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# Psychedelics and Neural Plasticity: Therapeutic Implications

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**Psychedelic drugs have reemerged as tools to treat several brain disorders. Cultural attitudes toward them are changing, and scientists are once again investigating the neural mechanisms through which these drugs impact brain function. The significance of this research direction is reflected by recent work, including work presented by these authors at the 2022 meeting of the Society for Neuroscience. As of 2022, there were hundreds of clinical trials recruiting participants for testing the therapeutic effects of psychedelics. Emerging evidence suggests that psychedelic drugs may exert some of their long-lasting therapeutic effects by inducing structural and functional neural plasticity. Herein, basic and clinical research attempting to elucidate the mechanisms of these compounds is showcased. Topics covered include psychedelic receptor binding sites, effects of psychedelics on gene expression, and on dendrites, and psychedelic effects on microcircuitry and brain-wide circuits. We describe unmet clinical needs and the current state of translation to the clinic for psychedelics, as well as other unanswered basic neuroscience questions addressable with future studies.**

*Key words:* **psychedelics; psychoplastogens; plasticity; 5-HT2AR; circuits**

## Introduction

A unique and fascinating feature of psychedelics is that intake of one or a few doses is associated with long-lasting effects on behaviors, attitudes, mood, and personality in humans, but the mechanistic relationship between exposure to a single dose and long-term therapeutic effects still needs to be established. The term "psychoplastogen" was coined to distinguish compounds that produce rapid and sustained effects from those that induce plasticity following chronic administration (e.g., traditional antidepressants). By definition, psychoplastogens are therapeutics that rapidly induce neuroplasticity following a single dose leading to long-lasting changes in behavior. This can include classical psychedelics and psychedelic-like compounds. As the definition of "psychedelic" is somewhat vague, efforts have been made to classify molecules into distinct subclasses based on their pharmacological profiles and unique subjective effects. Classical psychedelics are defined as mind-manifesting drugs that produce their hallucinogenic effects through activation of serotonin 2A receptors (5-$HT_{2A}$Rs). This research space also currently includes psychedelic-like compounds, such as dissociative anesthetics (e.g., the NMDAR antagonist ketamine), entactogens (e.g., the 5-HT releaser 3,4-methylenedioxymethamphetamine, also known as MDMA or "ecstasy"), and deliriants (e.g., the anticholinergic drug scopolamine) (Fig. 1*A*).

Research on psychedelics waned after the passing of the Controlled Substance Act by Congress in 1970 (Nichols, 2016). Currently, there is renewed interest in the therapeutic potential of psychedelics, a class of compounds with "mind-manifesting" properties (i.e., compounds with properties that manifest characteristics of the mind) (Nichols and Walter, 2021). The FDA's "breakthrough therapy" designation, a process designed to expedite the development and review of drugs that may demonstrate significant improvement over available treatments, of several psychedelic-related compounds, reflects a growing optimism that these molecules might be useful for treating various neuropsychiatric disorders. This designation was granted for ketamine in 2013 for treatment-resistant depression, for MDMA in 2017 for post-traumatic stress disorder (PTSD), and for psilocybin in 2019 for treatment-resistant depression. In 2019, Janssen's SPRAVATO (S-ketamine) nasal

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D.E.O. is a co-founder and the chief innovation officer of Delix Therapeutics, Inc.; A.C.K. is on the board of scientific advisors for Empyrean Neuroscience and Freedom Biosciences. A.C.K. has consulted for Biohaven Pharmaceuticals. No-cost compounds were provided to A.C.K. for research by Usona Institute. The remaining authors declare no competing financial interests.

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spray was granted FDA approval for treatment-resistant depression, potentially paving the way for MDMA and psilocybin to follow suit. Ketamine therapy is currently the only "breakthrough therapy" of the three to be FDA approved. The European Medicines Agency has also approved Phase III parallel studies on ketamine backed by the Multidisciplinary Association of Psychedelic Research. It is possible that MDMA therapy could receive FDA approval for treating PTSD as early as 2023, while psilocybin's development timeline appears to be a bit longer. The psychedelics drug market has potential for reaching many patients.

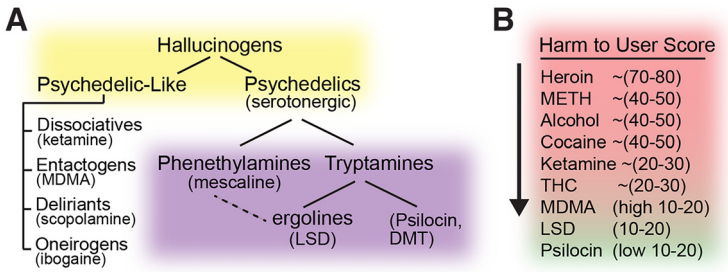


**Figure 1.** Psychedelics. ***A***, Psychedelics are mind-altering drugs that produce their hallucinogenic effects through activation of 5-$HT_{2A}$Rs. Psychedelic-like drugs include dissociative anesthetics (e.g., ketamine), entactogens (e.g., MDMA or "ecstasy"), deliriants (scopolamine), and oneirogens (ibogaine). ***B***, Psychedelics are much less harmful to users than other recreational drugs (see Nutt et al., 2010).

Several natural psychedelics were introduced to Western ethnobotanists by indigenous cultures that had discovered medicinal and/or religious uses for related plants and fungi. Chemists determined many of the psychoactive agents in these botanicals by the ~1960s, including psilocybin and its active metabolite psilocin (from "magic mushrooms"), *N,N*-dimethyltryptamine (DMT, from the plant mixture ayahuasca), salvinorin A (from the plant *Salvia divinorum*), and mescaline (from the peyote cactus). Because of their psychotropic effects, and relatively low potential for abuse (Fig. 1*B*), these substances have proven to be important tools to the field of psychiatry (Vargas et al., 2021). Lysergic acid diethylamide (LSD) is a prime example of a classical psychedelic, identified by serendipitous discovery. It was originally synthesized by Swiss chemist Albert Hoffman for purposes unrelated to perceptual alterations. Ketamine, a psychedelic-like compound, is a structural analog of phencyclidine and has been used as an anesthetic for many years. More recently, some have heralded the discovery of ketamine's antidepressant effects as "the most important discovery in half a century" for neuropsychiatry (Duman, 2018). Whether nature- or laboratory-made, psychedelics are a topic of fast-moving research.

While the subjective effects induced by psychedelics may offer some distinct benefits to patients (Yaden and Griffiths, 2020), there are potential pitfalls to psychedelic-assisted psychotherapy. These drugs induce perceptual alterations and are not well tolerated by all patients. The clinical use of psychedelics thus requires extensive patient preparation, monitoring, and follow-up, which is time-consuming and expensive (Olson, 2020). There are also side effects associated with psychedelics which may limit their clinical scalability (e.g., cardiotoxicity and abuse potential). To circumvent these issues, scientists are attempting to develop shorter-acting psychedelics or nonhallucinogenic analogs of psychedelics with no or limited mind-manifesting properties, but that retain therapeutic properties (Cameron and Olson, 2022). Whether such chemical modifications are compatible with therapeutic efficacy remains to be shown in the clinic.

One example of a potentially efficacious compound is the nonhallucinogenic psychedelic analog tabernanthalog (TBG), a compound structurally related to the naturally occurring compounds 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) and ibogaine. TBG induces structural neural plasticity both in *vitro* and *in vivo*, and produces both anti-depression-like and anti-addictive effects in rodents (Cameron et al., 2021). Similarly, *R*-ketamine may be less mind-manifesting than *S*-ketamine. The investigational new drug application for *R*-ketamine was recently approved, allowing Perception Neuroscience to begin clinical trials in the United States for major depressive disorder. In addition, (*2R,6R*)-hydroxynorketamine (*R,R*-HNK), a metabolite of *R*-ketamine with low affinity for NMDA-type glutamate receptors (Highland et al., 2021), produces antidepressant-like and plasticity-promoting effects without psychotomimetic effects in rodents (Zanos et al., 2016; Yao et al., 2018), and is now in Phase 1 clinical trials for major depressive disorder, sponsored by the National Institute of Mental Health.

Classical psychedelics, such as psilocybin, LSD, and other serotonergic psychedelics of the tryptamine and ergoline classes, have been instructive for understanding how analogs might produce therapeutic effects. Classical psychedelics bind to 5-$HT_{2A}$R, a GPCR that activates various intraneuronal signaling pathways. While LSD binds to the orthosteric site of the 5-$HT_{2A}$R, certain ergoline-like analogs of LSD bind to the 5-$HT_{2A}$R at an extended binding pocket (Cao et al., 2022). These analogs produce antidepressant-like effects without causing increases in the head-twitch response, a behavior associated with classical psychedelics (González-Maeso et al., 2007). Thus, a psychedelic and its analog can be differentiated mechanistically at the molecular level.

In this article, we review the current state-of-the-field focusing primarily on our own work on psychedelics. Highlights span a wide range of psychedelic research topics within the broader theme of therapeutic neural plasticity. We include receptor actions of the fast-acting antidepressant ketamine, as well as the effects of ketamine and other classical psychedelics (psilocybin, LSD, etc.) on the expression of genes relevant to neuroplasticity measured both structurally and functionally. We highlight the effects of psychedelics on circuits, both microcircuits and brain-wide circuits, to induce reopening of critical period-like neural plasticity and to produce behavioral effects. We compare mechanisms of plasticity for psychedelics with other plasticity-promoting molecules, such as traditional antidepressants and drugs of abuse with addictive properties (Fig. 2*A*,*B*). We present approaches for testing the effects of psychedelics in the human brain which presents unique challenges. Each section presents key experimental models and findings critical to understanding the therapeutic effects of psychedelics on neural plasticity. The clinical implication of this research is presented wherever possible, along with a discussion of any potential hurdles toward translation.

## Receptor binding of traditional antidepressants and ketamine

Promotion of neural plasticity is the central mechanism through which ketamine and other antidepressants bring about their clinical effects on mood recovery. Ketamine-induced plasticity has been investigated using ocular dominance plasticity (ODP) after

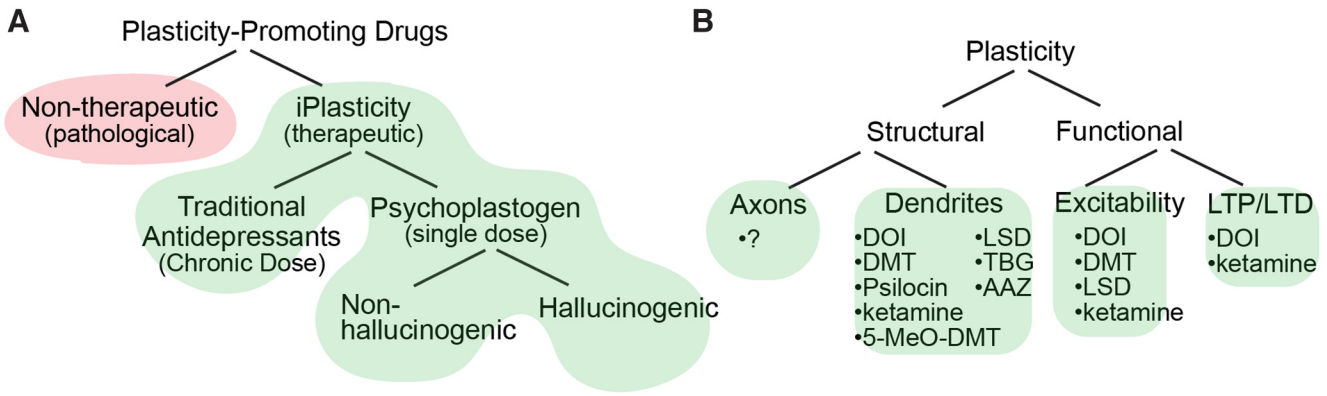


**Figure 2.** Psychedelics and neuroplasticity. ***A***, Many traditional antidepressants (SSRIs) promote iPlasticity: they induce juvenile-like plasticity in the adult brain (see Castrén, 2005; Umemori et al., 2018). A property of many psychedelics is that they are psychoplastogens: they are exogenously administered therapeutic drugs that promote long-lasting neuroplasticity after a single dose (see Olson, 2018). ***B***, To date, evidence of promoting structural or functional plasticity has been shown for several psychedelics or psychedelic-like drugs (see Olson, 2020; de Vos et al., 2021; Lukasiewicz et al., 2021; Jaster et al., 2021).

monocular deprivation in mammalian visual cortex, a classical model of cortical plasticity (Hübener and Bonhoeffer, 2014). Previous studies had shown that chronic treatment with the selective 5-HT reuptake inhibitor (SSRI) antidepressant fluoxetine reactivates a critical period-like plasticity in the adult visual cortex and allows the recovery of visual acuity in an amblyopic eye in a rat model (Maya Vetencourt et al., 2008), and this has been coined iPlasticity (Castrén, 2005). Using the same model, both ketamine and its metabolite *R*,*R*-HNK also reactivate ODP in the murine visual cortex but do so with a much faster time scale than fluoxetine does, consistent with their faster onset of antidepressant-like effects (Casarotto et al., 2021; Cannarozzo et al., 2022). *R*,*R*-HNK produces an ODP response comparable to that of fluoxetine, but preliminary data suggest that the size of the effects of ketamine is more restricted, albeit significant (Cannarozzo et al., 2022), perhaps because ketamine inhibits NMDARs, which is known to restrict ODP (Sawtell et al., 2003). The effects of fluoxetine and ketamine are dependent on signaling of BDNF through its neurotrophic tyrosine kinase receptor 2 (NTRK2, TRKB) (Maya Vetencourt et al., 2008; Casarotto et al., 2021). Importantly, antidepressants reactivate early-life plasticity also in mood-relevant circuitry (Autry et al., 2011; Karpova et al., 2011; Duman, 2018), suggesting that the enhanced ability to rewire abnormal networks, guided by environmental experiences, may underlie the antidepressant effect (Castrén, 2013).

The mechanisms through which ketamine promotes neural plasticity are unclear. Ketamine is considered to act by binding to and inhibiting NMDARs. However, other NMDAR antagonists do not show antidepressant effects (Zarate et al., 2006), and *R*,*R*-HNK does not bind to NMDARs at the doses that produce antidepressant-like responses in mice (Zanos et al., 2016). Therefore, increasing evidence suggests a dissociation between the inhibition of NMDARs and the antidepressant effects of ketamine.

Recently, ketamine has been found to allosterically increase signaling by BDNF by binding directly to TRKB, the high-affinity BDNF receptor (Casarotto et al., 2021). The affinities of ketamine to TRKB and NMDARs are similar, and concentrations sufficient for binding to both receptors are achieved during ketamine treatment. Importantly, *R*,*R*-HNK binds to TRKB, but not to NMDARs, at concentrations that promote neural plasticity, suggesting that TRKB may be the hitherto unknown signaling receptor for *R*,*R*-HNK (Zanos et al., 2016). Furthermore, other drugs with clinical antidepressant effects (SSRIs and tricyclic antidepressants) bind to this same site in TRKB with an affinity that is comparable to that of ketamine (Casarotto et al., 2021). SSRIs and tricyclic antidepressants bind to a pocket formed by the dimers of TRKB transmembrane domains (TMDs) that cross each other within the cell membrane. Data suggest a model where binding of antidepressants within the plasma membrane stabilizes a signaling-competent conformation of TRKB dimers and thereby increases the retention of TRKB within synaptic membranes where they are bound by synaptic BDNF (Casarotto et al., 2021). Removal of a single atom of oxygen (tyrosine 433 to phenylalanine mutation, Y433F) from the TRKB TMD region, where the antidepressants are predicted to bind, blocks binding of ketamine, fluoxetine, and imipramine to TKRB. This prevents both the plasticity-promoting and the antidepressant-like behavioral effects of these drugs. These data suggest that binding to the TRKB TMD may be the common site of action for all antidepressant drugs. The model further proposes that antidepressants, including ketamine, are not direct agonists of TRKB, but by promoting a signaling-competent configuration within the plasma membrane, they promote signaling by endogenous BDNF that is synaptically released in an activity-dependent manner. Therefore, as selection of active synapses versus the inactive ones is a critical feature of neural plasticity and iPlasticity, antidepressants, through binding to TRKB, promote activity-dependent synapse selection.

## Receptor binding of psychedelics

The mechanism by which a single psychedelic dose brings about long-lasting therapeutic effects for humans is only now starting to be explored in clinical studies (for review, see Knudsen, 2022; and see below). As mentioned above, classical psychedelics, such as LSD, DMT, and psilocybin, bind to the 5-$HT_{2A}$R, a GPCR that activates various intraneuronal signaling pathways. Since the subjectively reported intensity of the psychedelic experience of psilocybin in humans correlates with 5-$HT_{2A}$R occupancy and plasma psilocin levels (Madsen et al., 2019; Stenbæk et al. 2021), it will be informative to compare the behavioral effects of comparable drug exposures in humans and in nonhuman animals (Donovan et al., 2021) (i.e., doses that are associated with a 5-$HT_{2A}$R occupancy of 40%-70% in nonhuman animals). Whereas the correlation between plasma drug levels, cerebral 5-$HT_{2A}$R occupancy, and the perceived intensity of the

psychedelic experience is well established for psilocybin, these associations should also be established for other psychedelics, such as LSD and DMT. This would ensure that psychedelic drugs are compared at the same level of 5-$HT_{2A}$R occupancy, which could clarify whether different psychedelics have comparable effects or whether their effects are distinct because of differences in efficacy, functional selectivity, or polypharmacology (Griffiths et al., 2011; MacLean et al., 2011; Holze et al., 2022).

A question of particular relevance for the development of 5-$HT_{2A}$R agonists without hallucinogenic properties is whether the psychedelic experience itself is a prerequisite for the beneficial effects of the drugs (Olson, 2020; Yaden and Griffiths, 2020). Supporting the view that the psychedelic experience is required for their therapeutic effects, participants who have so-called mystical experiences during psilocybin sessions score significantly higher compared with baseline on the personality trait Openness, and the change is correlated to the intensity of the experience (MacLean et al., 2011). Mystical experiences include a sense of profound unity with all that exists, a sense of sacredness and of truth and reality, deeply felt positive mood, transcendence of time and space, and difficulty explaining the experience in words, and can be assessed with the Mystical Experience Questionnaire (Barrett et al., 2015). The strength of mystical experience also correlates with therapeutic effects in cigarette smoking cessation (Garcia-Romeu et al., 2014) and with diminished anxiety and depression in terminal cancer patients (Griffiths et al., 2016; Ross et al., 2016; Barrett et al., 2020). Alternatively, some preclinical studies have shown that psilocybin-induced neuroplasticity may not depend on 5-$HT_{2A}$R (Hesselgrave et al., 2021), suggesting a potential mechanism by which psychedelics could be therapeutic without the psychedelic experience, assuming that psychedelic experiences are 5-$HT_{2A}$R-mediated.

In healthy individuals, increased Openness is a key long-term effect of psychedelics; and interestingly, psilocybin studies in healthy individuals show that neocortex 5-$HT_{2A}$R binding as measured with PET is negatively associated with the peak-plateau duration of the experience and with the Mystical Experience Questionnaire total score (Madsen et al., 2021), meaning that individual differences in baseline cerebral 5-$HT_{2A}$R could determine likelihood to experience positive/therapeutic effects. In patients with moderate or severe, unipolar treatment-resistant depression, psilocybin given twice, 1 week apart, increases Openness and Extraversion at a 3 month follow-up (Erritzoe et al., 2018).

While molecular changes associated with neuronal plasticity (signaling pathways, gene expression, and protein synthesis) are difficult to assess *in vivo* in the human brain, BDNF and other plasticity-promoting factors can be measured in serum or whole blood (but not reliably in plasma or CSF) (Trajkovska et al., 2007). Although never documented in humans, peripheral measures of BDNF appear to reflect brain tissue content well in other species (Klein et al., 2011). Whether serum BDNF (and potentially other neurotrophic factors) are increased by psychedelics remains to be firmly established. Two studies measured plasma BDNF before and after LSD intervention, finding no change (Holze et al., 2021; Hutten et al., 2021), but it would be better to know the temporal profile of serum BDNF in the case that changes are more reliably measured there (de Almeida et al., 2019).

In addition to peripheral measurement of BDNF, another read-out of the effect of psychedelic compound binding of the 5-$HT_{2A}$R in human brain, is glutamate release, which unlike BDNF measurements, can be readily quantified in human brain (Dos Santos and Hallak, 2020; Mason et al., 2020). Temporal and regional profiles of glutamate release in the human brain have been correlated to changes in brain volume (McKinnon et al., 2009; Santos et al., 2018), perturbations in task-related fMRI, and in resting state functional brain connectivity (Sampedro et al., 2017; Barrett et al., 2020; Madsen et al., 2021; McCulloch et al., 2022). Knowing the temporal profile of these measures will provide a more complete understanding of processes important for the long-lasting effects of these drugs. Moreover, they will provide a basis for forming testable hypotheses about the neural plasticity changes relevant to clinical effects. Long-lasting changes in neural plasticity could potentially also be measured with functional imaging or SV2A PET ligands in humans (Raval et al., 2021; Knudsen, 2022).

**Effects of psychedelics on gene expression**

The long-lasting effects of psychedelics on mood in humans are paralleled by long-lasting structural changes in neurons in non-human animals. For example, a short 15 min to 1 h stimulation of cultured cortical neurons with ketamine or LSD leads to neuronal growth that persists long after the compounds have been removed from the culture media (Ly et al., 2021). Moreover, after psilocybin administration, a higher density of dendritic spines is observed in the mPFC of the mouse for at least 1 month (Shao et al., 2021), despite the fact that psilocybin is rapidly cleared from the body. It is well established that new dendritic spines require synaptic machineries to be functional (Knott et al., 2006). But, in order for protein machinery to be maintained long-term at synapses, cell-wide signals involving activity-dependent transcription must take place (Yap and Greenberg, 2018), potentially as a result of epigenomic changes (de la Fuente Revenga et al., 2021).

Pioneering work on the effects of neural activity on gene expression (relevant to the mechanisms of action for psychedelics), focused on immediate early genes (IEGs), which are implicated in long-term cellular responses to external stimuli and spiking activity. IEGs, such as c-Fos, are transcription factors that regulate gene expression, while other IEGs, such as Arc, are effectors. Leslie et al. (1993) measured the effects of the psychedelic DOI on c-Fos expression in rats. Elevated c-Fos expression is detected 30 min after drug administration, and reaches a peak at 3 h before declining to background (Leslie et al., 1993). This and subsequent work on LSD and psilocybin reveal region-specific elevation of c-Fos expression in frontal, parietal, piriform, and cingulate cortices, as well as the claustrum, and amygdala (Leslie et al., 1993; Erdtmann-Vourliotis et al., 1999; Frankel and Cunningham, 2002; Gresch et al., 2002; Davoudian et al., 2022).

Serotonergic agonists and psychedelics also increase expression of the effector IEG Arc (Pei et al., 2004). DOI-elicited elevations of Arc and c-Fos expression colocalize in the same cortical cells (Pei et al., 2004). Their expression depends fully on functional 5-$HT_{2A}$Rs (Leslie et al., 1993; Scruggs et al., 2000; González-Maeso et al., 2003; Nichols et al., 2003; Pei et al., 2004), and partially on AMPARs and NMDARs (Scruggs et al., 2000; Pei et al., 2004). The colocalization and similarities in receptor dependence suggest a single mechanism that drives the psychedelic-evoked expression of different IEGs.

If psychedelics act on similar receptors to initiate a single mechanism of action, it will be important to determine whether there is also a single-cell type that responds to psychedelics. Immunohistochemical staining shows that DOI- and LSD-evoked

c-Fos signals do not occur in 5-$HT_{2A}$R-expressing neurons in rat neocortex (Scruggs et al., 2000; Gresch et al., 2002). Yet, *Htr2a* mRNA transcripts are detected in c-Fos-positive cells after psychedelic treatment (González-Maeso et al., 2007; Martin and Nichols, 2016). This discrepancy may be because antibodies for 5-$HT_{2A}$Rs are not specific, or the *Htr2a* transcripts may not reflect protein levels. c-Fos expression in the neocortex may be preferentially induced in GABAergic interneuron (Abi-Saab et al., 1999; Martin and Nichols, 2016).

Microarrays used to screen targets in cortical tissues within hours after LSD administration reveal differential expression of not only IEGs, but also genes for synaptic function and immune suppression (Nichols and Sanders-Bush, 2002). In one notable study, González-Maeso et al. (2007) tested DOI, mescaline, LSD, psilocin, as well as nonhallucinogenic 5-$HT_{2A}$R agonists, such as ergotamine and lisuride. Differential expression of Egr-1 and Egr-2 distinguished hallucinogenic compounds from nonhallucinogenic compounds (González-Maeso et al., 2007). Other recent work highlights other genes exhibiting expression changes following psilocybin treatment (Donovan et al., 2021; Jefsen et al., 2021).

As mentioned earlier, psychedelic binding or activation of G-proteins, such as 5-$HT_{2A}$Rs and their associated pathways, contributes to gene expression responses (González-Maeso et al., 2007; Banerjee and Vaidya, 2020), epigenetic modifications alter transcriptional activation and repression (de la Fuente Revenga et al., 2021), and BDNF may mediate the cellular and molecular effects. For example, DOI causes a dose-dependent and 5-$HT_{2A}$R-dependent increase of BDNF mRNA in rat neocortex as early as 1 h after administration (Vaidya et al., 1997). Notably, the induction of IEGs is attenuated significantly if DOI is administered in BDNF KO mice (Benekareddy et al., 2013); and when TrkB is blocked, the ability of psychedelics to stimulate neurite growth in cultured neurons is abolished (Ly et al., 2018). This highlights the role of BDNF as a point of convergence for psychedelics and ketamine effects on dendrites (Ali et al., 2020; Savalia et al., 2021), BDNF signaling pathways (Li et al., 2010; Wang et al., 2022), and structural neural plasticity (Li et al., 2010; Phoumthipphavong et al., 2016). Direct comparison of the transcriptional impact of psychedelics and ketamine (Donovan et al., 2021; Davoudian et al., 2022; Lopez et al., 2022) should provide valuable insights into their therapeutic actions.

### Effects of psychedelics on dendrites

Synaptic dysfunction and altered synaptic plasticity are closely associated with neurologic and psychiatric disorders (Goto et al., 2010; Forrest et al., 2018; Wang et al., 2018). The 5-$HT_{2A}$R, a common target of psychedelics, is expressed on dendritic shafts and dendritic spines of cortical neurons in both rodents and primates (Jakab and Goldman-Rakic, 1998; Miner et al., 2003; Jones et al., 2009; Weber and Andrade, 2010; Yoshida et al., 2011). In recent years, accumulating evidence indicates that psychedelic compounds that bind 5-$HT_{2A}$Rs rapidly promote neural plasticity both structurally and functionally, suggesting that this is a potential mechanism underlying the therapeutic effects of psychedelics (Olson, 2018; Inserra et al., 2021a; Kadriu et al., 2021).

*In vitro* studies reveal that psychedelics promote dendritic growth and increase synaptic connections. DOI, one of the more readily accessible psychedelics to researchers, has been shown to increase dendritic growth (Persico et al., 2006; Ohtani et al., 2014; Ly, Greb et al., 2018; Ly et al., 2021), synaptic puncta, spine density (Yoshida et al., 2011; Ly et al., 2018), and spine size (Jones et al., 2009) in cultured cortical neurons. Like DOI, classical psychedelics from the tryptamine and ergoline families also promote dendritogenesis and spinogenesis in cultures of cortical neurons. This enhanced spine growth might be associated with synaptogenesis, as evidenced by an increase in the overlap of presynaptic and postsynaptic puncta (Ly et al., 2018). These neuroplasticity effects are blocked by cotreatment with the 5-$HT_2$R antagonist ketanserin and likely involve a TrkB- and mTOR-dependent mechanism (Ly et al., 2018).

*In vivo* studies reveal that psychedelics promote dendritic growth and increase synaptic connections as well. A high dose of DMT (10 mg/kg) increases spine density on pyramidal neurons in the PFC of adult rats, which is accompanied by an increase in spontaneous EPSCs recorded *ex vivo* (Ly et al., 2018). DOI treatment (2 mg/kg) increases the density of stubby and thin, but not mushroom, spines on cortical neurons in the mouse frontal cortex; it also enhances LTP at synapses onto these neurons (de la Fuente Revenga et al., 2021). Taking advantage of transgenic mice expressing fluorescent proteins in cortical neurons and *in vivo* two-photon microscopy, recent studies have begun to study the effects of psychedelics on the dynamics of synaptic structures. A single dose of DOI (10 mg/kg) promotes dendritic spine formation on L5 pyramidal neurons in the mouse sensory cortex within 1 d without affecting spine elimination (Cameron et al., 2021). Similarly, psilocybin promotes spine formation in the PFC and significantly increases spine density (Shao et al., 2021). Psilocybin increases the head size of spines on cortical neurons (Shao et al., 2021) and the AMPA/NMDA ratio at synapses of the hippocampal CA1 pyramidal neurons (Hesselgrave et al., 2021), both suggesting an increase in synaptic strength. Ketamine also increases dendritic spine density *in vivo* (Phoumthipphavong et al., 2016; Pryazhnikov et al., 2018; Moda-Sava et al., 2019), restoring lost spines in stressed mice (Moda-Sava et al., 2019), and the patterned formation of new spine clusters is necessary for the long-lasting anti-depressant-like effects of ketamine (Moda-Sava et al., 2019).

Studies of the effects of nonhallucinogenic psychoplastogens on dendrites will be important for understanding differences in their effects on neural plasticity with those of hallucinogenic psychedelics. TBG, a nonhallucinogenic, noncardiotoxic analog of ibogaine and 5-MeO-DMT, increases the complexity of dendritic arbors of cultured rat cortical neurons and increases dendritic spine formation in the mouse somatosensory cortex *in vivo* (Cameron et al., 2021). A more recent study shows that a single dose of TBG rescues the elevated anxiety, cognitive inflexibility, and sensory processing deficits in mice subjected to unpredictable mild stress. TBG also partially compensates for the unpredictable mild stress-induced dendritic spine loss, restores the electrophysiological properties of parvalbumin-expressing inhibitory interneurons, and normalizes baseline and sensory-evoked cortical neuronal activities (Lu et al., 2021). In a separate study, the psychedelic analog IHCH-7113 and several other 5-$HT_{2A}$R $\beta$-arrestin–biased agonists also demonstrate antidepressant-like activity in mice without hallucinogenic effects (Cao et al., 2022), although their dendritic and synaptic effects remain to be elucidated.

### Effects of psychedelics on microcircuitry

Since neuroplasticity is perhaps one of the most fundamental mechanisms of brain function, it is unsurprising that most psychotropic drugs induce some form of neuroplasticity in the brain. However, identifying the specific circuits impacted by plasticity-promoting drugs is essential for determining whether

a compound is likely to be therapeutic or produce pathologic states. For example, the chronic administration of psychostimulants produces robust structural and functional changes in mesolimbic circuitry, changes that are thought to underlie the addictive properties of these compounds (Lüscher and Ungless, 2006; Kalivas and O'Brien, 2008). In contrast, classical psychedelics are not generally considered to be addictive (Carhart-Harris and Goodwin, 2017; Nichols et al., 2017) as animals will not readily self-administer these compounds (Fantegrossi et al., 2008). Indeed, psychedelics are being used for treating abuse of addictive substances, such as heroin, cocaine, methamphetamine, alcohol, and nicotine (Winkelman, 2014; Morgan et al., 2017). The difference between psychedelics and addictive drugs like some psychostimulants and opiates likely relates to the specific circuits they strengthen and weaken. More research into the differences between these classes of compounds is warranted.

Currently, the most widely prescribed psychedelic-related compound is ketamine, a noncompetitive antagonist of NMDARs that has been used safely at high doses as an anesthetic for decades, and is now FDA-approved for depression (intranasally delivered *S*-ketamine) (Aan Het Rot et al., 2012; Krystal et al., 2019). Low-dose ketamine is being studied for the treatment of heroin, cocaine, alcohol, and nicotine abuse, and for the treatment of anxiety, panic disorder, PTSD, agoraphobia, anorexia, bulimia, binge eating, suicide prevention, and others (Rasmussen, 2016; Ezquerra-Romano et al., 2018).

Ketamine's half-life in the body is ~2 h (Autry et al., 2011), yet a single low-dose treatment elicits sustained (>1 week) antidepressant effects in patients (Berman et al., 2000; Zarate et al., 2006; Price et al., 2009), strongly suggesting it induces neuroplasticity (Duman, 2018). The ability of ketamine to promote ODP in the binocular primary visual cortex (bV1) has recently been reported (Grieco et al., 2020; Casarotto et al., 2021, Cannarozzo et al., 2022). Once a developmental time window or "critical period" for ODP is closed, the capacity for ODP is significantly reduced in visual cortex; this neurobiological feature presents scientists with a way to test the plasticity-promoting effects of drugs and their mechanisms for doing so in adult animals (Levi and Polat, 1996).

Clues about how ODP works in adults comes from studies of antidepressant treatments and other manipulations, which synergize with visual experience to reopen critical period-like plasticity (Solomon et al., 1957; Sale et al., 2007; Maya Vetencourt et al., 2008; Baroncelli et al., 2010; Montey et al., 2013; Kaneko and Stryker, 2014; Eaton et al., 2016; Greifzu et al., 2016; Gu et al., 2016; Hensch and Quinlan, 2018; Umemori et al., 2018; Steinzeig et al., 2019; Casarotto et al., 2021; Lesnikova et al., 2021). ODP may be promoted by reducing parvalbumin-expressing (PVs) interneuron activity in bV1 (Caillard et al., 2000; Donato et al., 2013; Reh et al., 2020). In cortical microcircuitry, PV cells, which are the fastest spiking neuron type in the brain, participate in feedforward inhibitory circuits, setting the very short time window in which excitatory inputs can be integrated (Hu et al., 2014). Sensory manipulations or drug treatments that inhibit PV cells may result in PV-mediated cortical disinhibition that creates a permissive state for ODP to occur in the presence of visual experience (Kuhlman et al., 2013; Gu et al., 2016; Sun et al., 2016; Grieco et al., 2020; Sadahiro et al., 2020).

As chronic high-dose ketamine treatment is used as a model for schizophrenia-like behavior in animal models and reduces PV interneuron function in this model (Frohlich and Van Horn, 2014; Jeevakumar et al., 2015; Koh et al., 2016), it was hypothesized that a single low-dose ketamine treatment might reduce PV interneuron activity therapeutically to promote cortical disinhibition and ODP. Low-dose ketamine treatment reduces L2/3 PV cell activity by reducing the strength of their L4 excitatory inputs, resulting in increases in excitatory neuron responses in L2/3 of bV1, consistent with a PV-mediated cortical disinhibitory mechanism (Grieco et al., 2020, 2021). Ketamine also promotes ODP and recovery from amblyopia in adult animals, and all of this is dependent on neuregulin-1 (NRG1) and ErbB4 signaling by PV cells (Grieco et al., 2020). NRG1-ErbB4 signaling is well known to be strongly restricted to PV cells and to play an important role in neurodevelopment, neuroplasticity, and schizophrenia (Corfas et al., 2004; Mei and Xiong, 2008). Similarly, TrkB activation in PV neurons induces adult ODP and TrkB is required for this effect (Winkel et al., 2021).

Many questions remain about the actions of other psychedelics or psychedelic-like compounds on microcircuits, including whether they share the common mechanism of PV-mediated cortical disinhibition (Reh et al., 2020) or whether they leverage very diverse microcircuit actions to potentially bring about the same psychedelic effect.

### The effects of psychedelics on brain-wide circuits

Recently, Doss et al. (2022) reviewed the actions of classical psychedelics (LSD and psilocybin) on brain-wide circuitry, focusing on the several prominent models that have emerged in the literature. Although few studies have systematically characterized the actions of psychedelics on brain-wide circuits with regards to neuroplasticity, it is important to bring to the readers' attention the circuitry likely to be involved. One model of the action of psychedelics on the brain entails modulation of the cortico-striatal thalamo-cortical loop. In this formulation, 5-$HT_{2A}$R agonizing psychedelics result in modulation of cortical and subcortical circuitry (Preller et al., 2019; Vollenweider and Preller, 2020), altering the flow of information in the brain via changes in how PFC L5 pyramidal neurons expressing 5-$HT_{2A}$R regulate important thalamic nuclei (reticular nucleus, mediodorsal thalamus) (Inserra et al., 2021b). Other key circuit components of the cortico-striatal thalamo-cortical loop, such as ventral striatum, pallidum, sensory cortex, and posterior parietal cortex (PPC), are implicated in this process as well (Doss et al., 2022). Another model of psychedelic actions on brain-wide circuits is the "relaxed beliefs under psychedelics" model, whereby acute psychedelic treatment is thought to cause inhibition of top-down regulation of the brain by higher-order cortical regions, such as PFC and PPC, resulting in prediction errors and enormous increases in updates in "prior beliefs" (Carhart-Harris and Friston, 2019). The default mode network is strongly implicated in the "relaxed beliefs under psychedelics" as the PFC, PPC, and hippocampus strongly express 5-$HT_{2A}$Rs (Beliveau et al., 2017), suggesting that psychedelics could impair default mode network imposition on the brain, resulting in increases in possible expressible brain states (i.e., increased brain entropy). In a third model (the cortico-claustral-cortico model) of the actions of psychedelics on brain-wide circuitry, the enigmatic brain structure known as the claustrum, which also strongly expresses 5-$HT_{2A}$R, is thought to play an important role (Crick and Koch, 2005; Mathur, 2014; Nichols, 2016).

Although not yet explored in detail, going forward it will be important to determine the effects of psychedelics on 5-$HT_{2A}$R-expressing neurons and their associated circuits throughout the brain longitudinally and with regard to neuroplasticity.

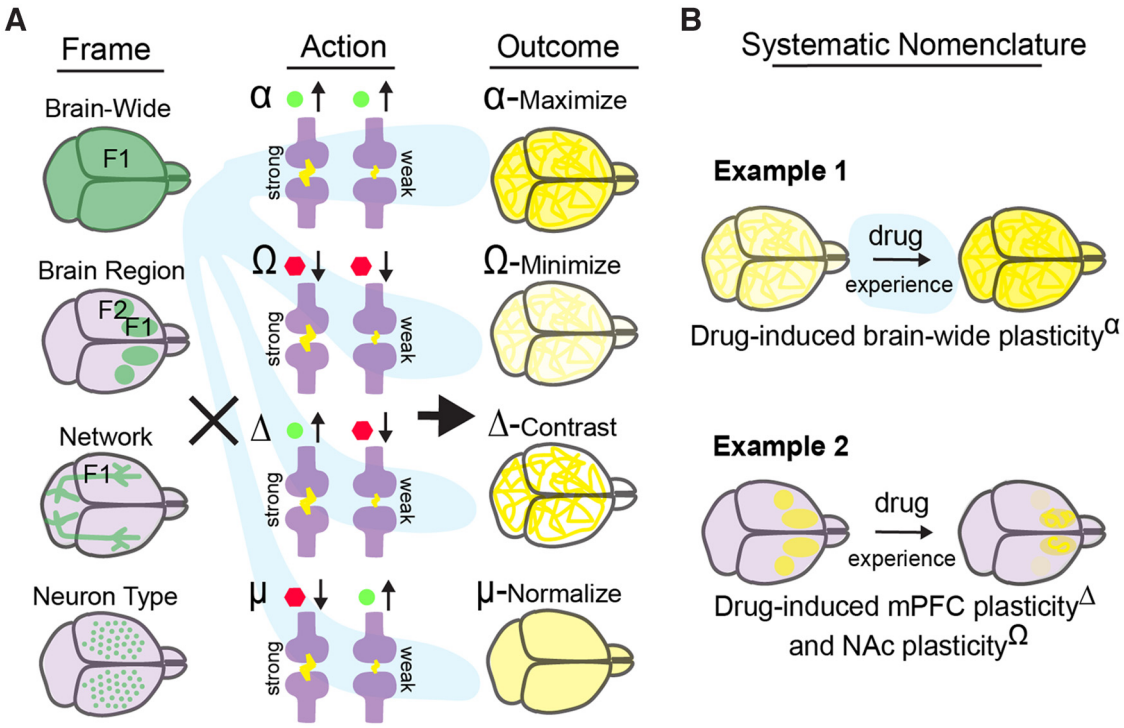


**Figure 3.** Models of neuroplasticity. ***A***, While various terms have been used to describe neuroplasticity in the brain (i.e., Hebbian plasticity, homeostatic plasticity, hyperplasticity, and others), there is an ongoing deficiency in the field for clearly communicating aspects of these processes meaningfully. Here we propose the use of four actions of neuroplasticity ($\alpha$, $\Omega$, $\Delta$, and $\mu$) within a particular frame of action (brain-wide, brain region, network, neurons, etc.) to communicate outcomes (maximize, minimize, contrast, normalize) for paths of activity in the brain. Experience modifies the nature of the outcomes. ***B***, Examples of the use of a systematic nomenclature for describing neuroplasticity in the brain. Other examples (not shown) are "Drug induced plasticity$^{\Delta}$ in active networks" and "Time-delayed plasticity$^{\mu}$ in inhibitory neurons."

## Discussion

There has been considerable recent progress in understanding the mechanisms of plasticity induced by psychedelics. Research has just begun to determine the specific receptor interactions that may bring about their effects (e.g., 5-$HT_{2A}$R, TrkB, NMDA, etc.), although the specific polypharmacological profile of each drug may endow it with unique properties. It will be clarifying to determine whether 5-$HT_{2A}$R occupancy is a better predictor of psychedelic-induced subjective effects than *in vitro* measures of potency and efficacy of the different compounds. Furthermore, it will be very informative to determine whether there are different receptor occupancy thresholds for inducing plasticity and therapeutic effects versus hallucinogenic effects (e.g., low- vs high-dose DMT). Receptor occupancy thresholds should be considered for all potential targets of a given psychedelic to help determine whether multiple receptors are required for the subjective and/or therapeutic effects of each compound. Analogs that induce neuroplasticity but do not produce hallucinogenic effects will help to elucidate the receptor activation patterns essential for each of these effects (e.g., LSD vs ergoline analogs). These research directions and others will also help to determine the differences between fast-acting compounds and other compounds that induce plasticity following chronic administration (e.g., ketamine vs fluoxetine).

The determination of gene expression programs important for psychedelic-induced neuroplasticity is still in progress, with the ultimate goal of broadening our understanding of findings that psychedelics induce IEG expression (e.g., cFOS and Arc) and growth-factor expression (e.g., BDNF, Egr1/2). It is still unclear whether the effects of psychedelics on gene expression are cell type-specific (e.g., excitatory, inhibitory cells or various subtypes). Similarly, the subcellular (i.e., axon vs dendrites and their synapses) localization of early effects will need to be determined.

Studies of structural and functional plasticity *in vivo* for each psychedelic will be important. For structural plasticity, it will be critical to determine whether effects mostly involve dendrites or whether some psychedelics can affect axon plasticity. For functional plasticity, it will be important to determine whether effects mostly involve LTP or whether LTD could be equally as important. Changes in the excitability of neurons must be determined as well, although very few studies to date have investigated these with regard to psychedelics. As nearly every psychotropic drug induces neuroplasticity, of which there are many forms, often with opposing effects for certain variables, mapping each drug to a particular aspect of neuroplasticity mechanisms will be a major goal of the field (Fig. 3*A*). Ideally, plasticity mechanisms that are consistent across both *in vivo* and *in vitro* experiments will be identified to facilitate novel psychedelic-related drug discovery. It is not yet known whether psychoplastogens bring about their therapeutic effects using the same underlying form of neuroplasticity.

For microcircuitry, it will be important to know what circuit motif elements are necessary for psychedelic effects (e.g., feedforward inhibitory circuits). On a brain-wide scale it will be interesting to determine whether specific circuits mediate the various therapeutic effects of psychedelics (e.g., antidepressant, anti-addictive, and anxiolytic) or if psychedelic effects are general across the brain. If different circuits are important for different therapeutic effects, such distinctions could be useful for developing circuit-specific psychoplastogens tailored to specific disease indications.

It will be important to determine the role of experience (i.e., sensory enrichment, deprivation) or other environmental associations

(i.e., cues or context) in the therapeutic efficacy of psychedelics. The iPlasticity concept proposes that psychedelics may induce a permissive state for neuroplasticity that requires the stabilization of new connections guided by network activity produced by experience (Castrén, 2005). An example of this is the reopening of critical periods in adulthood which has been shown for a number of pharmacological manipulations, including fluoxetine (Maya Vetencourt et al., 2008; Karpova et al., 2011), ketamine (Grieco et al., 2020; Casarotto et al., 2021), *R,R*-HNK (Cannarozzo et al., 2022), and MDMA (Nardou et al., 2019). Drug treatment may induce iPlasticity in many brain regions, but the context-dependent use of circuits might stabilize active synapses and determine where iPlasticity brings about a long-term functional change in the network structure and function (Fig. 3*B*). This represents an interesting possibility as the intense preparation and support included into psychedelic sessions may contribute to the apparently more effective antidepressant response to psychedelics than to conventional antidepressants treatment that is typically not combined with any supporting therapy. If this is the case, then the clinical caretaker (i.e., the psychedelic guide) is a very important component of psychedelic therapy.

In conclusion, the field needs to grapple with the role of animal models in understanding the actions of psychedelics. There are likely aspects of the human condition that cannot be adequately captured by animal models. For example, the questions of whether or not the subjective experience induced by psychedelics is proportionate to the therapeutic value of psychedelics, or if nonhallucinogenic psychoplastogens are effective, are unlikely to be answered with animal models, and will require rigorous clinical studies. However, these models can serve as important starting points from which we can build a more comprehensive understanding of how psychedelics impact brain function.

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