Catalysts for change: the cellular neurobiology of psychedelics

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ABSTRACT **The resurgence of interest in the therapeutic potential of psychedelics for treating psychiatric disorders has rekindled efforts to elucidate their mechanism of action. In this Perspective, we focus on the ability of psychedelics to promote *neural plasticity*, postulated to be central to their therapeutic activity. We begin with a brief overview of the history and behavioral effects of the classical psychedelics. We then summarize our current understanding of the cellular and subcellular mechanisms underlying these drugs' behavioral effects, their effects on neural plasticity, and the roles of stress and inflammation in the acute and long-term effects of psychedelics. The signaling pathways activated by psychedelics couple to numerous potential mechanisms for producing long-term structural changes in the brain, a complexity that has barely begun to be disentangled. This complexity is mirrored by that of the neural mechanisms underlying psychiatric disorders and the transformations of consciousness, mood, and behavior that psychedelics promote in health and disease. Thus, beyond changes in the brain, psychedelics catalyze changes in our understanding of the neural basis of psychiatric disorders, as well as consciousness and human behavior.**

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INTRODUCTION

Human use of psychedelic drugs traces a remarkable historical arc, extending from the prehistoric realm of myth to the laboratories and clinical treatment rooms of the modern day, where these compounds' mysteries are finally yielding to concerted inquiry. And yet our purpose and that of our ancestors are one and the same: to harness the potential of these compounds for insight and healing.

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Abbreviations used: AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CREB, cyclic adenosine monophosphate response element-binding protein; DMT, *N*,*N*-dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; 5-HT, serotonin; 5-HT_{1A}R, serotonin type 1A receptor; 5-HT_{2A}R, serotonin type 2A receptor; 5-HT_{2C}R, serotonin type 2C receptor; 5-MeO-DMT, 5-Methoxy-*N*,*N*-dimethyltryptamine; K_d, dissociation constant; LSD, lysergic acid diethylamide; mGluR, metabotropic glutamate receptor; mRNA, messenger ribonucleic acid; mTOR, mechanistic target of rapamycin kinase; pCREB, phosphorylated cyclic adenosine monophosphate response element-binding protein; pERK, phosphorylated extracellular signal-regulated kinase; PFC, prefrontal cortex; PI3K, phosphatidylinositol 3-kinase; pPKC, phosphorylated protein kinase C; pPLC, phosphorylated phospholipase C; SRC, sarcoma proto-oncogene, nonreceptor tyrosine kinase; TrkB, tropomyosin receptor kinase B.

Evidence for human consumption of psychedelics in traditional medicine and religious ceremonies stretches back into prehistory (Sayin, 2014; Guerra-Doce, 2015; Froese *et al*., 2016). These naturally occurring psychedelics include ayahuasca, a brew of several plants indigenous to South America containing *N*,*N*-dimethyltryptamine (DMT); 5-MeO-DMT, found in a variety of plant species as well as in the toxic secretions of the Sonoran Desert toad; and psilocybin, found in a myriad of fungus species, mostly of the genus *Psilocybe*. By contrast, lysergic acid diethylamide (LSD), an alkaloid derivative of the fungus ergot, was first synthesized in 1938 and marketed as an adjunct to psychotherapy that could enhance introspection and self-awareness. Indeed, until psychedelics were listed by the U.S. Drug Enforcement Agency as Schedule I drugs in 1970, thousands of studies were published on the therapeutic potential of psychedelics for psychiatric disorders and on their research potential for understanding psychosis (Nichols and Walter, 2020).

Over the past two decades, as human subject research on psychedelics has begun to revive, several small clinical trials have shown the remarkable potential of psychedelics to treat psychiatric disorders (Goldberg *et al*., 2020; Reiff *et al*., 2020). A parallel research effort has explored the neural mechanisms of psychedelics for both their profound acute effects on perception and cognition and post–acute effects underlying long-term changes in mental health. In this Perspective, we lay out the case for psychedelics as catalysts of

change, linking the experience induced by psychedelics and their effects on *neural plasticity*. We focus on the current understanding of the cellular and subcellular mechanisms underlying these drugs' actions. But first, to provide context, we discuss the profound effects these drugs have on the human mind and body.

BEHAVIORAL AND PHYSIOLOGICAL EFFECTS OF PSYCHEDELICS IN HUMAN SUBJECTS

The acute behavioral effects of psychedelics (i.e., the "*psychedelic experience*") constitute a profound alteration in consciousness with both pleasant and challenging components (Carbonaro *et al.*, 2016; Roseman *et al.*, 2017). These challenging aspects are mirrored by an acute physiological stress response shortly after drug administration, as indicated by increases in plasma corticosteroid levels, heart rate, and blood pressure (Hasler *et al.*, 2004; Strajhar *et al.*, 2016). Although there are concerns of negative long-term consequences with drugs that produce such powerful effects, there is no evidence for increased incidence of suicidality or psychiatric illnesses in the months following psychedelic experiences; in fact, studies show the opposite (Hendricks *et al.*, 2015; Johansen and Krebs, 2015). Similarly, in spite of widespread recreational use and characterization of psychedelics as "drugs of abuse," psychedelics present low addictive potential (Garcia-Romeu *et al.*, 2016). Several studies have also demonstrated the safety of psychedelics when administered in controlled settings (Brown *et al.*, 2017).

Multiple clinical trials over the past 20 years have demonstrated the potential of these agents for treating psychiatric disorders (Reiff *et al.*, 2020), including depression and anxiety (Muttoni *et al.*, 2019; Goldberg *et al.*, 2020), substance use (Johnson *et al.*, 2014; Bogenschutz *et al.*, 2015), and obsessive-compulsive disorders (Moreno *et al.*, 2006), with the degree of therapeutic benefit correlating with the intensity of the patient's psychedelic experience (Roseman *et al.*, 2017). Remarkably, one or two administered doses of psilocybin result in rapid and prolonged changes in mood and outlook, with symptomatic relief lasting at least 3–12 months (Carhart-Harris *et al.*, 2016a; Griffiths *et al.*, 2016; Ross *et al.*, 2016; Johnson *et al.*, 2017). In healthy subjects, psilocybin promotes long-lasting increases in well-being and positive perspective on life experiences (Griffiths *et al.*, 2011; Nicholas *et al.*, 2018). Thus, psychedelics facilitate long-lasting behavioral changes, presumably mediated by long-lasting structural changes in the brain. To understand how that might happen requires a finer-grained exploration of their actions in the brain.

PHARMACOLOGY AND 5-HT$_{2A}$ RECEPTOR SIGNALING

Psychedelics have a chemical structure similar to serotonin (5-HT), and are divided into two broad categories that differ in their receptor subtype specificity. The indolealkylamines (e.g., LSD, psilocybin, DMT, 5-MeO-DMT) include tryptamine- and lysergic acid derivatives and β-carbolines and exhibit comparatively less specificity for the 5-HT type 2A receptor (5-HT$_{2A}$R); in particular, they show significant agonism at 5-HT$_{1A}$Rs as well as adrenergic and dopaminergic receptors (Halberstadt and Geyer, 2011; Rickli *et al.*, 2016). The phenylalkylamines (e.g., mescaline, DOM, DOI) bind more specifically to 5-HT$_{2A}$Rs as well as 5-HT$_{2C}$Rs. DOI in particular is commonly used in animal studies, but there are no published studies on its effects in human subjects.

Despite their expansive binding profile, the effects of psychedelics in humans strongly correlate with 5-HT$_{2A}$R occupancy in the central nervous system (CNS) and are almost entirely blocked by 5-HT$_{2A}$ antagonists (Vollenweider *et al.*, 1998; Valle *et al.*, 2016; Madsen *et al.*, 2019; Preller *et al.*, 2020), thus motivating focus on the 5-HT$_{2A}$R. Indeed, psychedelics are typically defined as psychoactive agonists of the serotonin 5-HT$_{2A}$ receptor (5-HT$_{2A}$R). It is important to note, however, that 5-HT$_{2A}$R antagonists are not perfectly selective either, and there is some evidence suggesting the involvement of other receptors in the neurophysiological effects of psychedelics (Halberstadt and Geyer, 2011; Pokorny *et al.*, 2016). Thus, the involvement of other receptors in the behavioral and therapeutic effects in humans should not be entirely excluded.

Expression of 5-HT$_{2A}$R mRNA and protein in the brain is widespread. It is most prevalent in excitatory neurons in the *neocortex* but is also expressed in inhibitory interneurons (Jakab and Goldman-Rakic, 1998; Weber and Andrade, 2010). Importantly, depression and other mood disorders are associated with increased 5-HT$_{2A}$R density in the brain, especially in the *prefrontal cortex* (PFC) (Meyer *et al.*, 2003; Bhagwagar *et al.*, 2006), and antidepressant treatments are associated with decreased density (Yatham *et al.*, 1999; Meyer *et al.*, 2001), as is the administration of psychedelics (Buckholtz *et al.*, 1988).

The 5-HT$_{2A}$ receptor is a Class A, rhodopsin-like, *G-protein–coupled* receptor (Lopez-Gimenez and Gonzalez-Maeso, 2018) for which 5-HT, the endogenous ligand, is a full agonist with a K_d of just over 1 nM (Sleight *et al.*, 1996). Canonically, 5-HT$_{2A}$Rs couple with the G-protein G$_q$ (Figure 1), catalyzing the production of phospholipase C and inositol triphosphate to mobilize intracellular calcium, activate calcineurin, and inhibit type 1.2 voltage-gated calcium channels (Hoyer *et al.*, 1994; Day *et al.*, 2002). In addition, 5-HT$_{2A}$R signaling through G-proteins from the G$_i$ family and subsequent inhibition of cAMP formation have also been observed (Garnovskaya *et al.*, 1995). Either of these pathways can contribute to neural plasticity (Tedford and Zamponi, 2006; Betke *et al.*, 2012).

BIASED AGONISM MODEL FOR PSYCHEDELIC ACTIONS

Psychedelic agonists of 5-HT$_{2A}$R are associated with profound changes in perception and cognition, whereas other ligands such as 5-HT are not. The basis for this difference is commonly explained using the ternary complex model of receptor activity, which suggests that drug molecules act to shift the equilibrium between a receptor's different conformational states. As each of these receptor states has a different affinity for various downstream binding partners, this can result in a drug exhibiting "bias," such as preference for activating G-protein–dependent versus β-arrestin–dependent signaling (Kenakin, 2012). Long-standing evidence indicates that 5-HT$_{2A}$R signaling efficacy is ligand-dependent and prone to biased agonism across these pathways (Roth *et al.*, 1997; Berg *et al.*, 1998; Fitzgerald *et al.*, 1999; Egan *et al.*, 2000; Cussac *et al.*, 2008; Lopez-Gimenez and Gonzalez-Maeso, 2018). Molecular modeling, site-directed mutagenesis, and x-ray crystallography have identified the distinct psychedelic and nonpsychedelic ligand binding sites that ultimately lead to these differential functional signaling consequences (Wang *et al.*, 1993; Shapiro *et al.*, 2000; Kanagarajadurai *et al.*, 2009).

In the case of G$_q$-dependent signaling, both psychedelic (DOI) and nonpsychedelic (lisuride) agonists of 5-HT$_{2A}$R activate several shared downstream pathways, including pPLC, pPKC, pERK, and pCREB; however, the magnitude of these G$_q$-mediated responses is greater for psychedelic ligands (Figure 1) (Banerjee and Vaidya, 2020). Non-G$_q$ pathways likely contribute to psychedelic effects as well. For example, in mice lacking G$_q$ expression, the response to DOI is blunted but not eliminated (Garcia *et al.*, 2007). Furthermore, psychedelic-dependent phosphoproteomic and transcriptomic signatures are pertussis toxin–sensitive (Gonzalez-Maeso *et al.*, 2007; Karaki *et al.*, 2014), suggesting the involvement of G$_{i/o}$ signaling. Notably, G$_{i/o}$-dependent outcomes may depend on

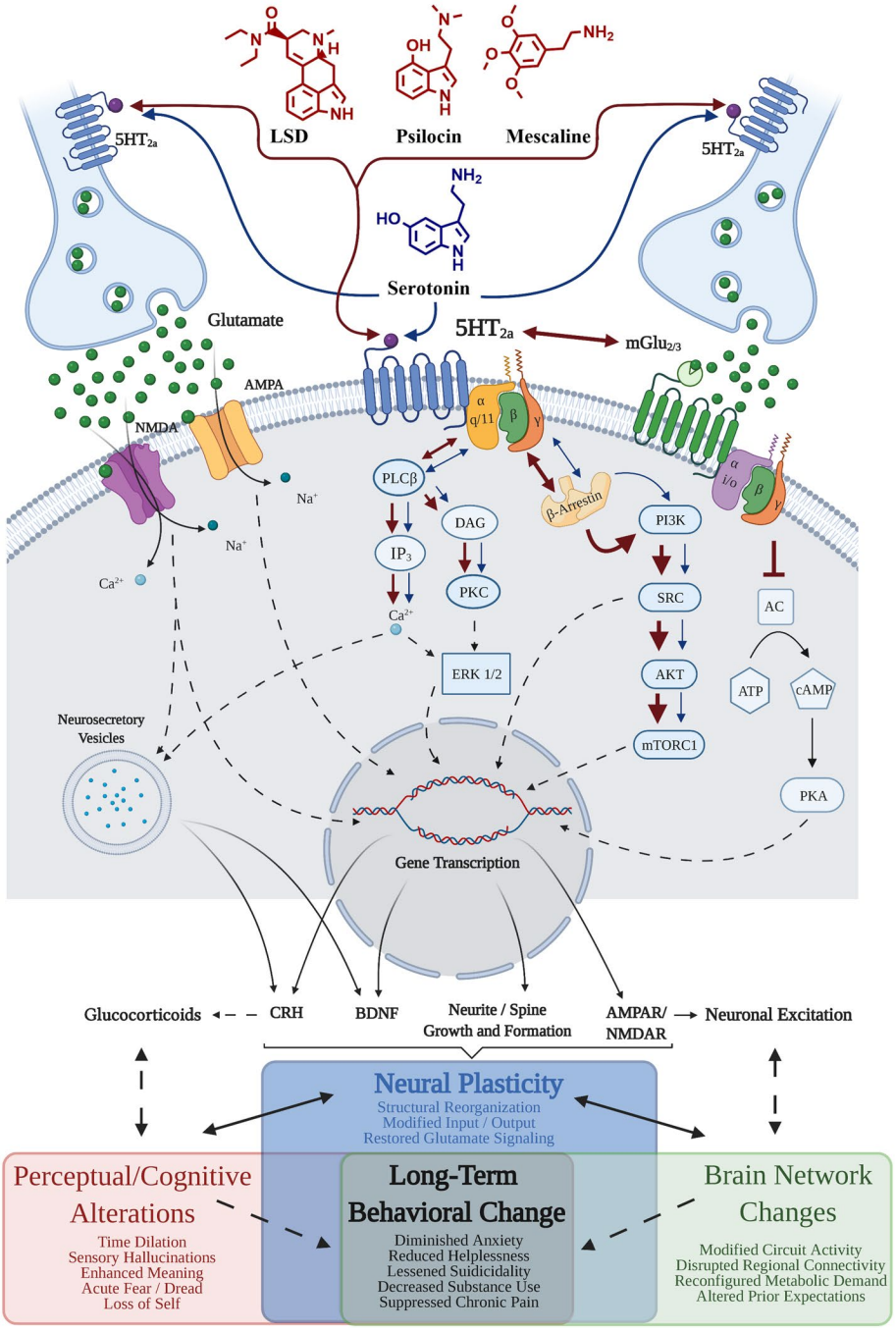

FIGURE 1: Molecular, cellular, and systems support for psychedelic-induced long-term changes. Psychedelic compounds (LSD, psilocin, mescaline) and serotonin bind with high affinity to serotonin 2A receptors. In mammalian systems, direct (solid arrows) and indirect (dashed arrows) consequences of G-protein and β-arrestin signaling downstream of serotonin 2A receptor activation intersect with glutamate release to yield enhanced neural plasticity. The relative engagement of intracellular signaling pathways (arrow weight) is distinct for psychedelics (red arrows) vs. serotonin (blue arrows). Neural plasticity is further supported by neuropeptide synthesis and release, structural changes to neuronal architecture, and altered expression, localization, and phosphorylation of ionotropic glutamate receptors. The consequences of this neural plasticity are modified by psychedelic-induced, large-scale changes in brain activity and attendant perceptual and cognitive changes in the processing of information. When psychedelic drugs are given in the context of a psychotherapeutic support model, these changes appear to ultimately support long-term changes in behavior and promotion of mental well-being.

participation of additional signaling partners, as 5-HT_{2A}Rs do not appear to participate directly in functional coupling with $G_{i/o}$ (Kim *et al.*, 2020).

Beyond G-protein–coupled pathways, agonism at 5-HT_{2A}Rs can also engage in β-arrestin signaling (Pottie *et al.*, 2020) via PI3K, SRC, and AKT (Figure 1), although the relevance of such

β-arrestin–dependent signaling for promoting psychedelic effects is still unclear. For example, while LSD's ability to promote a β-arrestin–biased conformation at 5-HT_{2A}Rs supports its psychedelic effects (Wacker *et al.*, 2017; Kim *et al.*, 2020), other psychedelics are functionally insensitive to β-arrestin knockout in mice (Schmid *et al.*, 2008; Schmid and Bohn, 2010). Close attention to differences in off-target binding profile (Halberstadt and Geyer, 2011; Rickli *et al.*, 2016) and time-dependent evolution in signaling (Wacker *et al.*, 2017) is needed for future studies to yield a more comprehensive picture of β-arrestin–induced effects across the full spectrum of psychedelic ligands.

INTERACTION BETWEEN 5-HT_{2A}R AND GLUTAMATE RECEPTOR SIGNALING

Glutamate signaling deficits are a prominent feature of schizophrenia (Iwata *et al.*, 2015) and major depressive disorder (Wise *et al.*, 2018) and can be ameliorated by antidepressant administration (Gonzalez-Burgos and Lewis, 2012; Sanacora *et al.*, 2012). Interestingly, psychedelics cause an increase in extracellular glutamate in the PFC (Scruggs *et al.*, 2003; Muschamp *et al.*, 2004), resulting in the release of neurotrophic factors that promote neural plasticity (de Almeida *et al.*, 2019; Holze *et al.*, 2021; Hutten *et al.*, 2021), as well as the activation of ionotropic glutamate receptors, which also contribute to neural plasticity (Lisman *et al.*, 2012).

Glutamate release also activates metabotropic glutamate receptors (mGluR), which regulate neural plasticity (Mukherjee and Manahan-Vaughan, 2013) and modulate the effects of psychedelic agonism at 5-HT_{2A}Rs. The agonists for two subtypes, mGluR2 and mGluR3, suppress the response to psychedelics, reducing their effects on neural activity and cellular signaling and the behavioral manifestations of psychedelics, as does (paradoxically) knocking out mGluR2 (Zhai *et al.*, 2003; Gonzalez-Maeso *et al.*, 2008; Moreno *et al.*, 2011; Benvenga *et al.*, 2018).

This interplay between mGluR2 and 5-HT_{2A}R signaling may arise from physical (transmembrane) interactions between the receptors (Gonzalez-Maeso *et al.*, 2008), which are expressed within close molecular proximity (Marek *et al.*, 2000; Hanks and González-Maeso, 2013). Further, several studies indicate that 5-HT_{2A}R and mGluR2 form heterodimeric complexes, integrating glutamatergic and serotonergic signaling and modulating subsequent G-protein coupling and downstream effects (Zhai *et al.*, 2003; Gonzalez-Maeso *et al.*, 2008; Moreno *et al.*, 2016). For example, when cells coexpressing mGluR2 and 5-HT_{2A}R receptors are treated with mGluR2/3 agonists, signaling is propagated through $G_{q/11}$, rather than the $G_{i/o}$ pathway usually activated by mGluR2. This effect is reduced in 5-HT_{2A}R knockout mice (Moreno *et al.*, 2016), suggesting that 5-HT_{2A}Rs and mGluR2 and mGluR3 can form heterocomplexes that have a distinct signaling profile. Importantly, signaling through this complex may facilitate the rapid antidepressant effects observed with psychedelics, as mGluR2 and mGluR3 have been implicated in the regulation of neural plasticity in the PFC, *amygdala*, and *hippocampus*, brain regions implicated in mood disorders, along with fear- and stress-associated learning (Walker *et al.*, 2015).

CELLULAR AND NETWORK-LEVEL ELECTROPHYSIOLOGICAL EFFECTS OF PSYCHEDELICS

The signaling pathways activated by psychedelic agonism at the 5-HT_{2A}R provide a basis for structural changes in the brain following the psychedelic experience (Figure 1). How these long-term changes relate to the acute effects of psychedelics is a critical but unresolved question. Psychedelics acutely modulate neural activity and *connectivity*, and these changes correlate with the phenomenology of the psychedelic experience (de Araujo *et al.*, 2012; Carhart-Harris *et al.*, 2016b; Valle *et al.*, 2016). Effects on neural activity are broadly consistent with an increase in excitability (Muthukumaraswamy *et al.*, 2013; Kometer *et al.*, 2015; Valle *et al.*, 2016; Timmermann *et al.*, 2019) and a switch from externally driven to internally driven neural activity in sensory areas of the brain (Bravermanova *et al.*, 2018; Timmermann *et al.*, 2018; Michaiel *et al.*, 2019). Psychedelics increase brain signal complexity (an indirect measure of signal diversity and information content), and these changes also correlate with specific aspects of the psychedelic experience (Schartner *et al.*, 2017). These changes in complexity likely reflect increased information flow along pathways that are not typically engaged in the absence of the drug. Similarly, synesthesia, in which sensory stimuli in one modality trigger sensations in another, is a common element of the psychedelic experience (Studerus *et al.*, 2010; Schmid *et al.*, 2015), thought to rely on existing but dormant connections between areas of the brain that typically process distinct sensations, for example, vision or audition (Maurer *et al.*, 2020).

Experiments confirm that psychedelics alter connectivity in the brain (Tagliazucchi *et al.*, 2016; Preller *et al.*, 2018, 2019), and this form of neural plasticity may underlie their therapeutic activity. For example, excessive amygdala reactivity and decreased connectivity between the amygdala and other brain regions, especially the PFC, are linked to psychiatric disorders (Quirk and Gehlert, 2003; Negron-Oyarzo *et al.*, 2016). Psychedelics alter connectivity between the amygdala and key brain regions during emotional stimulus processing, effects that may contribute to altered behavioral and neural responses to these stimuli characteristic of mood disorders (Rocha *et al.*, 2019; Barrett *et al.*, 2020a). Psychedelics acutely reduce connectivity within the default mode network (Carhart-Harris *et al.*, 2012; Palhano-Fontes *et al.*, 2015), a set of brain regions whose activity and connectivity correlate with self-referential mental activity in healthy subjects (Davey *et al.*, 2016) and rumination and depression symptoms in patients (Sheline *et al.*, 2009; Berman *et al.*, 2011). More broadly, psychedelics administered to healthy volunteers alter connectivity in multiple higher-order brain regions (Roseman *et al.*, 2014; Tagliazucchi *et al.*, 2016; Sampedro *et al.*, 2017; Preller *et al.*, 2018, 2020; Barrett *et al.*, 2020b). Thus, psychedelics induce acute changes in connectivity in brain regions that are implicated in multiple psychiatric disorders, but the mechanisms of these changes and whether these changes persist postacutely remain areas of active inquiry (Barrett *et al.*, 2020a).

NEURAL AND BEHAVIORAL PLASTICITY

The psychedelic-induced changes in neural activity and connectivity in human subjects described above are manifestations of acute effects on neural plasticity. These acute effects have also been studied in animal models, where DOI acts on both pre- and postsynaptic 5-HT_{2A}Rs to modulate glutamate signaling (Barre *et al.*, 2016; Berthoux *et al.*, 2019). Rodent models have also revealed long-term structural changes induced by psychedelics. Many of these changes manifest in structural changes at synapses, such as the growth of neurites, the cellular processes that connect neurons, and changes in *dendritic spines*, the specialized postsynaptic structures found most commonly at excitatory synapses on excitatory neurons (Holtmaat and Svoboda, 2009). Studies of cultured cortical neurons indicate that DOI acts on 5-HT_{2A}Rs to increase dendritic spine diameter (Jones *et al.*, 2009). Furthermore, psychedelics enhance de novo neurite and dendritic spine formation through the TrkB, mTOR, and 5-HT_{2A} pathway (Ly *et al.*, 2018), all implicated in promoting neuroplastic changes in the PFC (Meunier *et al.*, 2017). Finally, psychedelics induce *neurogenesis* in the rodent hippocampus

(Catlow *et al.*, 2013; Morales-Garcia *et al.*, 2017; Lima da Cruz *et al.*, 2018).

These long-term effects of psychedelics are likely mediated at least in part by changes in gene expression (Martin and Nichols, 2018). A single administered dose of psilocybin induces changes in neural plasticity–related gene expression in the hippocampus and PFC (Jefsen *et al.*, 2020), and 5-MeO-DMT induces large-scale changes in protein expression in cultured human brain tissue (Dakic *et al.*, 2017). Psychedelics interact particularly with signaling by the neural plasticity–associated protein brain-derived neurotrophic factor (BDNF). DOI acts on 5-HT_{2A}Rs to modulate the level of BDNF mRNA in the neocortex and hippocampus, likely via an activity-dependent mechanism and CREB signaling (Vaidya *et al.*, 1997; Musazzi *et al.*, 2014; Jaggar and Vaidya, 2018). DOI increases expression of mRNA for the neuroplasticity-associated protein Arc (Korb and Finkbeiner, 2011) via a pathway that depends on glutamate and BDNF signaling (Pei *et al.*, 2000, 2004; Benekareddy *et al.*, 2013). Psychedelics trigger increases in plasma levels of BDNF in human subjects (de Almeida *et al.*, 2019; Holze *et al.*, 2021; Hutten *et al.*, 2021). Thus, psychedelics are able to mobilize multiple signaling pathways to promote neuroplastic changes in the brain. Given the importance in clinical trials of post–acute psychotherapy sessions, and the extended time course of some of the signaling cascades mentioned here, it seems likely that the pro-neuroplastic effects of psychedelics extend beyond the dosing session, that is, that psychedelics open a window of neural plasticity that lasts for days or weeks. However, this idea has not yet been tested experimentally.

Consistent with these effects on neural plasticity at the cellular level, there is considerable evidence that psychedelics modify learning and memory in vivo (Zhang and Stackman, 2015; Healy, 2021). This is likely a consequence of the role in cognitive function of 5-HT_{2A}Rs, whose activation enhances various types of learning and memory (Williams *et al.*, 2002; Harvey, 2003). For example, psychedelics enhance both the acquisition and extinction of fear conditioning in rodents (Catlow *et al.*, 2013; Zhang *et al.*, 2013). These studies are important in two regards: First, they suggest that psychedelics can promote long-term changes in behavior in the absence of preconceived notions about their potential therapeutic benefit, an emerging concern in clinical trials (Noorani, 2020). Second, they demonstrate that psychedelics have the potential to support learning of new behaviors, while also facilitating extinction of older learned behaviors. This suggests a window for enhanced but nonspecific neural plasticity that can be exploited for therapeutic benefit in partnership with mental health professionals.

STRESS AND INFLAMMATION

The intersection between psychiatric disorders, stress, and psychedelics is an emerging area of interest (Murnane, 2019; Brouwer and Carhart-Harris, 2020). Chronic stress is a major precipitating factor in the etiology of many psychiatric disorders that psychedelics have shown clinical efficacy in treating (McEwen, 2004). Animal models have shown that chronic stress induces behavioral and neural changes that can be reversed by antidepressants (Campos *et al.*, 2013; Moda-Sava *et al.*, 2019; Planchez *et al.*, 2019). Thus, it is both surprising and intriguing that acute stress may play a role in promoting the neuroplastic effects of psychedelics in the context of treating these same disorders. Like psychedelics, acute stress is pro-neuroplastic (Huang *et al.*, 2005; Cadle and Zoladz, 2015), and signaling at the 5-HT_{2A}R plays a role in this neural plasticity (Murnane, 2019). Along with this convergence on neuroplastic mechanisms to modify behavior, psychedelics trigger an acute biochemical stress response consisting of catecholamine and glucocorticoid release (Hemrick-Luecke and Evans, 2002; Hasler *et al.*, 2004; Galvão *et al.*, 2018), and it has been postulated that this stress response is critical for the transformative nature of the psychedelic experience (Brouwer and Carhart-Harris, 2020).

The mechanism underlying this stress response is unclear, but there are two obvious (and not necessarily mutually exclusive) possibilities. First, psychedelics may act directly at 5-HT_{2A}Rs in the hypothalamus to induce expression and/or release of corticotrophin-releasing hormone, elevating plasma concentrations of stress-associated glucocorticoids (Van de Kar *et al.*, 2001; Jorgensen *et al.*, 2002). This possibility is consistent with the established regulatory role of 5-HT in the hypothalamic–pituitary–adrenal axis, the primary system involved in stress regulation (Contesse *et al.*, 2000). Alternatively, the psychedelic-induced altered state of consciousness itself may trigger the acute stress response, as such states frequently include components that are challenging (e.g., fear- or anxiety-provoking). This raises the possibility that the pro-neuroplastic effects of psychedelics depend in part on the acute stress response that they induce, but whether the stressful components of the psychedelic experience are hindrances to or foundational for therapeutic benefit is in dispute (Carbonaro *et al.*, 2016; Roseman *et al.*, 2017; Wolff *et al.*, 2020).

The therapeutic and pro-neuroplastic effects of psychedelics may also be linked to their anti-inflammatory action (Inserra *et al.*, 2021). Inflammation and immune system alterations are commonly associated with psychiatric disorders (Beurel *et al.*, 2020; Thompson and Szabo, 2020), and 5-HT plays a key role immune system function (Herr *et al.*, 2017). Recent work shows that psychedelics have potent inhibitory effects on cytokines, which are immune signaling molecules that directly modulate synaptic function and neural plasticity (Wang *et al.*, 2012; Vezzani and Viviani, 2015). 5-MeO-DMT acutely reduces levels of proinflammatory cytokines in humans (Uthaug *et al.*, 2020), and DOI has been shown to inhibit peripheral cytokine cascades through 5-HT_{2A}R activation (Yu *et al.*, 2008; Nau *et al.*, 2013). These data suggest that psychedelics may be useful in treating inflammatory diseases generally, but there may be more direct effects on inflammation in the brain as well. Microglia, the resident immune cells in the brain, express several 5-HT receptor subtypes (Krabbe *et al.*, 2012; Glebov *et al.*, 2015) and respond directly to DOI treatment (Krabbe *et al.*, 2012). This raises the possibility that systemically administered psychedelics could directly modulate microglial function, which becomes aberrant in mood disorders (Haroon *et al.*, 2017) as well as in neurodegenerative disorders (Perry and Holmes, 2014). The therapeutic potential for the anti-inflammatory effects of psychedelics is just beginning to be explored, including a phase 1 clinical trial in healthy older volunteers with the goal of using LSD to treat Alzheimer's disease (Family *et al.*, 2020).

CONCLUSIONS

As psychedelic science emerges from the shadows and attracts new resources, further research will deepen our understanding and advance the responsible therapeutic use of these compounds. Psychedelics induce acute effects on gene expression, neurotransmitter and neuroendocrine release, neural activity, connectivity, and perception and cognition, ultimately leading to profound long-term effects on mood and behavior (Figure 1). Elucidating the mechanisms that connect the acute effects of psychedelics to these long-term changes is critical but is complicated by our limited mechanistic understanding of the psychiatric disorders that these drugs are effective at treating. Thus, understanding how these drugs work in clinical settings may also provide needed insight into the neurobiological

GLOSSARY

Amygdala is a region of the brain involved in regulation and expression of emotions, as well as memory and decision making. It is tightly coupled to the hippocampus and prefrontal cortex.

Connectivity refers to the connection strength between neurons, groups of neurons, or regions of the brain.

Dendritic spines are protrusions from the dendrites of some types of neurons (usually excitatory cells) that are the loci of excitatory synaptic terminals. Changes in spine size are indicative of changes in synaptic strength.

Glutamate signaling refers to communication between neurons via the neurotransmitter glutamate. Glutamate receptors can be ionotropic, that is, ligand-gated ion channels, or metabotropic, that is, G-protein–coupled receptors. Glutamate signaling is commonly modified by neural plasticity.

G-protein–coupled receptors are proteins that span the plasma membrane of cells (e.g., neurons) that induce intracellular signaling changes in response to extracellular chemical signals.

Hippocampus is a region of the brain located near the amygdala that is involved in memory formation and retrieval. It is tightly coupled to the amygdala and prefrontal cortex.

Neocortex is a mammal-specific part of the brain that is organized into regions with specific functions including sensation, speech and language production, planning, and reason.

Neural plasticity (adj. *neuroplastic*) refers to changes in connectivity between neurons, including the amount of neurotransmitter released or the magnitude of response to the neurotransmitter. Proneuroplastic effects refer to increases in neural plasticity.

Neurogenesis is the process of creating new neurons in the brain. In humans, neurogenesis is generally limited following the completion of embryonic brain development

Prefrontal cortex (PFC) is a region in the neocortex that is highly developed in primates and especially humans. It contributes to attention, executive control, regulation of mood and emotion, and monitoring the current state of the body.

Psychedelic experience refers to the acute effects of psychedelics while the drug is present in the CNS. This experience can include distorted perception of time, altered sensory perception, heightened emotional response to music, hallucinations, altered sense of self, ego dissolution, and a sense of connection to a larger truth or absolute reality not typically glimpsed in everyday life (the so-called "mystical experience"). Challenging aspects of the psychedelic experience include anxiety, fear, and confusion.

basis for psychiatric illnesses. Within the context of psychedelics as change agents, an important next step is to identify long-term changes in brain structure that relate to therapeutic activity, which will require support from both clinical and preclinical research programs.

Studies should focus on neural plasticity, both its locus and acute and long-term mechanisms. Critical unresolved questions include the following. Do psychedelics open a window of neural plasticity? If so, is this effect nonspecific or focused in regions of the brain that are particularly relevant to behavioral phenotypes associated with human psychiatric disorders? How long does the window last? Which signaling pathways are essential for facilitating neural plasticity? Are there alternative strategies for promoting neural plasticity that may translate into more effective therapeutic interventions in patients? Despite (or perhaps because of) all the data accumulated so far, the field is left with many more questions than it started with. We predict that over the next decade, our understanding of the therapeutic potential of psychedelics will be considerably expanded.

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