), and I$\kappa\beta$-α) were also studied, showing major elevations in SGK1 across both areas, variable edits in DUSP1 contingent on the dose, and elevated I$\kappa\beta$-α protein levels in the Hippocampus at increased doses but not in the prefrontal cortex[30].

Psilocybin Effect Comparison Between Rat Prefrontal Cortex and Amygdala

Similar to Jefsen et al., 2021, Mertens et al. (2020) compare the rat prefrontal cortex and amygdala when exposed to psilocybin. The results were that the primary psychophysiological interaction (PPI) figure displayed that post-psilocybin treatment, there was amplified functional connectivity amidst the amygdala and visual areas while face processing set against the rest. In particular, amplified functional connectivity was noticed within the amygdala and areas such as the intracalcarine and supracalcarine cortex, cuneus, precuneus, and lateral occipital cortex. Secondary examinations revealed more powerful functional connectivity between the amygdala and similar visual areas during happy and neutral faces but not fearful faces. Post-psilocybin treatment examinations for the vmPFC displayed increased functional connectivity with visual regions during face processing. Additionally, the vmPFC showed considerably increased interaction with the right amygdala during face processing pre-psilocybin treatment. The findings hinted that changes in amygdala and vmPFC connectivity were not fundamentally related to the clinical results, such as depression, rumination, or anxiety levels, however decreased connection between the vmPFC and right amygdala following treatment was related to decreased rumination scores[27].

Amygdala

Increased amygdala responses to emotional faces

Beginning to investigate the amygdala, Roseman et al. (2018) revealed that amplified amygdala reactions to emotional faces one day post-psilocybin administration was related to favorable clinical results in patients with TRD seven days later. This is in comparison to the reduced amygdala reactivity commonly observed with selective serotonin reuptake inhibitors (SSRIs), a typical group of antidepressants. In contrast to SSRIs, which are typically silent emotional reactions, psilocybin seems to amplify emotional salience, enabling emotional confrontation and catharsis. Patient results hint that psilocybin stimulates recognition of all emotions, contrary to past treatments that promoted emotional avoidance. The research findings are parallel with this, revealing an unseen therapeutic mechanism for psilocybin in TRD[31].

Also, in studying emotional face responses, Grimm et al.'s (2018) work showed psilocybin's effect on amygdala connections while facing emotional face processing. It was discovered that psilocybin majorly decreased reaction times to all emotional faces—angry, fearful, and happy—compared to the placebo. However, it did not impact the precision of emotion recognition[32]. This decreasing effect was steady across multiple emotional categories, hinting at a modification in processing efficiency rather than specific edits tied to specific emotions. Functional connectivity examinations displayed strong connections between the amygdala and many other regions of the brain, including the contralateral amygdala, striatum, lateral occipital cortex, fusiform gyrus, insula, thalamus, frontal pole, and supplementary motor cortex. Remarkably, post-psilocybin administration, there was reduced connectivity between the left striatum and right amygdala during the examination of angry faces and reduced interaction between the right amygdala and medial frontal pole while processing happy faces. No major modifications were noticed for fearful faces, and there was no major interaction between drug condition and face emotion type for any of the emotional faces. These changes in linkage suggest that psilocybin moderates the amygdala's communication with other parts of the brain involved in emotional processing and cognitive regulation, perchance reflecting edits in emotional saliency and cognitive moderation. On top of this, reduced interaction post-psilocybin treatment related to decreased negative mood, including decreased state anxiety and self-rated depressed mood, suggesting a connection between modified amygdala connectivity and enhanced mood states under psilocybin treatment[32].

Also supporting decreased reaction time for angry and fearful reaction faces, Armand et al. (2024) focused on the results of psilocybin on amygdala response, while in an emotional faces paradigm, baseline statistics showed pronounced amygdala reactions to angry, fearful, and neutral faces compared to geometric figures. Post-psilocybin intervention, the amygdala's reaction to angry faces substantially reduced, while reactions to fearful faces reduced but not substantially. Neutral face reactions remained largely unaffected. Relationships amongst subjective drug intensity (SDI) and amygdala reactions displayed a substantial negative relationship with fearful faces, hinting that increased psychedelic experiences corresponded with greater decreases in fear processing. Despite these results, whole-brain studies revealed numeric decreases in reactions to angry and fearful faces across multiple regions during psilocybin, though not statistically substantial after various testing corrections. The study suggests that psilocybin may reduce the amygdala's sensitivity to negative emotional stimuli, in parallel with previous studies indicating reduced amygdala reactivity to negative scenes and emotions post-psychedelic treatment. However, methodological considerations, such as possible problems with the emotional faces paradigm's signal-to-noise ratio, underscore the need for advanced paradigms in future research. The results are also in parallel with past research that shows decreased amygdala reaction to negative stimuli during psychedelics like LSD, supporting the role of SDI as an informative measure of psychedelic impacts[33].

Changes in Functional Connectivity

Returning to Mertens et al. (2020) to investigate changes in functional connectivity. The results were that post-psilocybin administration amplified functional connectivity was analyzed amongst the amygdala and multiple visual areas, such as the intracalcarine and supracalcarine cortex, cuneus, precuneus, and right lateral occipital cortex amid face processing in comparison to the remainder. Notably, there was a remarkable amplification in connectivity with visual regions in reaction to happy and neutral faces but not fearful faces. The secondary examination showed that connectivity was notably stronger during the processing of happy and neutral faces. This increased connectivity in visual areas did not show major differences for fearful faces. The amygdala's amplified connectivity with these visual areas hints at an increased integration of visual and emotional processing post-psilocybin treatment[27].

Kraehenmann et al. (2015) studied the impact of psilocybin on effective connectivity in a network engaged in threat assessing, the full model, which includes bidirectional networking between the primary visual cortex (V1), amygdala, and lateral prefrontal cortex (LPFC), was shown to be the most optimal fit for the placebo and psilocybin situations. The psilocybin treatment decreased the threat-induced moderation of the top-down network from the amygdala to V1, revealing a reduced amygdala-dependent adjusting of visual regions during threat assessment. This decrease hints that psilocybin lowers the amygdala's effect on visual threat perception, theoretically leading to lowered sensitivity to danger. However, the research found no major impact of psilocybin on top-down networks from the LPFC to the amygdala, which could suggest that the drug's effect on amygdala responsiveness may be credited to direct modulation of the amygdala instead of amplified prefrontal control. This finding underscores a distinct system of psilocybin's action in relation to regular antidepressants, focusing on the moderation of visual stimuli analysis instead of just increasing prefrontal regulation over the amygdala[34].

Now to start looking at major brain networks, we will analyze the results of Stoliker et al. (2024), which looks at how psilocybin affects interactions between the amygdala and major brain networks, such as the Default Mode Network (DMN), Central Executive Network (CEN), and Salience Network (SN). Psilocybin treatment yields enhanced connectivity within the CEN, hinting at increased cognitive control, while it decreases connectivity within the DMN and SN. Particularly, the DMN displays decreased interactions with the amygdala, displaying

reduced top-down inhibition from higher-order cognitive regions. In contrast, the CEN displays enhanced connectivity to the amygdala, hinting at stronger cognitive interactions. The SN's interactions with the amygdala are diminished, pointing to reduced salience identification post-psilocybin administration. These edits are related to subjective impacts such as modified cognition and emotion, indicating that psilocybin moderates brain network interactions in ways that may influence its therapeutic uses[35].

Amygdala Psilocybin Reactivity and Mood Changes

Examining and understanding mood changes through Kraehenmann et al. (2015), psilocybin substantially amplified positive affect without impacting negative affect or state anxiety. Functional MRI scans showed a prominent drug effect located in the right amygdala, where psilocybin significantly decreased activation in response to both negative and neutral pictures, but no drug-by-emotion connection was found. Psilocybin did not impact the primary motor cortex stimulation. Detailed examination revealed that psilocybin preferentially attenuated the right amygdala over the left, specifically to negative stimuli. The decrease in amygdala reactivity is related to an increase in positive mood, which propose a mechanistic connection between psilocybin-induced amygdala modifications and boosted mood. A whole-brain examination verified these results, with substantial drug implications in the occipital, lingual, fusiform, and temporal gyri but no principle enhancement in regional activity under psilocybin. The research backs up the hypothesis that psilocybin stabilizes limbic hyperactivity, plausibly providing therapeutic results for mood disorders by moderating amygdala stimulation. The outcomes also underscore the non-valence-specific impact of psilocybin on amygdala operations and propose that future research with time-varying stimulus situations may grant data on the temporal dynamics of psilocybin's effects on emotion processing[34].

In Kelly et al. (2024), 4-OH-DiPT, a rapid psilocybin derivative, was revealed to fundamentally amplify fear extinction cognition by diminishing freezing reactions to conditioned stimuli (CS) in a dose-dependent relationship, specifically in female mice. This derivative reveals intense activity at 5-HT2A receptors in the basolateral amygdala (BLA), resulting in amplified spontaneous inhibitory postsynaptic currents (sIPSCs) and action potential firing in BLA interneurons. The 5-HT2A-dependent stimulation of BLA interneurons by 4-OH-DiPT reveals a mechanism for diminishing learned fear through amplified gamma-aminobutyric acid (GABA)ergic restriction of BLA principal neurons[36].

Gene Expression

In Funk et al. (2024), psilocybin administration significantly amplified Fos protein expression in the amygdala, specifically in the central amygdala of male rats used in the study. This expression takes place in a dose-dependent situation and is studied in neurons and oligodendrocytes. The stimulation of the central amygdala indicates it plays a critical part in the therapeutic effects of psilocybin, possibly facilitating neuroplastic modifications in this area of the amygdala and its interconnected regions, which are engaged in emotional processing, stress, reward, and addiction[37].

Psilocybin and Ketamine Response

Uniquely, Wojtas et al. (2023) will examine not only psilocybin but also responses to ketamine. This study researched the results of ketamine and psilocybin on neurotransmitter systems inside the rat amygdala, centering on dopamine, serotonin, GLU, and GABA levels. Psilocybin treatment at 2 and 10 mg/kg substantially increased dopamine and serotonin amounts, proposing amplified monoaminergic activity. This was differentiated by ketamine, which resulted in a stronger dopamine enhancement but a slightly lower impact on serotonin. Remarkably, psilocybin lowered GLU amounts in the amygdala. Meanwhile, ketamine amplified them, suggesting divergent impacts on excitatory neurotransmission. Furthermore, psilocybin slightly increased GABA levels, encouraging inhibitory neurotransmission, whereas ketamine prompted a more significant GABA increase. The 2 mg/kg administration of psilocybin significantly amplified the GABA/GLU ratio, underscoring a change towards increased inhibitory control in the amygdala, a modification not reflected by ketamine. These results highlight the mechanisms by which psilocybin and ketamine affect neurotransmitter equilibrium in the amygdala, revealing insight into their special neuropharmacological profiles[38].

Hippocampus

Neurogenesis

Specifically looking at neurogenesis, Catlow et al. (2013) examined the results of psilocybin on neurogenesis within the hippocampus by treating the region with multiple doses of psilocybin (0.1, 0.5, and 1.0 mg/kg), the 5-HT2a receptor stimulator 25I-NBMeO, the stimuli of ketanserin, or a saline vehicle to mice, before Bromodeoxyuridine (BrdU) injections to mark new cells. Outcomes displayed that low-level administrations of psilocybin (0.1 mg/kg) amplified the number of new neurons (BrdU/ neuronal nuclei (NeuN+) cells), revealing amplified neurogenesis. Meanwhile, larger doses (1.0 mg/kg) considerably reduced cell survival and neurogenesis. Ketanserin also decreased neurogenesis, and 25I-NBMeO led to a reduction in emerging cells at all treatment levels. This analysis underscores psilocybin's outcome on neurogenesis in

the hippocampus, with possible therapeutic uses[39].

Brain Networks

Going back to brain networks, but this time in the hippocampus, in Siegel et al. (2024), psilocybin stimulates acute and persistent modifications in hippocampal interconnection, displaying its profound effect on brain activity. At first, psilocybin interrupts connectivity in the hippocampus region, specifically impacting the anterior hippocampus, a primary part of the DMN. During the drug's peak effects, this change is displayed in decreased functional connectivity within the anterior hippocampus and the DMN. Incredibly, these connectivity modifications reach far beyond the drug's presence, lasting for weeks, which may display the long-lasting therapeutic benefits of psilocybin. The acute interruption in hippocampal function is believed to amplify cognitive and emotional flexibility, possibly enabling the antidepressant-like results noticed in clinical settings. This persistent change in connectivity could display a neuroplastic edit that highlights psilocybin's efficacy in addressing mood disorders[40].

Neurotransmitters

Examining different brain networks, Wojtas et al. (2023) researched the impact of psilocybin and ketamine on neurotransmitter amounts in the rat hippocampus, displaying significant results. Psilocybin at administrations of 2 and 10 mg/kg amplified dopamine levels in the hippocampus, with ketamine at 10 mg/kg displaying a more compelling effect. Both psilocybin administrations and ketamine substantially enhanced serotonin (5-HT) levels in the hippocampus; however, ketamine was less effective from this perspective. Psilocybin decreased GLU amounts in the hippocampus, compared to ketamine, which amplified GLU levels. Additionally, psilocybin marginally increased GABA levels in the hippocampus, while ketamine caused a more substantial increase. Specifically, the GABA/GLU ratio in the hippocampus enhanced with the 2 mg/kg psilocybin dose, signaling a change towards inhibitory neurotransmission. At the same time, ketamine did not substantially modify this ratio in the hippocampus. These outcomes indicate that psilocybin and ketamine have clear impacts on neurotransmitter dynamics inside the hippocampus, suggesting possible variations in their mechanisms of action, especially in how they adjust the balance among excitatory and inhibitory signals in this critical brain region[41].

Fear Extinction

Beginning to look at fear extinction, which could be applied to therapeutic medication, Catlow et al. (2013) looked into the results of psilocybin on the diminishing of conditioned fear feedback in hippocampus trace fear conditioning. Mice were treated with different administrations of psilocybin (0.1, 0.5, and 1.0 mg/kg), ketanserin (1.0 mg/kg), or a saline vehicle before the conditioning. During the acquisition stage, all mice rapidly mastered to relate the CS, such as a tone, with the unconditioned stimulus. For example, slight foot shock, as displayed by amplified freezing behavior throughout the CS and trace interval. However, modifications were introduced in the extinction stage, where the CS was introduced absent the US. Mice administered with low psilocybin treatments (0.1 and 0.5 mg/kg) displayed a quick decrease in freezing behavior by the third extinction test, revealing a hastened eradication of the conditioned fear reaction. This hints that minimal doses of psilocybin prompted the separation of the CS from the US, loosening the emotional memory connection. In comparison, increased treatments of psilocybin (1.0 mg/kg) and ketanserin didn't display this quick eradication impact, with mice holding higher levels of freezing behavior for an extended period. By the 10th trial, all experimental batches eventually displayed reduced freezing. Still, the minimal dose psilocybin batch attained this considerably quicker[39].

Additionally, Du et al. (2023) displayed that psilocybin treatment before fear extinction training drastically increased the eradication of fear responses in fear-conditioned mice. Primarily, the treatment caused a marked decrease in freezing behavior, a specific measure of fear response. This result was credited to psilocybin's ability to reverse the heightened freezing linked with fear conditioning, showing an advancement in fear extinction. At the neurobiological scale, psilocybin treatment resulted in substantial modifications in hippocampal neuroplasticity. It recovered dendritic complexity and spine density. Meanwhile, balancing levels of brain-derived neurotrophic factor (BDNF) and mechanistic target of rapamycin (mTOR) decreased due to fear conditioning. On top of this, there was a remarkable enhancement in the amount of doublecortin (DCX)- and BrdU-positive cells, indicating amplified neurogenesis. These outcomes hint that psilocybin's handling of fear extinction is closely connected to its effect on neuroplasticity in the hippocampus, which may reinforce its potential therapeutic outcomes for anxiety and other fear-related disorders[42].

Hesselgrave et al. (2021) investigated the impact of psilocybin on chronic stress-induced anhedonia in mice, researchers displayed that a 1 mg/kg administration of psilocybin majorly inverted the hedonic deficits linked with chronic stress. Particularly, the administered mice revealed a marked amplification in sucrose preference and female urine preference, indicating a renewal of hedonic sensitivity. This antidepressant-like result was uncovered to be independent of the 5-HT2A receptor, as demonstrated by the lack of effect of ketanserin, a selective 5-HT2A/5-hydroxytryptamine receptor 2C (5-HT2C) stimulist, on psilocybin's efficacy. Furthermore, psilocybin was displayed to amplify synaptic plasticity within the hippocampus, a fundamental area of the brain engaged in mood regulation and

memory. This was demonstrated by a significant amplification in the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/N-Methyl-D-Aspartate (NMDA) receptor ratio in hippocampal slices from psilocybin-administered mice, proposing that psilocybin supports synaptic strengthening. These findings highlight that psilocybin's therapeutic effects may be more than just the direct stimulation of the 5-HT2A receptor, underlining potential substitute pathways through which psilocybin could employ its mood-enhancing and neuroplastic results. This research not only provides a look into the detailed pharmacological profile of psilocybin but also hints at new routes for investigating its therapeutic effects in the environment of stress-related mood conditions[43].

Discussion

Looking back on the collection of research and data surrounding psilocybin's effect on synaptic plasticity, neurotransmission, and functional connectivity, it is clear that psilocybin has a profound and possibly transformative impact on the brain, specifically in the prefrontal cortex, amygdala, and hippocampus. Psilocybin specifically affects the serotonergic system by activating 5-HT2A receptors, which results in modified neurotransmission, amplified synaptic plasticity, and modifications in brain network connectivity.

Beginning with the prefrontal cortex, research overviews how psilocybin substantially affects synaptic plasticity, neurotransmission, and functional connectivity in this portion of the brain. Notably, the data hints that psilocybin stimulates the dendritic spine growth and amplifies excitatory neurotransmission, which may underlie its ability to facilitate cognitive flexibility and emotional regulation. These modifications in the prefrontal cortex probably play a part in recorded advancements in depressive symptoms and cognitive function, as the prefrontal cortex is critical for executive control and decision-making. Although the specific ways psilocybin stimulates these changes remain complex and possibly influenced by various interacting factors, such as the particular receptor subtypes stimulated and how long the impact lasts.

The amygdala's reaction to psilocybin has been thoroughly analyzed, specifically regarding emotional processing and fear extinction. The results consistently show that psilocybin reduces amygdala response to negative emotional stimuli, which relates to an increased positive mood and fewer symptoms of depression and anxiety. This hints that psilocybin may assist in recalibrating emotional reactions by reducing hyperactive amygdala responses often displayed in mood disorders. Furthermore, the research on psilocybin's effect on GABAergic inhibition in the BLA provides captivating observations into how psilocybin might facilitate fear extinction and emotional learning, possibly granting us a neurobiological foundation for its use in addressing conditions like PTSD. The interaction between decreased amygdala reactivity and modifications in functional connectivity with other sections of the brain, such as the prefrontal cortex, also highlights the significance of learning psilocybin's impact within the widespread context of network-level connections rather than isolated regional modifications.

Going to the hippocampus, the research directs us to psilocybin's part in stimulating neuroplasticity and amplifying synaptic function, which may advance its quick and lasting antidepressant-like results noticed in preclinical models. The hippocampus is important to memory creation and emotional control, and the capability of psilocybin to trigger modifications in this region is paralleled with the broader therapeutic abilities seen in patients with depression. The studies also hint that these hippocampal modifications may be partly connected to enhanced neurogenesis and changes in gene expression, further backing the possible ability for sustained therapeutic outcomes. However, the time-scale dynamics of these results, including their duration post-psilocybin treatment and their connection with behavioral results, require more investigations to know their clinical applications fully.

Similarities and Differences in Research

Prefrontal Cortex

Similarities: The research has a pattern of focusing on the substantial impact of psilocybin on synaptic plasticity across multiple parts of the brain. Particularly the prefrontal cortex and hippocampus. Shao et al. displayed quick and long-lasting growth of dendritic spines in the prefrontal cortex, which is essential for cognitive and perceptual modifications, in parallel with similar neural plasticity amplifications noticed in the hippocampus[30]. On top of this, psilocybin's effect on gene expression is displayed in the prefrontal cortex plus the hippocampus, where it upregulates genes like c-Fos, Dusp1, and Sgk1, all of which are correlated with synaptic plasticity and reactions to stress[28,30]. Functional connectivity modifications are an alternate standard feature, with research revealing changes in connectivity amongst the prefrontal cortex and between the prefrontal cortex and areas of the brain, such as the amygdala, specifically during tasks that result in emotional processing[27,29].
Differences: Regardless of the major similarities, research also shows some critical contrasts in how psilocybin impacts parts of the brain. When looking at structural changes, Shao et al. focus on the prefrontal cortex, revealing an amplification in dendritic spine density, particularly in this section of the brain. Jefsen et al. (2020) broadened the analysis to include the prefrontal cortex and the hippocampus, finding differential gene expression patterns between these areas. For example, specific genes such as Arc and Ptgs2 are upregulated in the hippocampus in contrast to the prefrontal cortex, where they are not, indicating region-specific impacts of psilocybin. Furthermore, while

functional connectivity modifications are observed in both the prefrontal cortex and its exchanges with the amygdala, Mertens et al. (2020) underscore that these modifications in connectivity are not explicitly related to clinical results such as depression and anxiety. Notably, the research hints that even though there is amplified connectivity between the prefrontal cortex and visual regions, the alterations in the prefrontal cortex-amygdala connection do not associate with clinical advancements, directing us to a more intricate connection between functional connectivity and therapeutic results.

The observed contradictions in psilocybin's neurobiological effects may stem from the methodological variability in the studies, such as differences in dosing protocols, post-treatment assessment timelines, or differences in demographics across studies. Regional specificity in brain responses—such as the hippocampus's role in memory-related gene expression versus the prefrontal cortex's involvement in higher-order cognition—could also explain divergent structural and functional outcomes. These specific regions of the brain also possess different responsibilities which could explain their result differences. Additionally, the interplay between acute pharmacological action (such as serotonin receptor agonism) and longer-term neuroplastic adaptations might produce temporally distinct effects that are inconsistently captured in isolated experiments. Finally, individual variability in baseline neural circuitry, genetic predispositions, or psychological states could modify psilocybin's impact in a patient to patient basis, leading to heterogeneous findings even within similar brain regions or clinical cohorts.

Amygdala

Similarities: Amongst research, a recurring pattern is the substantial changes in the amygdala's activity and its interactions with other sections of the brain post-psilocybin administration. Roseman et al. (2018), Grimm et al. (2018), and Armand et al. (2024) all noted modification in amygdala response to emotional stimuli, specifically emotional faces, post-psilocybin treatment. This change in amygdala reaction is connected with therapeutic impacts, specifically in patients with TRD, where enhanced or modified amygdala reactions are related to improved clinical results. Additionally, research, such as those by Kraehenmann et al. (2015), Mertens et al. (2020), and Stoliker et al. (2024), suggested edits in the functional connectivity among the amygdala and other areas of the brain that play a role in emotion processing and cognitive control. Research consistently suggests that psilocybin modifies the amygdala's connection with networks such as the DMN, Central Executive Network (CEN), and visual processing areas, underscoring a significant manipulation of emotional and cognitive processing under the influence of psilocybin.

Differences: Regardless of these common findings, research also displays remarkable differences in the particular effects of psilocybin on the amygdala. For instance, Roseman et al. (2018) show an amplification in amygdala reaction to emotional faces post-psilocybin, which goes against the findings of Armand et al. (2024), where the amygdala's reaction to angry and fearful faces reduced post-psilocybin treatment. This result may mirror differences in experimental designs, test-subject populations, or the particular emotional stimuli used. Likewise, while Mertens et al. (2020) and Kraehenmann et al. (2015) both studied the functional connectivity modifications, they noted alternate patterns: Mertens et al. (2020) underscored enhanced connectivity between the amygdala and visual areas during emotional face processing, specifically for happy and neutral faces, while Kraehenmann et al. (2015) concentrated on the decreased top-down modulation from the amygdala to visual areas in threat assessment. Additionally, research like that of Kelly et al. (2024) and Funk et al. (2024) plunged into molecular and cellular mechanisms. For example, gene expression and neurotransmitter rates are not as prominently confronted in the other studies. These molecular results, including modifications in Fos protein expression and neurotransmitter rates like dopamine and serotonin, highlight specific neuropharmacological mechanisms of action for psilocybin rather than its effects on wider brain connectivity and emotional processing.

The differences observed in psilocybin's effects on the amygdala may come from variations in experimental contexts, such as differences in emotional stimuli (such as emotional faces vs. threat-related tasks), timing of post-treatment assessments (acute vs. longer-term effects), or participant states (such as healthy volunteers vs. clinical populations). Contrasting connectivity findings—such as enhanced amygdala-visual coupling during neutral stimuli (Mertens et al.) versus reduced top-down modulation in threat processing (Kraehenmann et al.)—could reflect task-dependent neural engagement, where psilocybin's impact shifts based on cognitive-emotional demands. Divergence between molecular and systems-level studies (Kelly/Funk's focus on Fos expression vs. Roseman/Armand's fMRI-based results) may display an challenge in reconciling localized cellular changes with broader network dynamics. Finally, individual differences in baseline amygdala reactivity, genetic factors influencing serotonin receptor density, or variations in psilocybin's pharmacokinetics across studies could further explain inconsistent outcomes in emotional processing and connectivity patterns.

Hippocampus

Similarities: Studies on psilocybin's impact on the hippocampus show a repeating pattern of its influence on neuroplasticity and potential therapeutic effects. Research by Catlow et al. (2013) and Du et al. (2023) both underscore that psilocybin stimulates neurogenesis, with Catlow et al. noticing amplified

numbers of BrdU-positive cells having enhanced neurogenesis at reduced doses, while Du et al. reveals that psilocybin enhances dendritic complexity and spine density, and balances neurotrophic factors like BDNF and mTOR. These results are backed by Siegel et al. (2024) and Wojtas et al. (2023), which investigate neurotransmitter dynamics and connectivity modifications. Siegel et al. show that psilocybin causes acute and lasting effects on hippocampal connectivity, affecting the DMN and hinting at long-term cognitive and emotional benefits. Wojtas et al. (2023) show that psilocybin edits neurotransmitter levels, such as boosting dopamine and serotonin, while reducing GLU, backing the theory that psilocybin impacts brain chemistry in a method that may enhance its therapeutic effects. Together, these studies accentuate psilocybin's part in amplifying neuroplasticity and hint at therapeutic potential in mood and anxiety disorders.

Differences: While research acknowledges psilocybin's effect on the hippocampus, their results and specifics differ. Catlow et al. (2013) stated that the results of psilocybin on neurogenesis are dose-dependent, with reduced doses boosting cell proliferation and increased doses impairing cell survival chances. This goes against Du et al. (2023), which underscores psilocybin's part in fear extinction and neuroplasticity, displaying advancements in dendritic complexity and synaptic connectivity instead of focusing only on cell proliferation. Siegel et al. (2024) focus on the effect of psilocybin on hippocampal connectivity, suggesting that acute interruptions in the DMN and constant modifications may underlie cognitive flexibility and therapeutic results. This is specifically from Wojtas et al. (2023), which concentrates on neurotransmitter dynamics, showing that psilocybin enhances dopamine and serotonin levels while reducing GLU, compared to ketamine's results. Thus, while the overall concept of enhanced neuroplasticity and therapeutic potential is the same, the studies differentiate in their specific results and suggestions of neuroplasticity, connectivity, and neurotransmitter alterations.

The contradictions seen in psilocybin's hippocampal effects may be the result of discrepancies in dose regimens (low vs. high doses altering distinct neurogenic phases) or temporal windows of analysis (acute vs. lasting plasticity), as seen in Catlow's dose-specific neurogenesis versus Du's focus on dendritic remodeling during fear extinction. Divergent methodologies (such as Siegel's emphasis on network-level DMN disruptions versus Wojtas's neurotransmitter-level comparisons with ketamine) possibly underscore the variations in hippocampal function (such as connectivity vs. molecular signaling) rather than mutually exclusive outcomes. Differences in experimental procedures, such as behavioral tasks (fear extinction) versus resting-state imaging or molecular assays, could further underline distinct pathways (synaptic rewiring vs. monoaminergic modulation) that collectively contribute to psilocybin's plasticity. Finally, interspecies differences or time-lagged measurement intervals may obscure unified interpretations, as acute neurotransmitter shifts and chronic structural adaptations represent possible different temporal layers of psilocybin's action.

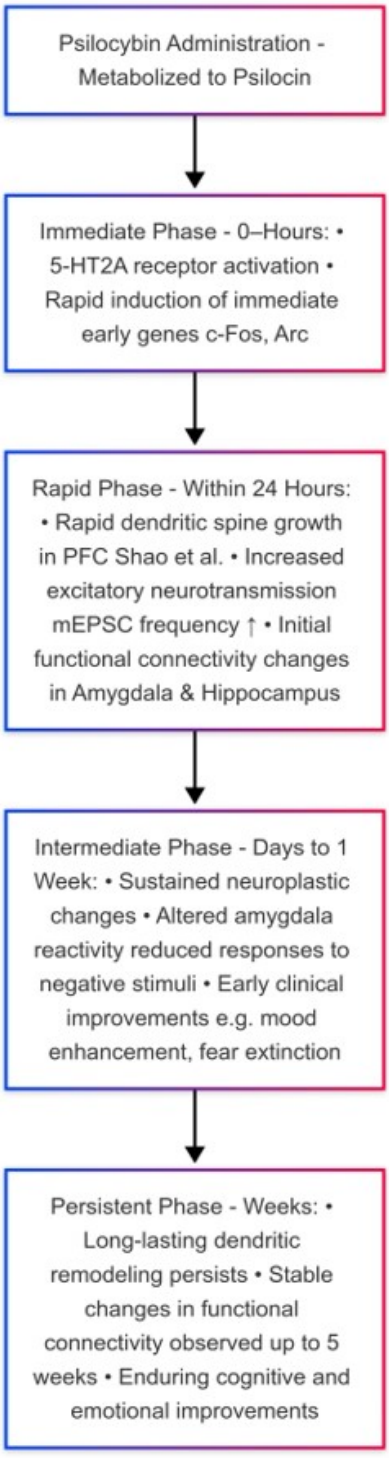

Fig. 2 Model of The Time Course of Psilocybin's Effects

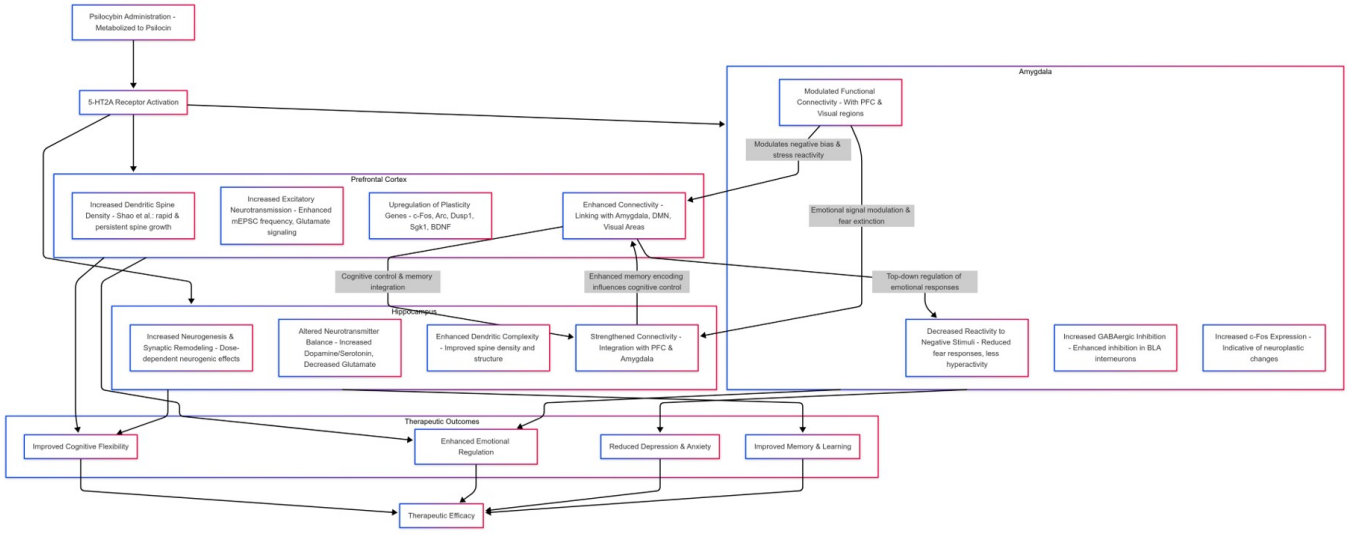

Fig. 3 Unified Mechanistic Model of How Psilocybin's Effects in the Prefrontal Cortex, Amygdala, and Hippocampus Interact

This diagram shows how psilocybin, once metabolized to psilocin, activates 5-HT2A receptors to begin neuroplastic effects. It amplifies dendritic spine density, excitatory neurotransmission, and plasticity gene expression in the Prefrontal Cortex, improving its connectivity with the Amygdala and other regions. In the Amygdala, psilocybin decreases reactivity to negative stimuli, enhances GABAergic inhibition, and modulates functional connectivity to support emotional regulation. In parallel, it supports neurogenesis, synaptic remodeling, and dendritic complexity in the Hippocampus while adjusting neurotransmitter balance. The Prefrontal Cortex exerts top-down control over the Amygdala and Hippocampus, with inter-regional feedback loops reinforcing cognitive control and memory encoding. Together, these coordinated changes lead to enhanced cognitive flexibility, amplified emotional regulation, decreased depression and anxiety, and better memory and learning, leading towards overall therapeutic efficacy.

Limitations and Gaps in Current Research

Long-Term Studies

A significant limitation amongst studies on psilocybin's impact on several brain regions, such as the prefrontal cortex, amygdala, and hippocampus, is the scarcity of long-term research. Most examinations center on the acute results after a single or few treatments of psilocybin, resulting in substantial gaps in our knowledge of the persistence and resilience of the recorded neural modifications. For example, while acute amplification in dendritic spine density and synaptic protein quantities have been recorded, the long-term effect of these modifications and their relationship to maintained behavioral consequences remain unknown. Tackling this void in current research is critical to comprehending the therapeutic possibilities of psilocybin.

Sex Differences and Variability

The fluctuation in individuals' reactions to psilocybin, affected by variables like sex, genetic predisposition, and psychiatric history, makes forecasting psilocybin administration results and customizing therapeutic techniques substantially difficult. Modern studies are constrained in their research of sex-specific reactions, specifically in the amygdala and hippocampus, regardless of their known differences in brain structure, function, and sensitivity to psychiatric disorders amongst males and females. Future investigations should concentrate on understanding these discrepancies to expand more tailored and successful treatment methods.

Cellular-Level Changes

Although research has studied protein expression and rapid early gene reactions post-psilocybin administration, studies specifically analyzing cellular-level modifications such as synaptic density, dendritic spine morphology, and axonal remodeling have been lacking. High-resolution imaging methods and electron microscopy could reveal critical knowledge of the structural changes underlying neural plasticity triggered by psilocybin, specifically in the amygdala and hippocampus.

Variability in Dosage and Administration

Substantial variability in dosage and treatment methods across studies on psilocybin's impact often perplexes studies on its impact. This contradiction obstructs the generalization of results and establishes ideal therapeutic dosing routines. Uniform protocols are required to specify the connection between dosage, administration, and the consequential neural and behavioral outcomes.

Species Differences

The majority of the studies on psilocybin have been tested on animal models, specifically rodents, which aren't able to fully duplicate human neurophysiological reactions. The significance of rodent models to human brain function, particularly in regions such as the hippocampus, remains unclear, requiring more translational studies to patch this void in current research and confirm results are relevant to human brain responses.

Behavioral Correlates

There is a remarkable lack of detailed research bridging psilocybin-induced modifications in neural plasticity to particular behavioral and cognitive responses. For instance, while amplified neuroplasticity has been noticed post-psilocybin administration, the range to which these modifications translate to advancements in memory, learning, emotional regulation, or other behavior assessments is poorly comprehended. Further research should focus on setting up these connections to study the therapeutic potential of psilocybin thoroughly.

Integration of Multimodal Approaches

Much research employs single techniques, such as fMRI, gene expression analysis, or behavioral assessments, but it needs to merge these approaches. A multimodal methodology combining neuroimaging, molecular biology, and behavioral assays could provide a more robust understanding of the systems fundamental in psilocybin-induced synaptic plasticity across multiple brain areas.

Lack of Comparative Studies

Comparative research among psilocybin and other psychedelic or non-psychedelic compounds is limited. Such studies could help us know whether psilocybin presents special advantages in advancing neural plasticity juxtaposed to other therapeutic compounds, therefore assisting in recognizing its relative potency and safety.

Psilocybin's Status as a Schedule I Substance

Psilocybin, for a long time, has been labeled a Schedule I substance, which, according to the Drug Enforcement Administration, is a drug with no currently accepted medical use and a high potential for abuse. Labeling psilocybin in the same category as heroin, cannabis, and methylenedioxymethamphetamine (ecstasy). This, plus psilocybin's federally illegal status in the United States, makes it challenging to perform high-level research on psilocybin's effects on humans and other species and limits the range of possible research on psilocybin. This status could be disputed because much of the research currently performed on psilocybin suggests that it may have therapeutic and potential medical uses.

Overview of Psilocybin Varieties

Psilocybin is discovered in certain mushrooms and exists in various species, each with possibly different levels of psilocybin and related compounds like psilocin. The most researched variety is psilocybe cubensis, which has become the specific focus of modern studies because of its extensive availability and elevated psilocybin substance. Other varieties, like the psilocybe semilanceata (commonly known as "liberty caps") and psilocybe cyanescens, also have psilocybin but are less thoroughly studied.

Conclusion

This review consolidates evidence demonstrating psilocybin's capacity to regulate synaptic plasticity, neurotransmission, and functional connectivity within the prefrontal cortex, amygdala, and hippocampus—regions important for cognitive and emotional control. The studies reviewed display that psilocybin enforces its effects primarily through serotonin 2A receptor (5-HT2A) agonism, leading to downstream molecular and structural adaptations that support neuroplasticity.

In the prefrontal cortex, psilocybin administration has been associated with increased dendritic spine density and excitatory postsynaptic currents, suggesting an enhancement in synaptic integrity and plasticity. These effects are hypothesized to contribute to the observed improvements in cognitive flexibility and emotional regulation, which may underlie its potential antidepressant effects. Additionally, transcriptional analyses reveal that psilocybin alters the expression of immediate early genes (IEGs) such as c-Fos, Arc, and Egr2, which are critical for synaptic remodeling and neuroadaptive responses.

In the amygdala, psilocybin regulates emotional processing by weakening hyperactivity to negative stimuli while amplifying functional connectivity with cortical and visual regions. This may contribute to a recalibration of fear and threat responses, a mechanism potentially relevant to the treatment of anxiety

and trauma-related disorders. Furthermore, psilocybin enhances GABAergic inhibition in the BLA, suggesting a neurophysiological basis for its role in fear extinction and emotional resilience.

In the hippocampus, psilocybin promotes neurogenesis and synaptic remodeling, as evidenced by increased expression of neuroplasticity-associated genes such as Sgk1 and Dusp1. Studies also show modulation of glutamatergic and GABAergic signaling, leading to an altered excitatory/inhibitory balance that may support cognitive adaptation and emotional stability. Functional connectivity changes within the hippocampus and its interactions with the DMN suggest a broader impact on large-scale neural networks involved in self-referential processing and memory integration.

Despite these promising findings, several critical gaps remain. Longitudinal studies are needed to determine the persistence and functional consequences of psilocybin-induced plasticity at the molecular, cellular, and network levels. The dose-dependent effects of psilocybin on neurogenesis and synaptic remodeling require further elucidation, as excessive serotonergic activation may induce maladaptive plasticity. Additionally, research must address individual variability in response to psilocybin, including the influence of genetic predispositions, baseline neurochemical states, and environmental factors.

Future studies should integrate multimodal neuroimaging, electrophysiology, and transcriptomic analyses to comprehensively characterize psilocybin's effects on neuroplasticity. Comparative research with existing pharmacotherapies, such as selective serotonin reuptake inhibitors (SSRIs) and ketamine, may further clarify its unique therapeutic mechanisms. Understanding this will be significant for optimizing psilocybin's clinical uses and understanding its long-term effects for neuropsychiatric treatment.

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