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PSYCHEDELICS: CLINICAL EVIDENCE AND THERAPEUTIC MECHANISMS IN PSYCHIATRY

ABSTRACT

Interest and academic research on psychedelics and psychedelic-assisted therapy in the treatment of psychiatric disorders has increased dramatically in the past two decades. In many ways, psychedelics represent a new therapeutic paradigm in the context of medicine. A key feature of psychedelics is their ability to reliably induce an altered experiential state, which is often described as mystical-like, self-transcending and meaningful, while also often experienced as challenging and anxiety-provoking. The subjective quality and content of the psychedelic experience has been consistently linked to their therapeutic effects. Here we review current understanding of the psychological and neurobiological mechanisms of psychedelics, as well as evidence of psychedelic-assisted therapy in the treatment of psychiatric conditions.

KEYWORDS: PSYCHEDELICS, PSYCHEDELIC-ASSISTED THERAPY, PSYCHOPHARMACOLOGY, DEPRESSION

INTRODUCTION

> *"I suddenly became strangely inebriated. The external world became changed as in a dream. Objects appeared to gain in relief; they assumed unusual dimensions; and colours became more glowing. Even self-perception and the sense of time were changed. When the eyes were closed, coloured pictures flashed past in a quickly changing kaleidoscope. After a few hours, the not unpleasant inebriation, which had been experienced whilst I was fully conscious, disappeared. what had caused this condition?"*
> *-Albert Hofmann, on the discovery of LSD*

Psychedelics are a group of psychoactive substances that include both naturally occurring and synthetic compounds. The so-called "classic psychedelics" include lysergic acid diethylamide (LSD), psilocybin, mescaline, dimethyltryptamine (DMT), and herbal brews such as ayahuasca and yagé which contain DMT and MAO-inhibitors (1). While the neurobiological effects of psychedelics are complex and not fully understood, they all act as partial agonists or agonists at the serotonin receptor 2A (5-HT2A). Other compounds that are broadly considered psychedelic in their effects include MDMA and ketamine. However, the neural mechanisms and subjective effects of these drugs are different, although they also share many features (1,2). In this review, the word "psychedelic" is used to refer to the classic psychedelics which exert their canonical subjective effects primarily through activation of the 5-HT2A receptor.

Since the discovery of the psychoactive effects of LSD and mescaline in the West in the 1940s, psychedelics have drawn broad interest and enthusiasm as well as controversy. Initially psychedelics were suggested to mimic acute psychosis, which led to research attempting to illuminate the aetiological mechanisms of schizophrenia (1,3). This psychotomimetic paradigm has since been rejected, as it fails to adequately capture the nature of psychedelic experiences. However, the psychedelic state was also thought to uncover repressed or forgotten memories, and increase emotional connection to the unconscious mind, which spurred early interest for the study of psychedelics as therapeutic tools (3). From the 1940s to 1970s, an estimated 40 000 individuals were

treated with psychedelic-assisted psychotherapy, mostly using LSD but also psilocybin (1). Early trials investigating the effectiveness of psychedelics in the treatment of depression, anxiety and substance use disorders showed promising results (3,4). These studies, however, lacked the methodological standards of modern clinical trials. The popularization of psychedelics, their widespread non-medical use and their association with the counterculture of the 1960s eventually led to their criminalization, which effectively halted clinical research advances. In the past decades, however, a new wave of interest in psychedelic research, dubbed the psychedelic renaissance, has emerged (1-3).

Psychedelics are unique in their ability to consistently induce intense, immersive experiences that are often felt as highly significant and can lead to lasting therapeutic effects (5). The psychedelic experience is typically described as transcendental and deeply meaningful (1,2,5). Psychedelics induce broad alterations in perception, cognition, affect, and importantly, changes in the experience of selfhood, such as ego-dissolution and self-transcendence (2,5). Perceptual effects include visual distortions, illusions and pseudo-hallucinations (i.e. perceptions of hallucinatory objects or entities that are distinguished from ordinary external reality). Cognitive and affective effects include mood changes and emotional lability, euphoria and bliss (2,5). On the other hand, the psychedelic experience also tends to be challenging, with participants often reporting increased anxiety, uncertainty, loss of control and disorientation, and even (although less commonly) dissociative and psychotic symptoms (2,6). Importantly, the adverse psychological effects are less common in a safe and controlled environment, as discussed in more detail below.

Unlike traditional psychopharmacology treatments like antidepressants or anxiolytics, which aim to alleviate symptoms and improve daily functioning by altering neurochemistry and neuroplasticity, psychedelics do not require continuous treatment, which can be considered as an advantage regarding long-term safety (6). Another unique feature of psychedelic pharmacotherapy is their ability to induce intense subjectively meaningful experiences, which are linked to their therapeutic effects (7-8). In some respects, the therapeutic mechanisms of psychedelics resemble those of psychotherapy, as they involve processing of meaningful autobiographical content, insights and emotional breakthroughs. However, the experiences induced by psychedelics are rather more perplexing and radical compared to traditional psychotherapy, as they involve mystical-type and other self-transcendent experiences reaching beyond autobiographical content. Thus, psychedelic-assisted therapy is a markedly distinct and novel treatment modality in modern psychology and psychiatry. Here we review the evidence of the therapeutic potential and mechanisms of classic psychedelics in the treatment of psychiatric disorders, focusing on their neurobiological and psychological mechanisms.

CLINICAL RESEARCH

As mentioned above, psychedelics have predominantly been researched in two waves; first prior to their criminalization from the 1940s to 1970s, and then in the 21st century during the so-called psychedelic renaissance. In medicine, psychedelics have been studied mostly in the context of psychiatry and neuroscience. Here we review existing clinical research on psychedelics, focusing on clinical trials in the 21st century. We limit our scope to psychiatric conditions in this review, although anecdotal and preliminary evidence also suggests potential in treating some neurological and somatic disorders such as migraine and cluster headache, as well as chronic pain (9).

PSYCHOLOGICAL DISTRESS RELATED TO LIFE-THREATENING ILLNESS

Those diagnosed with a life-threatening illness, such as cancer, often develop clinically significant distress in the form of anxiety and depression, as well as feelings of helplessness, despair and loss of meaning, all of which can understandably be difficult to alleviate and resistant to treatment efforts (10). As the psychedelic experience often touches upon questions of one's existence and meaningfulness, it has been seen as a potential aid in reducing the suffering of those with life-threatening illnesses (10).

In the 1964 first study using psychedelics in terminally ill cancer patients to investigate the analgesic potential of LSD, authors observed that many patients receiving LSD talked openly about their illness, and showed a reduced fear of death (11). Modern studies have continued this line of research, investigating the psychological benefits of psychedelics in patients who are terminally ill or suffering from a life-threatening illness. A recent systematic review and meta-analysis found five trials predominantly on cancer patients assessing depressive and anxiety symptoms (12). The meta-analysis reported significant reductions in state and trait anxiety as well as depressive symptoms in those receiving

psychedelics compared to groups receiving control therapy. However, patient numbers per trial were low and the results showed high heterogeneity. Control groups also differed, from passive placebo to niacin and low-dose psilocybin or LSD (12). A more recent phase II randomized, placebo-controlled, double-blind crossover study, investigating the effects of LSD on psychiatric symptoms, included 20 patients with a life-threatening illness. The treatment group showed rapid and strong reductions in depressive and anxiety symptoms, lasting until the follow-up at 16 weeks after the second dosing (Cohen's d=-1.26 in general anxiety and d=-1.55 in depression scores at long-term follow-up) (13).

MOOD DISORDERS

Dozens of studies in the past decade have investigated the effectiveness of psychedelics for mood disorders. Most studies have investigated patients suffering from clinical depression, including treatment-resistant depression (9,14). The high prevalence and disease burden of depression, combined with the limited efficacy of current treatments, make the search for novel treatments particularly important.

Early studies using LSD to treat 'psychoneurotic' problems (a term corresponding to a variety of depressive and anxiety disorders in modern nomenclature) reported substantial benefits in the majority of participants (3). In modern clinical trials, Griffiths et al. (2006) were the first to show in healthy participants that psilocybin reliably induced mystical-type experiences that were associated with long-lasting beneficial effects on mood, as well as positive attitudes about self and one's life (5). Subsequent studies have found similar benefits in patients suffering from clinical depression (9,14). A recent systematic review and meta-analysis found 16 randomized controlled trials (10 studies used a passive placebo, 4 studies used a low-dose psychedelic, and 2 studies used an active drug placebo) with a total number of 472 participants investigating psilocybin, and 2 randomized placebo-controlled trials with a total number of 31 participants investigating ayahuasca in the context of clinical depression (9). Both psychedelics improved depressive symptoms, with psilocybin showing a slightly larger therapeutic effect compared to ayahuasca (Hedge's g -1.47 vs. -1.20). Additionally, one recent open-label trial suggested that psilocybin combined with psychotherapy is safe and potentially effective in the treatment of bipolar disorder type II (15). As an important preliminary finding, two studies have also reported robust reductions in suicidality following treatments with psilocybin and ayahuasca (Hedge's g=2.46 and g=1.81, respectively) (9).

One phase II double-blind RCT compared two doses of psilocybin with daily treatment with the antidepressant drug escitalopram, with both groups receiving psychological support. In the primary outcome measure of depressive symptoms, psilocybin was equal to escitalopram. The psilocybin group showed higher rates of remission (57%) compared to the escitalopram group (27%), but the difference was not significant after correcting for multiple comparisons (16). Finally, a recent phase II trial enrolled 104 participants with major depressive disorder to receive either a single dose of psilocybin or niacin with psychological support. They reported substantial reductions in depressive symptoms (MADRS score mean change difference 12.3 points) as well as functional disability (Sheehan Disability Scale mean change difference 2.31 points) in the psilocybin vs. active placebo group. There were no significant differences in remission rates, but 42% of participants in the psilocybin group showed a sustained response in depressive symptoms, compared to 11% in the niacin group (17).

In terms of patient experiences in depression, one of the most important subjective themes in psychedelic treatment is a restoring of a sense of connectedness via mystical-type experiences (18,19). Participants describe a healing reconnection to their own emotions and different parts of themselves, to other people, and to nature. As discussed below, the ability of psychedelics to induce states of experiential connectedness may be an important therapeutic mechanism particularly in conditions that are characterized by a sense of isolation and lack of meaningfulness. Other themes relevant to depression and anxiety in the psychedelic experience include processing of autobiographical events and memories, insights and novel perspectives into the psychological mechanisms sustaining one's symptoms, altered self-perception and identity change, expanded emotional spectrum and self-transcendent experiences (18,19).

SUBSTANCE USE DISORDERS

In early studies investigating LSD-assisted psychotherapy in the 1950s, alcohol use disorder was one of the most promising and popular treatment targets. Krebs & Johansen (2012) conducted a meta-analysis from early studies investigating LSD-assisted therapy for alcohol use disorder, covering 6 RCTs, with a total of 536 participants. They found an odds ratio of 1.96 for reducing alcohol misuse, and 1.8 for complete abstinence in LSD groups compared to controls. Individual early studies also showed

benefits of LSD for heroin use disorder (4).

In the 21st century, individual studies have investigated the effectiveness of psychedelic-assisted therapy for alcohol use disorder, tobacco use disorder, as well as opioid use disorder. In the first open-label study of psilocybin combined with motivational enhancement therapy, psilocybin rapidly reduced heavy drinking days, as well as alcohol craving, which remained significantly lower at 36-week follow-up (21). The findings were replicated in a subsequent RCT of 93 participants, which reported reduced mean daily alcohol consumption as well as less heavy drinking days (10% vs. 24% of heavy drinking days) in the psilocybin vs. the active control group (22).

Regarding tobacco use disorder, Johnson et al. conducted an open-label study with 15 participants seeking help with smoking cessation. They combined cognitive behavioural therapy with 2-3 doses of psilocybin, and confirmed tobacco use by measuring urine cotinine levels. Tobacco abstinence was confirmed in 80% of the participants at 6-month follow-up, with the majority reporting immediate smoking cessation after psilocybin administration (23).

In addition to classic psychedelics, ibogaine, an atypical psychedelic with a polypharmacological profile including opioid receptor agonism, has shown promise in preclinical and observational studies in the treatment of substance use disorders, particularly opioid use disorder (20).

2.4 Anxiety disorders and post-traumatic stress disorder (PTSD)

Several clinical trials on psychedelics have included anxiety symptoms as an outcome measure. However, few have specifically attempted to target anxiety disorders. A recent RCT investigating psychedelic-assisted therapy with 2 sessions of LSD or placebo, enrolled 46 patients suffering from anxiety with and without a life-threatening illness. They reported significant and large reductions in global anxiety as well as depressive symptoms (Cohen's d=1.18 and d=1.1, respectively) 16 weeks after treatment (13). Although promising results have been obtained for MDMA-assisted therapy in the treatment of PTSD, we found no modern trials investigating classic psychedelics in treating PTSD. Earlier psychedelic studies in the 1960s and 1970s included patients with trauma-related symptoms, including concentration camp survivors (24). The studies reported marked improvement in the majority of subjects, but no firm conclusions can be drawn from these because of the limitations in methodology and changes in diagnostic categories over time. Regarding other anxiety disorders, preliminary studies have shown potential effectiveness in treating obsessive-compulsive disorder, but no randomized trials have been conducted thus far (9).

In addition to the conditions outlined above, retrospective and pilot studies, as well as preclinical evidence, have suggested a potential for psychedelics in the treatment of body dysmorphic disorder, borderline personality traits, functional neurological symptoms and chronic pain. Here, the evidence remains preliminary (9).

OPEN QUESTIONS AND CHALLENGES FOR CLINICAL RESEARCH

Safety and adverse effects

In clinical studies, psychedelics have generally shown a good safety profile and tolerability. Although unsupervised psychedelic use can be abusive, posing a risk for the safety of the user, they are not considered addictive (9, 25). In preclinical studies psychedelics do not elicit reinforcement effects (25). Cardiovascular effects, i.e increased blood pressure and heart rate, are modest, and no evidence of organ damage, neurotoxicity or neuropsychological dysfunction has been observed with classic psychedelics (25). The most common physical adverse effects of psychedelic drugs are nausea, gastrointestinal discomfort, vomiting, diarrhoea, headache and dizziness. These reactions are predominantly mild, and transient (6). Common psychological adverse effects are dysphoric reactions, anxiety and panic symptoms, sometimes with psychotic-like features. These effects are nearly always transient, and prolonged psychotic reactions have not been observed in clinical settings in the past 25 years (6). As discussed below, the set and setting, meaning the subject's mental state and environmental context, are important factors in mitigating potential harms. The potential anxiety-provoking and emotional lability effects of psychedelics have to be taken into account when selecting participants for clinical studies. However, meta-analyses suggest a good safety profile regarding suicidality. On average, psychedelics seem to reduce suicidality although studies with larger sample sizes are needed to affirm this (9).

One potential serious adverse effect concerning specifically psychedelics, is hallucinogen persisting perception disorder (HPPD), in which users can re-experience the perceptual effects that occur under the influence of psychedelics. These are most commonly visual perceptual distortions and flashbacks, which may be disturbing and impair functioning. The incidence of HPPD is unknown, but is considered very low (25).

Another class of safety concerns arise from the fact that patients are highly vulnerable and hyper-suggestible in a psychedelic state, stressing the need for informed consent and protocols that minimize the potential for therapist misconduct.

The problem of placebo control

One interesting and difficult challenge in psychedelic research is the question of placebo control. If we assume that the subjective psychedelic experience is an important element in the therapeutic effects, it is very difficult to plan experimental designs with adequate blinding. Therefore, it is a valid concern that expectancy effects may inflate effect sizes in clinical studies (14). Some studies have used active controls such as niacin or the antihistamine diphenhydramine, or administered low doses of the investigated psychedelic in the control group, but so far, no ideal solution has been discovered to the problem of placebo.

THE ROLE OF SUBJECTIVE EXPERIENCE AND CONTEXTUAL FACTORS IN PSYCHEDELIC-ASSISTED THERAPY

The intriguing nature and therapeutic effectiveness of psychedelic experiences, as observed in clinical trials, have driven efforts to understand their therapeutic mechanisms. Mapping and exploring the mechanisms of psychedelic-assisted therapy has become a key focus in the recent resurgence of psychedelic research (8,26-27). However, understanding these mechanisms is challenging due to the multiple levels at which psychedelics operate, from neurobiological to psychological, relational, and spiritual phenomena. This complexity is further compounded by the sensitivity of psychedelics to contextual factors and the intricate interplay of various mechanisms across different levels. Therefore, making sense of psychedelics and psychedelic-assisted therapy is arguably one of the most complex tasks in psychopharmacological research.

According to one position, supported by evidence from preclinical studies with rodents (28-29), the therapeutic benefits of psychedelics are solely due to their neurobiological effects, rendering subjective experiences as causally insignificant. This perspective has led to questions about whether therapeutic neurobiological changes could be induced without altered states of consciousness, and the need for research programmes to develop 'non-hallucinogenic' psychoplastogens (30). While it's debated whether subjective effects are essential for psychedelics' therapeutic benefits, and whether these psychoplastogens, if feasible, should be preferred over psychedelics in healthcare, currently non-subjective psychoplastogens remain rather a theoretical possibility than actual treatment modality (8).

However, compelling evidence supports the centrality of subjective experience for psychedelic-assisted therapy, with numerous findings suggesting that subjective effects predict therapeutic outcomes. Remarkably, evidence suggests that rather than intensity of experiences, the quality and content of subjective experiences, such as the degree of mystical-type experiences and the occurrence of psychological insight and emotional breakthroughs, predicts therapeutic outcomes and other positive long-term effects (7-8,31-32).

Another line of research which supports the idea that subjective experiences are crucial for psychedelic-assisted therapy is the well-known context-dependent nature of their effects, often referred to as 'set and setting' (33). Factors such as the user's background, intentions for use and the cultural and environmental context significantly influence the psychedelic experiences. Psychedelics are known to increase suggestibility and amplify meaning, making the user extremely sensitive to contextual cues and priming (34-35). Therefore, clinical trials are conducted in carefully crafted settings, often combined with psychotherapeutic treatments. While psychedelics can improve wellbeing in non-clinical settings, the therapeutic setting, intentions and synergy with other therapeutic practices are essential for maximizing their potential as therapeutic agents. Thus, there are good reasons to assume that understanding psychedelics' mechanisms of action requires considering subjective and psychological effects, likely correlated with network-level neural changes (8).

Understanding the various changes induced by psychedelics in a unified way is a central challenge in psychedelic research. Currently, we lack a comprehensive understanding of the basic therapeutic changes, let alone their interactions or the higher-order patterns and mechanisms that underpin these therapeutic mechanisms. It remains an open theoretical question whether an integrated account of the various mechanisms of psychedelics will emerge, or whether the mechanisms of psychedelics span multiple explanatory levels that cannot be reduced solely to neurobiological or psychological mechanisms (8).

As both the phenomenology and neurobiology of psychedelics is complex and diverse, it is also possible that partially separate mechanisms contribute to the therapeutic

effects in different conditions. As an example, participants with depression tend to report increased connectedness to their feelings, other people and the world; whereas those suffering from a life-threatening illness often describe a confrontation with existential questions and their fear of death (10,11,18). In the following sections, we review the proposals for the mechanisms of psychedelic-assisted therapy, first on the neurobiological and then on the psychological level.

NEUROBIOLOGICAL MECHANISMS OF PSYCHEDELICS

Classic psychedelics share the same pharmacologic core structure comprising an aromatic group separated from a basic amine by a two-carbon linker and can be further divided into three main classes of chemical compounds. These include naturally occurring tryptamine analogues (such as psilocybin and DMT), semi-synthetic ergolines (such as LSD) and phenylalkylamines (such as mescaline). They can readily cross the blood-brain barrier due to their small size and relative hydrophobicity leading to high brain-to-plasma ratios. While their hallmark subjective effects, such as the mystical-type experiences, are primarily mediated via agonism or partial agonism at the 5-HT2A receptor, the exact neurobiological mechanisms, through which psychedelics exert their promising therapeutic effects, are not currently fully understood. In this section, we review the mechanisms of action of psychedelics, focusing on substances which are currently most commonly used in clinical trials and the mechanisms which are most robustly linked to the therapeutic effects (1,2,28,30).

RECEPTOR LEVEL MECHANISMS AND CELLULAR SIGNALLING

Psychedelics have complex receptor level pharmacology, binding to several biogenic monoamine G protein-coupled receptors with clinically meaningful affinities. Tryptamine analogues psilocin, the active metabolite of psilocybin which is found in several species of fungi, and DMT, which is found in varying amounts in several plants and contained in the traditionally used plant-based brew ayahuasca, act as partial agonists at 5-HT1, 5-HT2, 5-HT5, 5-HT6 and 5-HT7 receptors (29-30). LSD, which can be derived from naturally occurring ergot alkaloid lysergic acid, has agonist activity at almost all (12 of 14) human 5-HT receptors, α1 and α2 adrenergic receptors and all five dopamine receptors (D1, D2, D3, D4 and D5) (30). Mescaline, naturally found in some species of cacti (e.g. lophophora williamsii), is less studied but has been shown to act as an agonist at 5-HT1A, 5-HT2A,B and C receptors (36). Agonism at dopaminergic receptors and antagonism at α2 receptors may also contribute to the effects of mescaline. In addition to monoamine receptors, psychedelics have been shown to activate TAAR1 trace amine receptors (36-37) and bind to tropomyosin receptor kinase B (TrkB) receptor - the receptor for brain-derived neurotrophic factor (BDNF) (38). Moreover, DMT, which has been shown to be endogenously produced in the tissues of several mammalian species, including humans (39), activates σ1 receptors (40). Agonism at σ1 receptor has been shown to modulate the behavioural effects of DMT and protect against hypoxic-ischaemic brain injury in preclinical studies (40-41).

Despite the difference in their chemical structure and receptor binding profiles, psychedelics produce remarkably similar subjective experiences in humans. Converging evidence from clinical and preclinical trials support the conclusion that their canonical psychedelic effects are primarily mediated via agonistic actions at the 5-HT2A receptor. For example, it has been shown that pretreatment with 5-HT2A antagonist ketanserin abolishes the psychedelic effects of psilocybin and LSD and markedly reduces the effects of ayahuasca (which in addition to DMT contains various psychoactive harmala alkaloids) (42-44). Furthermore, the intensity of psilocybin-induced subjective effects has been shown to be well correlated with cerebral 5-HT2A receptor occupancy (45). Consistently, 5-HT2A knockout mice lack the psychedelic-induced head-twitch response (a behavioural proxy of psychedelic effect) and selectively restoring 5-HT2A receptor expression in the cortical neurons has been shown to recover head-twitch response to LSD administration (46). This suggests that psychedelic effects could be mediated via 5-HT2A activation especially in the cortex.

Intriguingly, not all 5-HT2A receptor agonists, such as lisuride and recently developed non-psychedelic psychoplastogens such as TBG (47), produce psychedelic effects despite high receptor affinities. It has been proposed that 5-HT2A-mGlu2R complex binding is necessary for psychedelic effects, supported by evidence of abolished head-twitch response in mGlu2 knockout mice (48). In addition, a recent study showed compelling preclinical evidence that psychedelic potential is dependent on 5-HT2A-Gq-PLC pathway and Gq-efficacy (which was shown to be high for

psychedelic and low for non-psychedelic 5-HT2A agonists) but not on β-arrestin2 recruitment (49).

Since the research has mostly focused on the 5-HT2A receptor as the mediator of both subjective and therapeutic effects of psychedelics, there is a relative lack of understanding of the contribution of other receptor targets. Pretreatment with dopamine antagonist haloperidol did not block psilocybin-induced subjective effects but actually increased effects measured with the dread of ego-dissolution psychometric rating subscale (36). The 5-HT1A receptor has been shown to modulate the subjective effects of psychedelics (43), and recent preclinical evidence suggests a significant contribution of the 5-HT1A receptor in the therapeutic effects of 5-MeO-DMT and a possibility to design non-psychedelic 5-methoxytryptamine which could retain therapeutic efficacy (50).

NEUROPLASTICITY AND CRITICAL PERIOD REOPENING

A remarkable feature of psychedelics is the ability to produce sustained therapeutic effects lasting several months after single administration (5,9-10). While the subjective effects and related psychological mechanisms, reviewed later in this article, are implicated, explanations at the neurophysiological level have been related to their capacity to induce neuroplasticity.

Neuroplasticity can be defined as a process which mediates the expression of external and internal environment of an individual in neuronal structure and function through development and learning (51). Moreover, it has a crucial role in the capacity of the brain to evaluate and store information, and adapt to a dynamic environment. Many stress-related psychiatric conditions, such as major depressive disorder (MDD), substance use disorder (SUD) and PTSD, have been associated with cortical atrophy, synaptic weakening and loss of connectivity, especially in the prefrontal cortex and hippocampus, consistent with dysregulation of neuroplasticity (46). A growing body of evidence from preclinical studies suggests that psychedelics may restore these pathological changes by inducing structural and synaptic plasticity (52).

Psychedelics engage several signalling pathways associated with neuroplasticity. 5-HT2A receptors are typically coupled with Gq and β-arrestin, and the activation of these pathways can lead to production of brain-derived neurotrophic factor (BDNF) (58). Activation of presynaptic 5-HT2A receptors can lead to a glutamate burst resulting in subsequent activation of postsynaptic AMPA receptors engaging synaptogenic signalling cascades involving BDNF and mTOR (52). Binding of BDNF to its receptor, TrkB, activates signalling pathways including mTOR-mediated signalling, leading to neuritogenesis, spinogenesis and synaptogenesis (54). While Ly et al. (54) found evidence that psychedelic-induced neuroplasticity is dependent on 5-HT2A, TrkB and mTOR activation, since blocking these targets with their respective antagonists, ketanserin, ANA-12 and rapamycin, also blocked psychedelic-induced plasticity, others have found evidence that neuroplastic effects can be elicited independent of 5-HT2A activation (38,55-56). Moreover, Moliner et al. (2023) showed that psychedelics bind directly to TrkB receptor with high affinity, allosterically facilitating the effects of endogenous BDNF released from active synapses, and can rapidly increase translocation of TrkB receptors from intracellular vesicles to the cell surface thus making them available for BDNF binding (38). In a recent study, Vargas et al. (57) showed that psychedelics promote plasticity by activating intracellular, rather than cell-surface 5-HT2A receptors, providing possible explanation why serotonin does not produce psychedelic-like effects on neuronal growth. Additionally, psychedelics are also known to increase the expression of immediate early genes (IEGs) associated with neuroplasticity and induce transcriptional regulation of the extracellular matrix, suggested as a convergent mechanism for lasting cellular changes induced by classic and non-classic (e.g. ibogaine, ketamine and MDMA) psychedelics (58).

Intriguingly, it has recently been shown that psychedelics can reopen the social reward learning critical period, the time course of which is proportional to the duration of their acute effects in humans, lasting up to two weeks for psilocybin and up to three weeks for LSD (58). Importantly, these results imply that psychedelics induce metaplasticity (rather than hyperplasticity), which can be described as regulation of the extent to which synaptic plasticity can be induced (59). Moreover, it is important to note that plasticity itself does not have any predetermined direction. Rather, whether the connections are strengthened and maintained or eliminated is determined by the experience-dependent activity in the neural networks, implying that plasticity can be adaptive or maladaptive depending on the context (51). The context-dependent nature of plasticity has important implications for psychedelic-assisted therapy, emphasizing the importance of proper guidance not only during the acute effects, but also throughout the whole critical period window.

SYSTEMS NEUROSCIENCE MECHANISMS

5-HT2A receptors are highly expressed in the cortical layer 5 pyramidal neuron apical dendrites, especially in the prefrontal cortex (44). Additionally, they are expressed in inhibitory GABAergic interneurons and subcortical structures, such as the thalamus. Psychedelics have been shown to produce a net excitatory effect in most cortical pyramidal neurons, consistent with increased brain glucose metabolism in most cortical and subcortical areas after psilocybin administration (60). In the past decade, several neuroimaging studies have investigated the acute effects of psychedelics on brain activity, connectivity and network dynamics. Functional magnetic resonance imaging (fMRI) studies have consistently found reduced functional integration within and increased integration between most large-scale brain networks, suggesting a shift towards increased global integration (61). Increased cross-talk between segregated brain areas could contribute to associative thinking and insights experienced during acute psychedelic experience. Especially, decreased within-network connectivity in the default mode network, which is associated with self-related processing and ruminative thinking patterns could have implications in the therapeutic effects of psychedelics. Consistently, decreased network modularity after psilocybin treatment has been associated with long-term reductions in depression scores 6 weeks and 6 months post-treatment (62). Another consistent finding in fMRI studies is increased connectivity between thalamus and sensory areas, supporting the decreased thalamic gating (44). Both magnetoencephalography (MEG) (63) and fMRI studies (61) have shown that psychedelics acutely increase spontaneous signal diversity, which could be associated with phenomenally rich experiences and departure from rigid thinking associated with psychiatric conditions, such as MDD, towards exploration of novel views of one's situation and flexible thinking patterns.

THEORIES OF PSYCHEDELIC ACTION

Recently, theoretical frameworks have been proposed in an attempt to explain how psychedelic-induced phenomenology could emerge from known neuronal and network mechanisms. As the presented models are based on different observations or assumptions, they could be viewed as complementary, rather than mutually exclusive frameworks for understanding the psychedelic effects.

The cortico-striato-thalamocortical (CSTC) model suggests that psychedelics alter thalamic gating by stimulating 5-HT2A receptors located within several parts of CSTC loops, resulting in feedforward information overload of the cortex and aberrant cortico-cortical integration and neuronal activity. It proposes that this leads to characteristic psychedelic effects of altered sensory perception and cognition as well as ego-dissolution. The CSTC model is supported by impaired sensorimotor gating after administration of psilocybin or LSD and increased thalamic functional connectivity (44).

The cortico-claustro-cortical (CCC) model proposes that psychedelics disrupt signalling between prefrontal cortex and claustrum by 5-HT2A-mediated mechanisms resulting in inappropriate ability of association networks to respond to changing task demands. In support, an fMRI study has found reduced functional connectivity between claustrum and prefrontal cortex after psilocybin administration (30).

The relaxed beliefs under psychedelics (REBUS) and anarchic brain model (2) integrates the free energy principle, which is closely related to hierarchical predictive coding, and the entropic brain hypothesis to inform psychedelic action and therapeutic mechanisms. It proposes that by inducing a heightened state of brain entropy via 5-HT2A-mediated mechanisms, psychedelics reduce the precision weighting of high-level priors (predictions, expectations or beliefs about internal and external environments) coinciding with liberation of bottom-up signalling. Relaxation of the high-level priors is proposed to lead to decreased top-down and increased bottom-up information flow, enabling the brain to explore a wider range of explanations and to enable revision of rigid prior beliefs encoded deep in the brain's functional architecture. In contrast, other models suggest that certain priors may also strengthen during psychedelic experiences. The strong priors (SP) model suggests that hallucinations involve decreased bottom-up signalling coupled with aberrant top-down expectations (30).

THE PSYCHOLOGICAL MECHANISMS OF PSYCHEDELIC-ASSISTED THERAPY

This section reviews the main proposals for psychological mechanisms of psychedelic-assisted therapy, focusing on: 1) psychological and experiential processes during the acute experience, and 2) mid- and long-term changes in psychological skills, personality traits, values, beliefs and capacities post-experience. The key research task has been to identify relevant aspects of the acute experience and mid/long-term changes, and correlate these with reductions in symptoms of mental health disorders and improvements

in wellbeing. Data on various psychological mechanisms primarily come from studies using validated psychometric questionnaires and qualitative reports from both clinical and non-clinical settings.

NOVEL PERSPECTIVES AND OPENING OF THERAPEUTIC WINDOW

A key factor in the therapeutic efficacy of psychedelics may be their ability to increase the malleability of our experience and loosen entrenched cognitive and emotional patterns. Psychologically, these entrenched patterns can be seen as maladaptive cognitive schemas, and increased malleability as psychological flexibility. As stated by the REBUS model, psychedelics are believed to destabilize higher-order priors or beliefs, inducing states of less constrained cognition where new perspectives become more accessible (2,64-65). This can be particularly beneficial for mental health issues characterized by rigid patterns of thought, emotion and behavior, and a maladapted narrowed sense of self, identity and possibilities (66). By temporarily overcoming and untangling these maladaptive and rigid perspectives, psychedelics may lead to potentially more adaptive perspectives, which often emerge from the therapeutic context and self-transcendent experiences (34,64).

One way these novel perspectives manifest are as various therapeutically relevant insights, a phenomenon linked to the combination of relaxed prior beliefs and increased neuronal entropy (2,64). Psychedelics can induce insights ranging from one's personal behaviour and values to interpersonal dynamics, and even to spiritual, ethical and societal issues. These insights can be existentially and therapeutically significant, potentially leading to long-lasting changes in cognitive schemas, beliefs and values (32,67).

In the long-term, these processes occurring during psychedelic experiences may contribute to the learning of new perspectives, ways of orienting and skills in a therapeutically beneficial way. As noted, through their neuroplasticity-inducing and psychological effects, psychedelics can open a therapeutic window, an enhanced learning period post-experience, during which new perspectives and insights can be consolidated (8). Therefore, psychedelics may lead to extended processes of behavioural change, identity formation and learning, concerning psychological skills, emotional capabilities, attitudes and self-related beliefs, depending on the specific psychedelic experience and therapeutic work post-experience (34,65). This 'integration period' is considered crucial for successful psychedelic-assisted therapy, and various integration practices have been suggested, although evidence-based research into the integration of psychedelic experiences is limited (68).

FACILITATION OF PSYCHOTHERAPEUTIC PROCESSES AND SKILL LEARNING

Psychedelics can facilitate common psychotherapeutic processes, an approach historically associated with psycholytic therapy. In a therapeutic setting, psychedelic experiences can activate resources, improve therapeutic relationships, and aid in confronting and understanding personal problems (27). Psychological insights into personal goals, values and maladaptive patterns have been correlated with therapeutic improvements (32,69-70). Psychedelic experiences often involve emotionally charged autobiographical material, and can enhance the depth of affective processing, associative thinking, and capacity to process personal issues insightfully, indicating lowered psychological defences and enhanced meaning-making abilities (71). Psychedelics may inherently reward experiential acceptance and discourage experiential avoidance, leading to confrontation with and acceptance of previously difficult emotional content (72). These kinds of emotionally resolving experiences are encapsulated in the concept of 'emotional breakthrough' (73). Psychedelics can also foster (self-)compassion, decentring and mindfulness, enabling more accurate metacognitive observation of conscious experiences with less reactivity – traits that can also increase long-term (74).

Converging with mechanisms proposed in third wave cognitive therapies, these psychotherapeutic processes may contribute to long-term learning of relevant psychological and metacognitive skills, reducing rigid and maladaptive behaviour and thought patterns seen in mental health disorders. Psychedelic-assisted therapy has been observed to increase psychological flexibility, which mediates decreases in mental health symptoms and encompasses aforementioned processes related to awareness and acceptance, as well as capacity for valued action (70,72). Similarly, cognitive flexibility, the ability to adaptively switch between different behaviours, appraisals, attitudes and reactions, has been observed to increase after psychedelic experiences (8).

SELF-TRANSCENDENT EXPERIENCES AND ENHANCED CONNECTION TO SOURCES OF MEANING IN LIFE

One of the most consistent findings in psychedelic research is that therapeutic improvements are mediated by various self-transcendent experiences, such as mystical-type experiences, ego-dissolution experiences, and self-transcendent emotions like awe and a sense of connectedness (5-6,65,69). Conceptually and phenomenologically, these experiences co-occur: mystical and ego-dissolution experiences are often prominent during the peak of the psychedelic trip, and less intense forms of self-transcendence occur at less intense phases or with lower doses. Theoretically, self-transcendence may be explained as the deconstruction of our ordinary sense of self and the broadening of attention and salience attribution (64,67,75). An important replicated finding is that participants receiving psychedelics in controlled settings often regard the experience as one of the most meaningful and spiritually significant events in their lives (5). Congruently, many cultures have used psychedelic substances in religious, ceremonial and ritual healing contexts, to enter altered states of consciousness that are considered helpful in healing illness and to attain insight (1).

A key aspect of the psychedelic state is what has come to be called mystical-type experiences, characterized by a positive mood state or euphoria, a sense of deep meaningfulness, transcendence of space and time, insight, sacredness and unity, sense of ineffability, and noetic and spiritual significance as well as the dissolution of self-boundaries (2,5,64). The depth of the mystical-like and ego-dissolution experiences have been consistently found to predict the therapeutic effects of psychedelics (6,7).

The concept of mystical experiences was originally formalized and brought into psychology by William James and later adapted into psychometric scales first by Walter Stace in the context of early psychedelic research (64). The concept's feasibility is debated due to its religious connotations and alleged perennialist assumptions (76). Ego-dissolution experiences, a less contentious and commonly used construct to describe psychedelic experiences, singles out experiences where the boundary between self and the world dissolves and self-referential processing diminishes or stops (75).

Various emotional and relational experiences can also be classified as self-transcendent, and may be crucial for the efficacy of psychedelics. Prominent among these are feelings of awe, compassion, love, gratitude, fascination, wonder, a sense of sacredness, and an enhanced sense of connection to oneself, others, the world and one's core values (18,64,67). Psychedelic experiences can also involve strong positive affect, which may work synergistically with self-transcendence to shift attention towards positively valenced sources of meaning and break patterns of negative emotionality and thought dominant in mental health disorders (64).

A plausible hypothesis is that through self-transcendence, psychedelics can shift and broaden one's attention away from self-centred concerns towards the wider world and positive sources of meaning and value, such as other people, the natural world and universe at large (65,67). The observed psychedelic value changes are often shifts towards self-transcendent values such as increases in pro-environmental, prosocial and spiritual values and associated behavioural changes (67). Positive experiences and self-transcendence in psychedelic experiences can lead to a positive feedback loop between reduced self-salience and attentional broadening, as posited by 'self-entropic broadening theory' (64). These experiences may lead to lasting changes in attitudes and orientation, which could be particularly important in disorders like depression and anxiety, which often involve negative, repetitive self-referential processing often manifested as rumination and guilt, feelings of deep isolation and a sense of meaninglessness (18,66). Excessive self-referential processing can narrow one's attention and sense of life possibilities, hindering connection to values and other sources of meaning, thereby exacerbating negative affective states in a vicious self-reinforcing cycle. Psychedelic experiences might temporarily disrupt these maladaptive patterns, engendering highly meaningful broadened states that enhance one's connectedness to the world and others, fostering a more adaptive orientation to the world. This hypothesis is supported by correlations between reductions in mental health symptomatology and self-transcendent experiences, as well as qualitative patient reports (5-8,18,67,69).

CHANGES IN PERSONALITY AND BELIEFS

Psychedelic experiences have been observed to have various potentially therapeutic effects on personality structure, attachment styles and beliefs. Psychedelics can increase openness to experience, extroversion, and decrease neuroticism, potentially broadening attentional and behavioural habits (77). They may also enhance attachment security in therapeutic settings (78). Psychedelics can induce long-term changes in beliefs, including revising

maladaptive self-beliefs and fostering adaptive beliefs about life's meaning and purpose (2). Psychedelics may also shift metaphysical beliefs towards panpsychism and idealism (79-80). These changes in metaphysical beliefs may mediate some improvements observed in wellbeing, perhaps by fostering a more meaningful worldview and resolving existential questions (80). However, the occurrence and therapeutic role of belief changes is a debated topic and potentially risky aspect of psychedelic use, as it has been suggested that psychedelics could potentially induce alternative beliefs, false 'insights', and could be used as tools of belief transmission (81-83).

MEANING ATTRIBUTION, SUGGESTIBILITY AND CONTEXTUAL EFFECTS

Psychedelics have been suggested to function as amplifiers of meaning, giving subjective experience a heightened sense of significance (35). This may contribute to self-transcendent experiences and meaning-making related to personal, interpersonal and philosophical issues. Additionally, psychedelics may increase suggestibility and 'cognitive penetration', allowing abstract concepts and ideas to be vividly experienced. These suggestibility effects, combined with enhanced meaning attribution, can potentiate therapeutic themes, issues and intentions primed by contextual factors (27,34) as well as the positive role of environmental factors, such as presence of therapeutic relationship and music – which independently contribute to affective processes and provide structure for the experience (65,84). Therefore, the therapeutic setting and contextual factors play a crucial role in psychedelic-assisted therapy (33). Therapeutic changes are most likely to occur in therapeutic settings and with appropriate therapeutic intentions. Wolff et al. (2024) found that common psychotherapeutic mechanisms were most activated by psychedelic experiences in therapeutic settings and negatively correlated with hedonistic and escapist intentions, and that different contexts and intentions led to different therapeutic mechanism profiles (27, see also 73).

CONCLUSIONS

The subjective effects of psychedelic substances are complex and diverse, characterized by unique and often radical alterations in experience that are described as mystical-like, deeply meaningful, but also challenging. Here we have reviewed evidence implying that the quality and content of the psychedelic experience consistently predicts both the subjective therapeutic effects as well as clinical improvement. Whether these subjective experiences are truly necessary for the therapeutic effects, or whether psychedelics act through some other experience-independent neurobiological mechanism, is still an open and debated issue. Clinical trials comparing the therapeutic effects of psychedelics between groups with and without 5-HT2A antagonist pretreatment could help to elucidate this issue.

Psychedelics have become a promising research area in psychiatry in the 21st century. Although the results from clinical studies so far are preliminary, psychedelic-assisted therapy has shown substantial benefits across a variety of psychiatric diagnoses. This suggests that psychedelics may target transdiagnostic mechanisms sustaining many psychiatric conditions, instead of relieving individual symptoms or targeting disorder-specific mechanisms. While some methodological limitations and problems demand attention, psychedelic-assisted therapy appears safe and well tolerated, as well as effective in the treatment of many psychiatric conditions. Further studies with larger sample sizes, more rigorous blinding, and investigations into the psychological mediators are necessary to answer open questions.

We encourage efforts to build integrative accounts of psychedelic effects which, regardless of ultimate validity, are valuable as they can enhance our understanding of mental health and the human mind, as already exemplified by novel psychedelic-informed theories about the mind, brain and the role of exceptional experiences (2,64). Theory building spurred by psychedelic research can shed light on: 1) transdiagnostic factors of mental health, 2) the transformative potential of exceptional subjective experiences, 3) neurobiological correlates of self-transcendent experiences, and 4) theoretical paradigms in psychiatry and psychology (2,7,26,64). Thus, psychedelic-assisted therapy and psychedelic research may not only provide new treatment options for mental health disorders, but also invigorate psychiatric theory building and therapeutic research, stimulating the development of holistic models of mental health and wellbeing. Findings of psychedelic research have already challenged reductionist biomedical mental health models, supporting broader bio-psycho-social models that emphasize subjective meaning and a sense of connectedness as key aspects of mental health, as well as endeavours to address mental health issues' root causes rather than just alleviating symptoms (7,26).

FUNDING AND CONFLICTS OF INTEREST STATEMENT

Jani Kajanoja and Oskari Kantonen are researchers in a clinical trial investigating psilocybin-assisted therapy for alcohol use disorder, sponsored by Clairvoyant Therapeutics. Juuso Kähönen is a board member of the Finnish Association for Psychedelic Research (PSYTY), and has received a grant from Ella and Georg Ehrnrooth Foundation for his PhD research. This review was independently conducted and has received no external funding.

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