

MINI-REVIEW

Psychedelics as neuroplasticity enhancers: Mechanisms, therapeutic applications, and translational challenges

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Abstract

Psychedelics are gaining recognition for their effectiveness as modulators of neuroplasticity in the treatment of a range of neuropsychiatric disorders. Psilocybin, lysergic acid diethylamide, N,N-dimethyltryptamine, and ketamine are substances that mainly affect the serotonergic and glutamatergic systems. They induce rapid synaptogenesis, dendritic remodeling, and changes in functional connectivity within crucial brain networks. The therapeutic benefits observed in depression, post-traumatic stress disorder, and substance use disorders—particularly when integrated with psychotherapy—are attributed to these neuroplastic mechanisms. Despite promising findings, challenges remain regarding safety, long-term effects, and the translation of preclinical results into clinical practice. This review discusses the ethical and legal considerations, as well as translational challenges, that must be addressed before psychedelic-assisted therapies can be fully integrated into modern psychiatry. It also outlines the pharmacological basis of psychedelic action, the molecular and cellular mechanisms underlying neuroplasticity, and the clinical potential of these treatments.

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1. Introduction

The ability of the nervous system to adapt throughout an organism's lifespan, known as neuroplasticity, presents opportunities both as a biosignature and as a therapeutic target for neuropsychiatric disorders.^{1,2} Psychedelics are substances that act on serotonin (5-HT) receptors in the brain to alter states of consciousness.^{3,4} These compounds have been shown to exert significant effects on neuroplasticity, producing changes in the structure and function of neurons.⁵ From a molecular perspective, psychedelics induce rapid neuronal stimulation, promote the formation of new synapses, and modify dendritic architecture.⁶ Their use as a novel and potentially effective therapeutic approach for several psychiatric disorders is increasingly recognized.^{7,8}

Nonetheless, considerable debate persists within the medical community regarding the rationale for their use, particularly with respect to their indications and possible risks.⁹

From the 1950s to the 1960s, the effects of common psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and N,N-dimethyltryptamine (DMT) on mental health and consciousness were extensively investigated.^{10,11} However, legislative restrictions and societal concerns subsequently led to a decades-long hiatus in research.¹²

Advances in pharmacology, neuroscience, and psychiatry over the past 20 years have sparked a scientific renaissance, reigniting interest in psychedelics as a therapeutic tool for mental health conditions such as addiction, post-traumatic stress disorder (PTSD), and depression.¹³ This resurgence—often referred to as the “psychedelic renaissance”^{14,15}—has also fostered improvements in decision-making, empathy, and self-awareness when psychedelic use is combined with mindfulness or psychotherapy. Furthermore, psychedelic research has become central to biotechnology and healthcare innovation, influencing the growth of the psychedelic biotechnology industry and attracting substantial private investment.¹⁶

Psychedelic substances can rapidly and profoundly alter the functional connectivity of brain circuits, including the default mode network, by modulating glutamatergic activity and increasing the expression of brain-derived neurotrophic factor (BDNF), a crucial facilitator of neuroplasticity.^{17–20} Both structural and functional neuroplasticity are important in the context of mental health treatment.²¹ Improving these processes provides a powerful means of healing trauma, remodeling maladaptive circuits, and restoring emotional and cognitive well-being. A major reason for the renewed scientific interest in psychedelics is their unique ability to induce rapid and sustained increases in both forms of plasticity.²² In contrast, conventional mental health treatments are not universally effective and may require weeks to months before their effects become apparent.^{23,24} Psychedelics, in comparison, have demonstrated the capacity to promote neuroplasticity after only a single dose, potentially transforming mental healthcare. This rapid enhancement of plasticity may increase responsiveness to psychotherapy and help “reset” dysfunctional neural circuits. Understanding the molecular mechanisms underlying these effects is now a central objective of psychiatric neuroscience.²²

Despite growing interest in psychedelics as neuroplasticity enhancers, several significant gaps remain. First, the precise molecular and cellular processes through which psychedelics promote both structural and functional neuroplasticity are not fully understood. For example, a

distinctive and intriguing feature of psychedelics is that a single dose or a small number of doses can produce long-lasting changes in psychological domains such as attitudes, mood, and personality; however, the mechanisms linking these effects remain unclear.²⁵ Second, most available evidence derives from animal models and *in vitro* studies, with limited translation to human neurobiology.²⁶ Third, individuals undergoing psychedelic-assisted therapy currently lack reliable biomarkers and neuroimaging tools to objectively monitor neuroplastic alterations.²⁷

2. Pharmacological basis of psychedelic compounds, their receptors, and effects on brain plasticity

The pharmacologic properties of classic serotonergic hallucinogens (psychedelics) vary slightly.²⁸ Certain mushrooms, such as *Psilocybe cubensis*, contain psilocybin, which is rapidly metabolized into its active compound, psilocin, following ingestion.²⁹ While LSD shows strong affinity for 5-HT_{1A/D}, 5-HT_{2A/B/C}, and 5-HT₆ receptors, as well as dopamine D_{1/D2} and α -adrenergic receptors, psilocin and psilocybin exhibit their greatest affinity for multiple 5-HT receptor subtypes. They commonly act as agonists at D₂ and 5-HT_{2A} receptors.^{5,30} Both DMT and its analog 5-methoxy-N,N-dimethyltryptamine are agonists at 5-HT_{1A/D}, 5-HT_{2A/B/C}, and 5-HT₆ receptors. Ayahuasca contains non-psychedelic β -alkaloids that function as monoamine oxidase A inhibitors in addition to DMT.³¹

These β -alkaloids allow DMT to be absorbed through the digestive system and reach the brain unmetabolized. When DMT is administered without the accompanying ayahuasca components, its effects begin within minutes after ingestion and last approximately 15 min when injected or inhaled. In contrast, the pharmacology of ayahuasca is strongly influenced by DMT, producing effects that appear roughly 30 min after ingestion and persist for nearly three hours, peaking at 1.5–2 h, corresponding to peak DMT plasma concentrations.^{5,32} Psychedelics are considered physiologically safe, as no significant physical toxicity has been documented.^{33–36}

Hallucinogenic effects typically depend on dose, route of administration, body weight, tolerance, age, and metabolism, with higher doses often intensifying subjective experiences compared with lower doses.^{34,37,38} Other important determinants include mental state, environment, mood, and personality.^{39,40} “Classic psychedelics” are a class of psychoactive substances that induce mind-altering effects primarily through agonism at serotonergic receptors, particularly 5-HT_{2A} receptors.⁴¹ Psilocybin, LSD, DMT, and DMT-containing ayahuasca

are among the most widely used recreational psychedelics, and they have been shown to affect physiological, cognitive, and emotional states, including producing mood changes and heightened emotional processing.⁴²

Substances with diverse pharmacological actions are classified as non-classic psychedelics. For example, ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor; 3,4-methylenedioxymethamphetamine (MDMA) acts as a 5-HT and dopamine reuptake inhibitor and releaser; ibogaine is a multitarget indole alkaloid; salvinorin A is a kappa-opioid receptor agonist; and tetrahydrocannabinol functions as a partial agonist of cannabinoid receptors. Dissociative hallucinogens exert their effects primarily by blocking NMDA receptors. These include ibogaine, which also influences the autonomic nervous system, and the novel ketamine analog methoxetamine, a dissociative anesthetic with potential use in treating depressive disorders.^{43,44} Ketamine additionally influences sigma receptors and several neurotransmitter systems, such as the monoaminergic and glutamatergic pathways. Its antidepressant effects have been linked to opioidergic signaling pathways, metabotropic glutamate receptors, and the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.⁴⁵

Psychedelic compounds can be categorized based on their primary receptor pharmacology and mechanisms of action, rather than solely by chemical structure. In this review, the classification in Table 1 follows a pharmacological framework, grouping compounds according to the principal neural receptors they modulate and the resulting functional outcomes. Specifically, classic psychedelics (e.g., psilocybin, LSD, and DMT) act primarily as 5-HT_{2A} receptor agonists, producing altered perception and enhanced sensory processing;⁴⁶ non-classic

psychedelics such as ketamine and phencyclidine function as NMDA receptor antagonists, generating dissociation, and rapid antidepressant effects;⁴⁷ atypical psychedelics such as ibogaine and salvinorin A target kappa-opioid or multiple receptor systems;⁴⁸ entactogens (e.g., MDMA, 3,4-methylenedioxymethamphetamine) modulate monoamine transporters, promoting empathy and euphoria;⁴⁹ and cannabinoid-like psychedelics act through cannabinoid receptors (CB₁/CB₂), influencing time perception and relaxation.⁵⁰ Different categories of major psychedelics are summarized in the table below, along with their receptor targets and representative effects.

3. A glimpse of molecular and cellular mechanisms of psychedelic-induced plasticity

Psychedelics promote neuronal branching, increase dendritic spine density, and accelerate the development of new synapses. Both *in vitro* and *in vivo* investigations have demonstrated these effects, which are associated with improved memory, learning, and emotional processing.⁵¹ As agonists of the 5-HT_{2A} receptor, traditional hallucinogens such as LSD and psilocybin activate a series of intracellular signaling events. Phospholipase C (PLC), BDNF, mammalian target of rapamycin (mTOR), and tropomyosin receptor kinase (TrkB) are involved in this process, and signaling through these molecules facilitates both neurogenesis and synaptic plasticity.^{42,52} Psychedelics also alter the function of glial cells, such as microglia and astrocytes, which may help reduce neuroinflammation. This regulation contributes to a favorable environment for neurogenesis and brain repair.⁵³ Ketamine does not act in the same manner as traditional psychedelics. Blockade of NMDA receptors leads to disinhibition of AMPA receptors,

Table 1. Classification of major psychedelics based on their primary receptor pharmacology and representative psychophysiological effects

Type of psychedelic	Examples	Primary receptor targets	Representative effects	References
Classic psychedelics	Psilocybin, LSD, DMT	5-HT _{2A} receptor agonism	Altered perception, enhanced sensory processing, mood changes, mystical experiences	47
Non-classic Psychedelics	Ketamine, PCP	NMDA receptor antagonism	Dissociation, out-of-body experiences, rapid antidepressant effects	48
Atypical psychedelics	Ibogaine, Salvinorin A	Kappa-opioid receptor (Salvinorin A*); multiple targets (Ibogaine)	Intense visions, dreamlike states, anti-addictive potential	49
Entactogens	MDMA, MDA	Monoamine transporter modulation (5-HT, DA, NE release)	Increased empathy, emotional openness, reduced fear, euphoria	50
Cannabinoid-like psychedelics	THC, synthetic cannabinoids	CB ₁ /CB ₂ receptors	Altered time perception, relaxation, anxiety, or paranoia (dose-dependent)	51

Note: The table outlines the principal receptor targets responsible for each compound's characteristic effects, providing a pharmacological framework underlying their diverse therapeutic and perceptual outcomes.

Abbreviations: MDA: 3,4-methylenedioxymethamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; NMDA: N-methyl-D-aspartate; PCP: Phencyclidine; THC: Tetrahydrocannabinol.

rapidly increasing BDNF levels and synaptogenesis. This process underlies ketamine's fast-acting antidepressant effects.^{22,54,55} The molecular pathways affected by classic psychedelics and ketamine are illustrated in Figure 1.

4. Psychedelics in psychiatric treatment: Role of neuroplasticity

4.1. Major depressive disorder

Ayahuasca, DMT, psilocybin, and LSD are among the psychedelics that have shown therapeutic potential in clinical investigations for treating stress-related disorders.⁵⁸ Similar to traditional antidepressants and the fast-acting drug ketamine, these substances provide cognitive, antidepressant, and anti-addictive effects that are thought to result from neurobiological alterations, particularly the induction of neuroplasticity.⁵

Neuroplasticity is impaired in major depressive disorder, with reduced synaptic density and disrupted prefrontal-limbic circuits.⁵⁹ Antidepressant treatments, including ketamine and psychedelics, restore plasticity by increasing BDNF signaling and synaptogenesis, thereby improving mood regulation and cognitive flexibility.^{42,56}

4.2. PTSD

By improving emotional processing, fear extinction, and memory reconsolidation, psychedelics such as MDMA and psilocybin have shown promise in the treatment

of PTSD.⁶⁰ Neuroplasticity is directly linked to these processes, especially in brain regions such as the prefrontal cortex, hippocampus, and amygdala.⁶¹

Neuroplasticity is crucial in the treatment of PTSD because trauma disrupts synaptic connectivity and alters fear- and memory-related circuits.⁶² Enhancing plasticity through therapies such as MDMA, psilocybin, and ketamine promotes dendritic remodeling, increases BDNF signaling, and strengthens prefrontal control over the amygdala, thereby reducing fear responses and facilitating extinction learning.^{63,64}

4.3. Substance use disorders

Psychedelics are being investigated as treatments for several substance use disorders, such as addiction to alcohol, nicotine, and opioids.⁶⁵⁻⁶⁷ Substances such as psilocybin, ayahuasca, and ibogaine are thought to reduce craving and increase behavioral flexibility by promoting neuroplastic changes in the prefrontal cortex and reward circuitry (such as the nucleus accumbens).⁶⁸ Research indicates that psychedelic-assisted treatment is associated with longer-lasting sobriety and lower relapse rates.⁴⁰

4.4. Psychotherapy as a plasticity-dependent integration process

Although psychedelics have not yet been definitively proven to be therapeutically effective in psychiatry, encouraging early research highlights their potential benefits and sheds

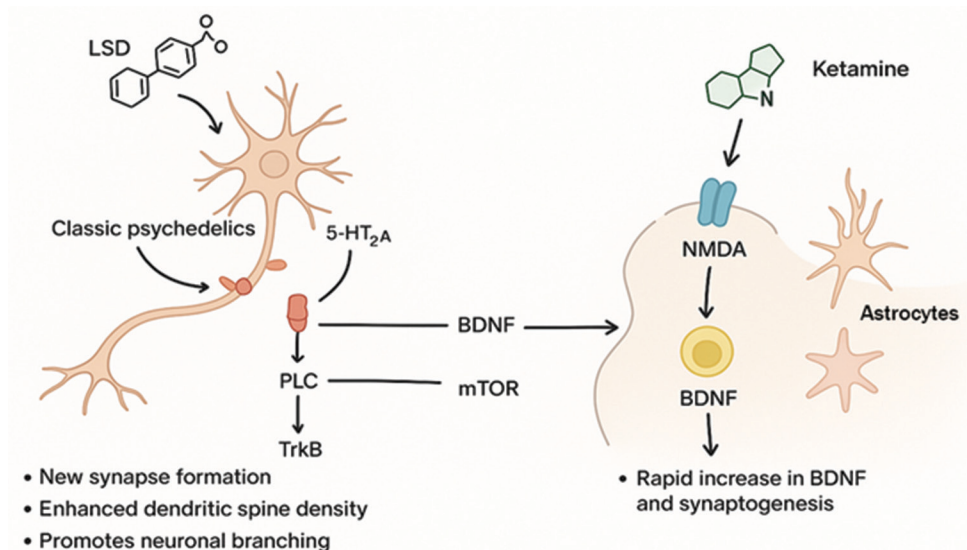


Figure 1. Molecular pathways by which classic psychedelics and ketamine enhance synaptic plasticity, neurogenesis, and brain repair. In this figure, directional changes in molecular pathways are shown: activation of 5-HT_{2A} receptors or modulation of NMDA receptors leads to upregulation of PLC, BDNF, TrkB, and mTOR signaling cascades, culminating in enhanced synaptogenesis and dendritic remodeling. Conversely, NMDA receptor blockade by ketamine removes inhibitory tone on excitatory neurons, indirectly increasing AMPA-mediated plasticity.^{42,56,57}

Abbreviations: BDNF: Brain-derived neurotrophic factor; mTOR: Mammalian target of rapamycin; PLC: Phospholipase C; TrkB: Tropomyosin receptor kinase; 5-HT_{2A}: Serotonin 2A receptor.

light on the underlying mechanisms of psychiatric disorders. Psychotherapy is effective because neuroplasticity allows the brain to strengthen healthy thought and behavior patterns while remodeling dysfunctional circuitry. Cognitive behavioral therapy (CBT), mindfulness, and exposure therapy are examples of psychotherapeutic approaches that improve emotional regulation, stress resilience, and adaptive learning by promoting synaptic remodeling in prefrontal-limbic pathways. In this way, psychotherapy leverages neuroplasticity to achieve long-term cognitive and emotional changes.⁶⁹⁻⁷²

4.5. Comparison with standard therapies

Conventional antidepressant medications such as selective serotonin reuptake inhibitors and psychotherapeutic approaches like CBT remain the mainstays of treatment for depression and related disorders.⁷³⁻⁷⁵ However, these approaches often require prolonged administration and exhibit delayed onset of action—typically several weeks—while a significant proportion of patients show only partial or no response.^{76,77}

In contrast, psychedelics such as psilocybin and ketamine can induce rapid and sustained improvements in mood and cognition after one or a few sessions, likely through enhanced neuroplasticity and modulation of glutamatergic and serotonergic systems.^{4,78-82}

While selective serotonin reuptake inhibitors primarily increase extracellular 5-HT to gradually normalize synaptic function, psychedelics directly activate 5-HT_{2A} receptors and rapidly trigger intracellular cascades involving BDNF, mTOR, and TrkB signaling, leading to structural synaptic remodeling.^{5,83-88}

Psychotherapeutic approaches like CBT rely on experience-dependent plasticity over extended timeframes; psychedelic-assisted psychotherapy may amplify this process by temporarily enhancing neural malleability and emotional openness.⁸⁹⁻⁹¹

Nonetheless, unlike established treatments, psychedelic therapies still face challenges related to standardization, dosing, long-term safety, and regulatory approval. Therefore, psychedelics should currently be viewed as potential adjuncts or alternatives to conventional therapies rather than replacements.^{92,93}

5. Risks and challenges (translational)

Maladaptive plasticity, in which unsuitable neural connections may form, is a potential risk associated with psychedelics. This could exacerbate certain mental illnesses or trigger psychotic episodes in susceptible individuals with schizophrenia or bipolar disorder.^{94,95} Increased

suggestibility while under psychedelic influence may also heighten vulnerability to deception or manipulation.^{96,97} Some traditional psychedelics, such as psilocybin and LSD, activate the 5-HT_{2B} receptor.⁹⁸ Chronic, high-dose use of these substances has been associated with cardiovascular risks, including cardiac valvulopathy, or damage to the heart valves.⁹⁹ Although this risk is reduced with restricted therapeutic use, it remains a crucial consideration for dosing, patient screening, and long-term safety evaluations.

The environment (setting) and the user's mental state (set) greatly influence psychedelic experiences.¹⁰⁰ Traumatic or destabilizing effects might result from unfavorable or unsafe environments. Integration support and appropriate psychological preparation are therefore crucial.^{39,101} Although a single dose or a small number of doses of psychedelics show therapeutic potential, the long-term effects of repeated use on brain structure and function remain unclear.¹⁰² Potential overstimulation of plasticity processes raises concerns about emotional dysregulation or cognitive instability.¹⁰³

Psychedelic use in clinical settings also raises complex ethical questions regarding patient vulnerability, risk disclosure, and informed consent.^{104,105} Regulatory landscapes vary widely across countries, and debates about decriminalization versus medicalization remain active.¹⁰⁶ Furthermore, if psychedelic-assisted therapy becomes increasingly medicalized, it may become an expensive treatment available primarily to wealthy individuals, thereby exacerbating health disparities. Ensuring equitable access and fair reimbursement models represents a significant social and ethical challenge.¹⁰⁷

Understanding the risks and translational limitations of psychedelics requires an interdisciplinary framework that integrates neuroscience, psychology, ethics, pharmacology, and policy studies.¹⁰⁸ From a neuroscientific perspective, concerns persist about maladaptive plasticity, neurotoxicity, and the reproducibility of long-term structural changes.^{80,109,110} Psychological and clinical fields highlight challenges in managing suggestibility, expectation bias, and potential emotional destabilization during therapy.¹¹¹⁻¹¹⁴ Ethical and sociocultural analyses underscore the importance of informed consent, patient autonomy, and equitable access, especially in culturally sensitive contexts. Pharmacological and regulatory perspectives emphasize variability in purity, dosing, and metabolic responses, along with stringent legal controls that hinder large-scale clinical translation.^{104,115-118} Finally, health economic and policy analyses stress the need for sustainable implementation frameworks to prevent inequities and over-commercialization. A truly translational understanding of psychedelics therefore

demands a multidimensional approach—bridging biological mechanisms with clinical ethics, social impact, and regulatory science.^{107,119,120}

6. Translational and future directions

To improve our understanding of the therapeutic potential of these substances, research spanning preclinical to clinical studies may concentrate on identifying the precise cellular mechanisms triggered by different psychedelic compounds.⁵ Recent research has focused on developing psychedelic-inspired molecules that promote neuroplasticity without inducing hallucinations. These non-hallucinogenic analogs aim to retain therapeutic benefits (e.g., BDNF activation and dendritic growth) while avoiding risks associated with altered perception or ego dissolution. These compounds could increase clinical acceptability and reduce regulatory resistance.⁵⁷

It may be possible to maximize plasticity during crucial windows by combining psychedelics with neuromodulatory methods such as transcranial magnetic stimulation or targeted behavioral therapies (such as exposure therapy or cognitive training). This combination could enhance emotional reprocessing, fear extinction, or learning.⁵¹ Future studies should monitor long-term changes in brain networks following psychedelic exposure. Neuroimaging techniques such as functional magnetic resonance imaging, electroencephalography, and diffusion tensor imaging can map changes in connectivity and circuit remodeling across months or years, helping clarify therapeutic mechanisms and the duration of their effects. Psychedelic therapy may eventually be tailored to individual genetic, neural, and psychological profiles. Using tools such as genomic testing, neuroplasticity biomarkers, and artificial intelligence-driven profiling, clinicians can predict which patients are likely to benefit and customize treatment protocols accordingly.^{27,121}

7. Conclusion

Psychedelics represent a new class of drugs with the potential to reset maladaptive brain circuits underlying mental illnesses by inducing rapid and long-lasting neuroplastic changes. Their unique ability to improve structural and functional plasticity forms the basis for novel therapeutic strategies that integrate psychotherapy and pharmacology. However, careful and comprehensive research is required due to unresolved questions regarding safety, long-term effects, and the possibility of maladaptive plasticity. Future priorities include the development of non-hallucinogenic analogs, personalized treatment approaches guided by biomarkers, and equitable clinical implementation models. If these challenges can be addressed, psychedelics may

transform mental healthcare by offering rapid, durable, and personalized interventions for disorders resistant to conventional therapies.

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Conflict of interest

The authors declare that they have no competing interests.

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