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PSYCHEDELICS AND NEUROPLASTICITY: FROM BENCH TO BEDSIDE

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ABSTRACT

Background: Psychedelic compounds such as psilocybin, lysergic acid diethylamide (LSD), N, N-dimethyltryptamine (DMT), mescaline, and methylenedioxymethamphetamine (MDMA) are undergoing a scientific resurgence after decades of prohibition. These agents have demonstrated rapid and sustained therapeutic benefits in psychiatric disorders including major depressive disorder, posttraumatic stress disorder (PTSD), and substance use disorders. Unlike conventional monoaminergic antidepressants, psychedelics appear to act via neuroplastic mechanisms that restructure synaptic and circuit level function. **Objective:** This review synthesizes current evidence on how psychedelics promote neuroplasticity across molecular, cellular, circuit, and behavioral levels, and evaluates their translational potential as next generation neuropsychiatric therapeutics. **Methods:** A narrative review of preclinical and clinical studies was conducted, focusing on structural spinogenesis and synaptogenesis, signaling cascades (BDNF–TrkB–mTOR axis), receptor pharmacology (serotonin(5-HT_2A)) and, and neuroimaging data. Comparative analysis with rapid acting antidepressants such as ketamine was integrated to highlight convergent biological mechanisms. **Results:** Preclinical data consistently demonstrate that psychedelics enhance dendritic spine density, synaptogenesis, and excitatory transmission in cortical and hippocampal circuits. These effects are mediated by BDNF TrkB and mTOR signaling and are dependent, though not exclusively, on 5-HT_2A receptor activation. Clinical studies show that one or two administrations of psilocybin or MDMA, combined with psychological support, yield rapid

and durable symptom improvements in depression and PTSD. Functional neuroimaging reveals large scale network remodeling, including increased prefrontal limbic connectivity and reduced default mode network rigidity. **Conclusion:** Psychedelics represent a novel class of psychoplastogens, capable of rapidly and sustainably remodeling brain structure and function. Their clinical efficacy appears to derive from durable neuroplastic changes rather than chronic receptor occupancy. However, major challenges remain, including disentangling hallucinogenic from therapeutic effects, developing reliable biomarkers of plasticity, and overcoming regulatory barriers. Future work on non-hallucinogenic analogues and precision biomarkers may pave the way for scalable, safe, and personalized psychedelic assisted therapies.

KEYWORDS: Psychedelics; Psilocybin; LSD; MDMA; Neuroplasticity; Synaptogenesis.

1. INTRODUCTION

Over the past two decades, there has been a striking resurgence of scientific and clinical interest in psychedelics such as psilocybin, lysergic acid diethylamide (LSD) a semisynthetic hallucinogen drug derived from ergot, N, N-dimethyltryptamine (DMT), and 3,4 methylenedioxymethamphetamine (MDMA). These substances, once relegated to the fringes of both science and culture, are now re-emerging as potential therapeutic agents capable of addressing some of the most pressing unmet needs in psychiatry.[1] Psychedelics were initially investigated in the mid-20th century for their psychoactive and therapeutic properties, with early studies reporting promising results in depression, alcoholism, and existential anxiety in terminal illness However, by the late 1960s and early 1970s, sociopolitical factors, concerns over misuse, and the passage of restrictive drug control laws curtailed their scientific exploration, relegating them to Schedule I status in most countries.[2]

In recent years, a convergence of rigorous neurobiological studies, advances in neuroimaging, and carefully designed clinical trials has catalyzed their scientific renaissance. Clinical evidence suggests that psychedelics may produce rapid, robust, and enduring improvements in psychiatric disorders such as major depressive disorder (MDD), treatment of resistant depression, post-traumatic stress disorder (PTSD), substance use disorders, and end-of-life anxiety.[3–5] Unlike conventional monoamine based antidepressants, which often require weeks of daily administration and are associated with variable efficacy and side effects, psychedelics can induce meaningful clinical improvements after just one or a few guided

sessions.[6] This has shifted the paradigm from chronic pharmacotherapy to episodic, experience dependent interventions with enduring outcomes.

Central to their therapeutic potential is the ability of psychedelics to promote structural and functional neural remodeling processes collectively referred to as neuroplasticity. Preclinical evidence demonstrates that psychedelics enhance dendritic spine growth, increase synaptogenesis, and promote neurotrophic signaling, particularly via brain derived neurotrophic factor (BDNF) and the mammalian target of rapamycin (mTOR) pathways.[7–9] These neurobiological changes are thought to underlie the long-lasting shifts in cognition, mood, and behavior observed after psychedelic therapy. In human studies, functional neuroimaging has revealed alterations in brain network connectivity, including decreased default mode network (DMN) activity, increased global connectivity, and reorganization of rigid patterns of neural activity that are often implicated in psychiatric disorders.[10–12]

The reemergence of psychedelic science has not only reinvigorated biological psychiatry but also challenged the dichotomy between pharmacological and psychotherapeutic approaches. Psychedelic assisted therapies integrate pharmacological action with profound subjective experiences, including mystical type or ego dissolving states, which may themselves facilitate cognitive flexibility and psychological insight.[13,14] Importantly, the therapeutic effects of psychedelics appear to be context dependent, with factors such as mindset, environment, and psychotherapeutic support often referred to as “set and setting” playing critical roles in shaping both neuroplastic outcomes and clinical efficacy.

This review aims to synthesize the growing body of evidence on psychedelics and neuroplasticity, from mechanistic insights derived from preclinical models to translational findings in clinical populations as well, challenges and opportunities associated with bringing psychedelic-based treatments from the laboratory bench to widespread clinical practice, including regulatory hurdles, safety considerations, and ethical frameworks.

2. Cellular and Molecular Mechanisms of Psychedelic Induced Neuroplasticity

2.1 Spinogenesis and Synaptogenesis

One of the most robust and consistent findings across preclinical models is that psychedelics induce rapid and sustained structural remodeling of cortical neurons. A central component of this remodeling is spinogenesis, the formation of new dendritic spines, and synaptogenesis, the establishment of functional synaptic connections. These processes provide the cellular

substrate for the long lasting psychological and behavioral changes observed following psychedelic administration.

Report from literature provided seminal evidence that several serotonergic psychedelics, including LSD, DMT, and the phenethylamine DOI, markedly increase dendritic arbor complexity and spine density in cultured rat cortical neurons.[15] Notably, the magnitude of these effects was comparable to, and in some cases exceeded, those of ketamine, the prototypical rapid acting antidepressant. These findings were not confined to cell culture systems; subsequent in vivo work confirmed that psychedelics enhance spine density and excitatory synaptic transmission in the prefrontal cortex (PFC), a brain region critically involved in mood regulation, executive function, and stress response.[16,17]

Earlier report extended these findings by demonstrating that a single administration of psilocybin produced a significant increase in dendritic spine density and enlargement in the mouse medial PFC within 24 hours.[17] Remarkably, a proportion of these newly formed spines persisted for at least one month, suggesting that psychedelics are capable of inducing long lasting changes in neural circuitry. This persistence distinguishes psychedelic induced neuroplasticity from many transient forms of structural remodeling observed with other pharmacological agents. Importantly, these morphological changes are paralleled by enhanced excitatory postsynaptic currents, indicating that the new spines are not merely structural artifacts but represent functional synapses.

These preclinical observations may help explain the clinical durability of psychedelic assisted interventions, in which a small number of treatment sessions can yield symptom relief lasting weeks or months. In disorders such as depression and PTSD, which are characterized by dendritic atrophy and reduced synaptic density in the PFC and hippocampus, psychedelic induced synaptogenesis may effectively restore network integrity and improve information processing.[18] Thus, spinogenesis and synaptogenesis constitute a mechanistic bridge linking molecular events to macroscopic changes in brain function and ultimately to therapeutic outcomes.

2.2 Key Signaling Pathways: BDNF–TrkB and mTOR

At the molecular level, the neuroplastic effects of psychedelics appear to converge on canonical signaling cascades that regulate neuronal growth, survival, and synaptic remodeling. Two of the most critical pathways are the brain derived neurotrophic factor

(BDNF) tropomyosin receptor kinase B (TrkB) axis and the mammalian target of rapamycin (mTOR) pathway. BDNF is a neurotrophin that plays a central role in supporting neuronal differentiation, dendritic growth, and synaptic potentiation. Binding of BDNF to its high affinity receptor TrkB initiates a signaling cascade involving PI3K-Akt and MAPK/ERK pathways, ultimately enhancing dendritic spine formation and strengthening synaptic connections. Psychedelics have been shown to upregulate BDNF expression both in vitro and in vivo, thereby creating a permissive environment for plasticity. The mTOR pathway represents another key mediator of psychedelic induced plasticity. mTOR is a serine/threonine kinase that regulates local protein synthesis at dendrites and synapses, enabling rapid structural remodeling. Activation of mTOR leads to increased translation of synaptic proteins such as PSD-95 and synapsin, which are critical for synapse maturation and stabilization. Importantly, inhibition of mTOR with rapamycin prevents psychedelic induced spinogenesis, highlighting its necessity for structural remodeling.[18] These mechanisms closely parallel those observed with ketamine, suggesting that different classes of rapid acting antidepressants converge on shared molecular machinery.

2.3 5-HT2A Receptor Activation and Intracellular Cascades

The 5-hydroxytryptamine 2A receptor (5-HT2A) is widely recognized as the primary molecular target mediating the effects of classic serotonergic psychedelics such as psilocybin, LSD, mescaline, and DMT. These compounds act as high affinity partial agonists at 5-HT2A receptors, which are abundantly expressed on layer V pyramidal neurons of the prefrontal cortex and, to a lesser extent, on other cortical and subcortical populations. Activation of these receptors initiates a cascade of intracellular signaling events that are believed to underlie both the acute subjective experiences and the enduring neuroplastic adaptations associated with psychedelic administration.

2.3.1 Gq/11-Coupled Pathways

5-HT2A receptors are G protein coupled receptors (GPCRs) that predominantly couple to the Gq/11 protein family. Activation of 5-HT2A receptors leads to stimulation of phospholipase C (PLC), resulting in hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 promotes release of Ca^{2+} from intracellular stores, while DAG activates protein kinase C (PKC).[15] This calcium dependent signaling is critical for downstream activation of transcription factors such as

CREB (cAMP response element binding protein), which regulate the expression of BDNF and other plasticity-related genes.[19]

2.3.2 β-Arrestin Signaling and Biased Agonism

Emerging evidence indicates that psychedelics may act as biased agonists, preferentially engaging non canonical signaling pathways through β-arrestin recruitment. β-arrestins not only desensitize GPCRs but also serve as scaffolds for signaling complexes that activate MAPK/ERK pathways, which are implicated in neuronal differentiation and synaptic plasticity. Distinct psychedelics may differentially bias signaling, which could help explain variability in subjective and therapeutic effects across compounds.

2.3.3 Cortical Glutamate Release and Network Effects

At the circuit level, activation of 5-HT2A receptors on pyramidal neurons enhances excitatory drive and increases glutamate release in cortical microcircuits, particularly within the PFC (245). This surge in glutamate subsequently activates AMPA and NMDA receptors on postsynaptic targets, further stimulating intracellular signaling cascades such as the mTOR pathway and calcium/calmodulin dependent protein kinase II (CaMKII). The net effect is a facilitation of synaptic potentiation and dendritic spine growth, providing a mechanistic explanation for psychedelic induced plasticity observed in animal models.

2.3.4 Cross-Talk with BDNF and mTOR

The 5-HT2A-driven increase in intracellular calcium and glutamatergic transmission creates a permissive environment for neurotrophic signaling. Elevated intracellular Ca^{2+} activates CaMK and ERK, which in turn enhance transcription and release of BDNF. BDNF-TrkB activation then feeds forward into PI3K-Akt-mTOR signaling, promoting local protein synthesis necessary for synaptic remodeling. Thus, the 5-HT2A receptor sits at the top of a signaling hierarchy that funnels into the canonical plasticity pathways.

2.3.5 Clinical and Translational Implications

Clinically, the centrality of 5-HT2A signaling is underscored by pharmacological blockade studies. Pretreatment with the selective 5-HT2A antagonist ketanserin reliably attenuates or abolishes the subjective psychedelic state in humans and prevents structural plasticity changes in rodents.[20] This strongly supports the view that 5-HT2A activation is necessary for both acute phenomenological experiences and long-term neural remodeling. From a translational perspective, the concept of biased agonism at 5-HT2A receptors raises the

possibility of designing next generation psychedelics or "psychoplastogens" that preferentially engage plasticity-related signaling while minimizing hallucinogenic effects.[21] Such agents could expand the therapeutic toolkit for psychiatric disorders without the need for intensive psychotherapeutic support.

2.4 Cross Talk with Other Neurotransmitter Systems

While the 5-HT2A receptor is the canonical molecular target of classic psychedelics, growing evidence demonstrates that their neurobiological and therapeutic effects cannot be explained by serotonergic signaling alone. Psychedelics modulate a wide array of neurotransmitter systems, including glutamate, dopamine, and sigma 1 receptors that converge on intracellular plasticity pathways. This multi receptor, network level pharmacology likely underpins the broad neuropsychological impact of psychedelics and may explain differences between compounds in terms of both subjective effects and clinical outcomes.

2.4.1 Glutamatergic Transmission

Psychedelic induced glutamate release in the prefrontal cortex (PFC) represents a critical mediator of downstream plasticity. Activation of 5-HT2A receptors on pyramidal neurons increases cortical excitatory drive, leading to enhanced extracellular glutamate levels. This glutamatergic surge stimulates AMPA and NMDA receptors, promoting calcium influx and activating signaling cascades such as CaMKII, ERK, and mTOR all of which are indispensable for synaptic remodeling.

Importantly, pharmacological blockade of AMPA receptors attenuates the plasticity-promoting effects of psychedelics, paralleling findings with ketamine.[22] This suggests that AMPA receptor throughput is a final common pathway for multiple classes of rapid acting antidepressants. In addition, psychedelics enhance long term potentiation (LTP) in hippocampal circuits, indicating that glutamatergic plasticity may extend beyond the PFC to regions implicated in memory reconsolidation and fear extinction.

2.4.2 Dopaminergic Modulation

In addition to serotonergic and glutamatergic effects, psychedelics also interact with dopaminergic systems, particularly in mesocorticolimbic circuits. LSD and psilocybin display partial agonist activity at D2 receptors, while also indirectly modulating dopamine release through cortical 5-HT2A activation. These interactions may contribute to the reward

sensitivity, increased salience processing, and motivational shifts reported during psychedelic experiences.

Functional imaging studies show that psychedelics increase striatal dopamine release, although to a lesser extent than psychostimulants. This dopaminergic engagement may be particularly relevant to addiction treatment, as it provides a neurochemical basis for reconfiguring maladaptive reward circuits. Furthermore, dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32), a signaling integrator downstream of dopamine receptors, is implicated in synaptic plasticity and may represent a point of convergence with serotonergic signaling.

2.4.3 Sigma 1 Receptor Activation

Beyond serotonergic and dopaminergic systems, certain psychedelics especially DMT act as agonists at the sigma 1 receptor (σ1R), an endoplasmic reticulum chaperone protein with neuromodulatory and neuroprotective functions. Activation of σ1R has been shown to enhance calcium signaling, stabilize mitochondrial function, and upregulate expression of neurotrophic factors such as BDNF and NGF.

In rodent models, σ1R activation promotes neuronal survival, dendritic growth, and synaptic maintenance, suggesting that this receptor may augment or prolong psychedelic induced plasticity. Interestingly, σ1R ligands have shown antidepressant and anxiolytic-like effects in preclinical studies, raising the possibility that DMT's therapeutic profile may derive partly from σ1R engagement in addition to its 5-HT2A agonism.[23]

2.4.4 Integrative Perspective

Taken together, the evidence suggests that psychedelics orchestrate a multi receptor symphony of signaling events that converge on neuroplasticity pathways. 5-HT2A activation initiates glutamate release and calcium influx; dopaminergic signaling modulates motivational and reward circuits; and σ1R engagement enhances trophic support and cellular resilience. These systems are not isolated, but rather interdependent, forming a neurochemical network that amplifies and sustains plasticity.

This multi receptor pharmacology has important translational implications. By targeting multiple pathways simultaneously, psychedelics may achieve a robustness of effect that single-target agents lack. At the same time, variability in receptor binding profiles among

different compounds (e.g., psilocybin vs. DMT vs. LSD) may account for distinct clinical signatures and therapeutic niches. Understanding these cross-system interactions could guide the rational design of next generation psychoplastogens optimized for efficacy, safety, and tolerability.

2.5 Epigenetic Mechanisms and Gene Expression Changes

The enduring effects of psychedelics on mood, cognition, and behavior raise an important question: how can a single or limited exposure produce long lasting neural adaptations? While synaptic signaling and receptor mediated plasticity explain immediate effects, sustained outcomes likely depend on epigenetic reprogramming and transcriptional regulation that consolidate plasticity into stable network level changes. Emerging evidence suggests that psychedelics modulate gene expression through activity dependent transcription factors, chromatin remodeling, and noncoding RNA pathways.

2.5.1 Immediate Early Gene (IEG) Induction

Psychedelics robustly induce immediate early genes (IEGs) such as *c-Fos*, *Egr1*, *Arc*, and *JunB* within cortical and limbic regions.[24] These genes serve as transcriptional switches that regulate downstream plasticity programs, including cytoskeletal rearrangement, synaptic protein synthesis, and dendritic spine stabilization. For example, *Arc* is critical for AMPA receptor trafficking during long-term potentiation, while *c-Fos* and *Egr1* are essential for memory consolidation and extinction learning.

Importantly, psychedelic induced IEG expression patterns overlap with those observed following enriched environmental stimulation or cognitive training, suggesting that psychedelics may mimic or amplify natural experience dependent transcriptional programs.[25]

2.5.2 Chromatin Remodeling and Histone Modifications

Beyond IEGs, psychedelics influence epigenetic states that determine transcriptional accessibility. Histone acetylation, mediated by histone acetyltransferases (HATs), loosens chromatin structure and facilitates gene expression, whereas histone deacetylases (HDACs) impose transcriptional repression. Preclinical studies suggest that psilocybin and DMT increase histone H3 acetylation in the prefrontal cortex and hippocampus.[26] thereby enhancing transcription of plasticity related genes such as *BDNF*.

Conversely, inhibition of HDACs potentiates the behavioral and molecular effects of psychedelics, indicating that histone acetylation is a permissive mechanism for psychedelic induced neuroplasticity. These findings resonate with broader evidence that HDAC inhibitors promote fear extinction and antidepressant like responses, positioning epigenetic regulators as promising adjuncts to psychedelic therapy.

2.5.3 DNA Methylation and Long-Term Gene Regulation

DNA methylation represents a more stable epigenetic modification, typically associated with transcriptional silencing. Limited but growing evidence suggests that psychedelics may alter DNA methylation patterns at genes linked to neuronal plasticity, stress response, and inflammation.[27] For instance, ayahuasca administration in humans was associated with differential methylation at CpG sites within neuroplasticity-related genes, correlating with clinical improvements in depression scores.[28]

Such findings raise the possibility that psychedelics induce lasting epigenomic signatures that stabilize therapeutic gains. However, whether these changes represent adaptive reprogramming or nonspecific stress responses remains to be clarified.

2.5.4 Noncoding RNAs and Post Transcriptional Regulation

MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs) have emerged as critical regulators of synaptic plasticity and psychiatric disease. Preliminary evidence indicates that psychedelic exposure modulates miRNA expression, including miR-132 and miR-212, which control dendritic growth and synaptic scaling. These noncoding RNAs fine tune transcriptional outputs, acting as molecular “brakes” or “accelerators” of plasticity programs initiated by receptor level signaling.

Future work on the psychedelic miRNA axis may uncover novel therapeutic biomarkers and intervention points for enhancing or prolonging psychedelic induced plasticity.

2.5.5 Integrative Perspective

Taken together, these findings support the view that psychedelics act not only as acute receptor agonists but also as epigenetic modulators. By recruiting IEGs, histone acetylation, DNA methylation, and noncoding RNAs, psychedelics reconfigure the transcriptional landscape of cortical and limbic circuits. This molecular reprogramming may consolidate

transient experiences into durable therapeutic changes, bridging the gap between short lived pharmacology and sustained clinical benefit.

Understanding these epigenetic signatures may also enable precision approaches matching patients to compounds that induce optimal gene expression shifts, or combining psychedelics with epigenetic drugs to synergistically enhance therapeutic outcomes.

3. Preclinical Evidence: Animal Models of Psychedelic Induced Plasticity

Preclinical models have been indispensable in elucidating the cellular, molecular, and behavioral effects of psychedelics. While human imaging and clinical studies provide correlative evidence of enhanced plasticity, animal research enables precise dissection of the causal links between psychedelic administration, neural remodeling, and behavioral outcomes. These models encompass rodents (mice and rats), zebrafish, and non-human primates, each offering unique advantages for mechanistic discovery.

3.1 Rodent Models of Structural Plasticity

Rodent studies provide the strongest evidence that psychedelics induce rapid and lasting structural changes in cortical circuits. Using two photon microscopies showed that a single dose of psilocybin increased dendritic spine density and head size in layer V pyramidal neurons of the mouse prefrontal cortex within 24 hours, with effects persisting for at least one month. Importantly, these changes correlated with improved behavioral flexibility in a fear extinction paradigm.[29]

Similarly, result of another work demonstrated that psychedelics such as LSD, DOI, and DMT enhanced dendritic arbor complexity and spine growth in cultured cortical neurons, with in vivo confirmation in rodents.[30] These findings suggest that psychedelics function as “psychoplastogens”, compounds capable of rapidly stimulating structural plasticity.

3.2 Synaptic Function and Electrophysiology

In addition to morphology, psychedelics modulate synaptic strength and excitatory transmission. Hesselgrave et al. reported that psilocybin enhanced excitatory postsynaptic currents in the medial prefrontal cortex (mPFC), consistent with greater AMPA receptor recruitment.[31] These synaptic changes were accompanied by elevated expression of PSD-95 and GluA1, proteins critical for excitatory synapse stability.

Interestingly, psychedelic induced electrophysiological changes mirror those observed with ketamine, suggesting that both classes of rapid-acting antidepressants converge on glutamate-mediated plasticity. This convergence reinforces the idea that synaptic remodeling, rather than monoamine reuptake inhibition, is central to durable therapeutic effects.

3.3 Behavioral Correlates of Plasticity

Rodent behavioral paradigms provide evidence that neuroplastic changes translate into functional benefits. Psilocybin and DMT enhance extinction of conditioned fear, a process relevant to PTSD. Similarly, rodents exposed to psychedelics display increased cognitive flexibility in set shifting and reversal learning tasks, reflecting enhanced prefrontal cortical adaptability.[32]

Chronic stress and depression models, such as chronic unpredictable stress (CUS) or learned helplessness, show rapid reversal of anhedonia and despair like behaviors following psilocybin or ayahuasca administration.[33] These behavioral effects often persist beyond the acute pharmacological window, implying that underlying structural changes support long term resilience.

Together, animal studies demonstrate that psychedelics induce multi-level plasticity structural, functional, and behavioral that is conserved across species.

4. Functional Connectivity and Network Reorganization

One of the most consistent findings from fMRI studies is that psychedelics reorganize large scale brain networks. Acute psilocybin and LSD administration reduce connectivity within the default mode network (DMN), a system implicated in self-referential processing and rumination.[34] Concurrently, psychedelics increase global integration and cross network communication, producing a more flexible and less rigid network architecture.

Importantly, these network level changes correlate with long term clinical improvements. Carhart Harris et al. showed that psilocybin treatment for depression reduced DMN hyperconnectivity and increased functional coupling between the mPFC and amygdala, paralleling symptom relief, similarly, LSD increased connectivity between sensory and associative networks, consistent with enhanced perceptual integration.[35] These observations support the idea that psychedelics relax maladaptive brain networks, enabling relearning and adaptive plasticity.

4.1 Structural MRI and Cortical Morphometry

Although fewer in number, structural MRI studies suggest that psychedelics may induce longer term changes in brain morphology. One study found that long term ayahuasca users exhibited increased cortical thickness in regions associated with emotional regulation, including the anterior cingulate cortex and insula. These findings parallel rodent data showing persistent dendritic spine growth after psilocybin.

Longitudinal imaging following therapeutic psilocybin sessions has also reported volumetric and surface area changes in the hippocampus and prefrontal cortex, though replication is needed.[36] Such structural changes may reflect consolidation of the acute neuroplastic state into durable network level adaptations.

4.2 Magnetic Resonance Spectroscopy (MRS) and Glutamatergic Signatures

MRS studies provide neurochemical evidence of psychedelic induced plasticity by quantifying in vivo metabolite concentrations. Psilocybin administration in healthy volunteers increased glutamate levels in the medial prefrontal cortex and hippocampus, consistent with the excitatory drive observed in rodent electrophysiology.[37] Elevated glutamate is thought to trigger downstream BDNF release and mTOR activation, key drivers of structural plasticity.

Moreover, MDMA has been associated with increased cerebral blood flow and lactate levels, suggesting heightened metabolic activity that may accompany synaptic remodeling. While still preliminary, MRS findings align with the hypothesis that glutamate surges act as a molecular gateway to neuroplastic reprogramming in humans.

4.3 EEG and MEG Biomarkers of Neural Flexibility

Electrophysiological measures further support psychedelic-induced plasticity. Psilocybin and LSD reduce alpha-band oscillations and increase broadband signal diversity, a marker of neural entropy. Higher entropy reflects greater flexibility in neural activity patterns, aligning with the subjective sense of expanded cognition and openness.

Notably, increased signal diversity correlates with reductions in depressive symptoms and trait rigidity. MEG studies have also shown that psilocybin enhances long-range synchronization in gamma frequencies, consistent with improved integration of distributed networks.[38] These dynamic changes suggest that psychedelics temporarily shift the brain into a hyperplastic state conducive to reorganization.

4.4 Peripheral Biomarkers: BDNF and Epigenetic Signatures

Peripheral measures provide indirect evidence of neuroplasticity. Several clinical studies have reported increases in serum BDNF following psilocybin or ayahuasca administration.[39,40] BDNF levels correlated with subjective mystical-type experiences and long-term improvements in depressive symptoms, supporting its role as a biomarker of therapeutic response.

Epigenetic changes have also been detected in peripheral blood mononuclear cells after ayahuasca and psilocybin administration, including DNA methylation shifts at plasticity-related genes.[41] While peripheral measures may not perfectly reflect central changes, they provide valuable translational biomarkers and may guide individualized treatment optimization.

5. Therapeutic Implications and Translational Challenges

The convergence of mechanistic, preclinical, and clinical evidence suggests that psychedelics represent a new therapeutic paradigm in psychiatry, rather than suppressing symptoms via chronic modulation of neurotransmission, they act as catalysts of neuroplasticity, opening a window for adaptive relearning and long-lasting network reorganization. However, the translation of these findings into clinical practice faces significant opportunities and challenges.

5.1 Rapid-Acting Antidepressant Effects

One of the most compelling therapeutic implications is the ability of psychedelics to produce rapid and sustained antidepressant effects. Clinical studies have consistently shown that a single high dose of psilocybin can alleviate depressive symptoms within hours, with benefits persisting for weeks to months.[42,43] These contrasts sharply with traditional SSRIs, which often require weeks of daily dosing and may provide incomplete relief. Mechanistically, the rapid induction of synaptogenesis and dendritic spine growth provides a plausible substrate for these enduring changes.[44] The convergence of psychedelic and ketamine induced plasticity also underscores the broader principle that enhancing structural remodeling may be a common final pathway for fast acting antidepressants.

5.2 Post-Traumatic Stress Disorder (PTSD) and Fear Extinction

PTSD is characterized by maladaptive fear memories and impaired extinction learning. Preclinical evidence shows that psychedelics facilitate fear extinction and reconsolidation updating. Human studies suggest that MDMA, in particular, enhances fear extinction when combined with psychotherapy, leading to FDA-designated "breakthrough therapy" status for PTSD.[45] The plasticity promoting effects of psychedelics may reopen a critical therapeutic learning window, enabling patients to reconsolidate traumatic memories in a safer emotional context. This highlights the importance of integrating psychedelics with psychotherapy, rather than using them as standalone pharmacological agents.

5.3 Addiction and Maladaptive Habit Circuits

Substance use disorders (SUDs) involve rigid, compulsive behaviors and dysfunctional reward learning. Psychedelics show promise in disrupting these maladaptive circuits. For example, psilocybin assisted therapy has demonstrated efficacy in reducing alcohol and tobacco use, with sustained abstinence in many participants.[46] Mechanistically, psychedelics may promote neuroplastic remodeling of cortico-striatal circuits, restoring cognitive flexibility and reducing compulsive behaviors.[47] Additionally, the profound subjective experiences induced by psychedelics such as ego dissolution and enhanced meaning making may synergize with biological plasticity to break addictive cycles.

5.4 Anxiety, Existential Distress, and End-of-Life Care

Psychedelics also hold therapeutic potential in reducing existential anxiety among patients with terminal illness. Randomized controlled trials show that psilocybin produces sustained reductions in death anxiety, depression, and demoralization in cancer patients. Neuroimaging evidence suggests that these improvements correlate with reduced DMN hyperactivity and greater emotional processing flexibility.[48] This application highlights the unique transdiagnostic potential of psychedelics, rather than targeting a single neurotransmitter imbalance, they may address the core neurobiological rigidity underlying multiple psychiatric syndromes.

5.5 Safety Considerations and Risks

Despite their promise, psychedelics are not without risks. Acute adverse effects include anxiety, transient paranoia, and physiological changes such as hypertension or tachycardia. Importantly, unregulated use outside controlled settings can lead to dangerous behaviors or exacerbate underlying psychotic disorders. Concerns also exist around excessive or

maladaptive plasticity. Just as psychedelics can facilitate beneficial learning, they may also reinforce harmful associations if administered without therapeutic guidance.[49] This underscores the importance of set and setting, as well as careful patient screening.

5.6 Regulatory, Ethical, and Logistical Challenges

The path to widespread clinical adoption faces multiple translational hurdles. Regulatory restrictions, most psychedelics remain Schedule I substances under international law, complicating research and clinical deployment. Scalability of therapy models, psychedelic therapy often requires extensive psychological support, raising questions about how to scale safely in diverse healthcare systems.[50] Training and standardization, there is currently no universally accepted framework for therapist training, dosage protocols, or integration practices.[51] Intellectual property debates, attempts to patent psychedelic compounds and protocols raise ethical concerns about accessibility and equity.[52] Addressing these barriers will be critical to ensure safe, equitable, and scientifically rigorous integration of psychedelics into modern psychiatry.

6. Mechanistic Gaps and Next-Generation Tools

Although preclinical studies have revealed that psychedelics engage canonical BDNF TrkB–mTOR pathways and modulate glutamate transmission via 5-HT2A activation, many details remain unresolved. For instance, the cell type specificity of these effects (excitatory vs inhibitory neurons, pyramidal vs interneurons) remains unclear.[53] Similarly, the temporal dynamics of structural plasticity how long dendritic spine changes persist, and whether they differ across brain regions require further mapping.[54] Emerging tools such as single cell transcriptomics, optogenetics, and spatial proteomics could elucidate how psychedelics orchestrate complex molecular cascades across neuronal and glial populations.[55] Furthermore, the exploration of non-hallucinogenic analogues ("psychoplastogens") may enable disentanglement of therapeutic neuroplasticity from subjective psychedelic experience.[56]

6.1 Personalization and Precision Psychiatry

Not all patients respond equally to psychedelic assisted therapy, and predictors of response remain poorly defined. Interindividual variability in genetic, epigenetic, and personality factors may shape therapeutic outcomes.[57] Additionally, differences in subjective experience quality such as intensity of mystical-type experiences have been linked to clinical efficacy. Future research must integrate biomarker discovery (EEG, fMRI, peripheral BDNF levels)

with computational modeling and stratification to optimize patient selection and personalize treatment protocols.[58] Precision approaches may reduce risks while maximizing benefits across diverse psychiatric populations.

Although psychiatric disorders remain the primary focus, psychedelics' plasticity enhancing effects may extend to neurological diseases such as stroke, traumatic brain injury, or neurodegenerative disorders.[59] Preclinical works already suggest roles for DMT and related tryptamines in promoting neurogenesis and functional recovery after ischemia.[60] Similarly, sigma-1 receptor engagement could be leveraged for neuroprotective applications in Alzheimer's or Parkinson's disease.[61] However, clinical translation in neurology is nascent and requires rigorous safety evaluation. The potential for psychedelics to act as broad-spectrum plasticity enhancers across mental and neurological conditions is a frontier worth exploring.

6.2 Ethical, Cultural, and Societal Dimensions

The reintroduction of psychedelics into medicine carries profound cultural implications. Historically, many of these substances have roots in Indigenous healing traditions, raising ethical questions around appropriation, reciprocity, and respect for traditional knowledge.[62] Furthermore, issues of access, affordability, and equity will determine whether psychedelic therapies benefit all patients or remain restricted to privileged populations.[63] Global discussions must also grapple with the tension between medicalization and decriminalization. Striking a balance between evidence-based clinical use and broader cultural integration will shape the trajectory of this emerging field.[64]

6.3 CONCLUSION

Psychedelics represent a paradigm shift in neuroscience and psychiatry, offering rapid and lasting benefits through their ability to enhance neuroplasticity where conservational treatments often fall short. Their therapeutic promise, however, is complex and shaped by biological, experimental, and social factors, requiring a multidisciplinary approach. Future progress will hinge on advancing scientific understanding, refining clinical applications, and addressing ethical, policy, and societal considerations that will determine their integrations into mainstream mental health care.

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