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The Effects of Psychedelics on Neuronal Physiology

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Abstract

Psychedelics are quite unique among drugs that impact the central nervous system, as a single administration of a psychedelic can both rapidly alter subjective experience in profound ways and produce sustained effects on circuits relevant to mood, fear, reward, and cognitive flexibility. These remarkable properties are a direct result of psychedelics interacting with several key neuroreceptors distributed across the brain. Stimulation of these receptors activates a variety of signaling cascades that ultimately culminate in changes in neuronal structure and function. Here, we describe the effects of psychedelics on neuronal physiology, highlighting their acute effects on serotonergic and glutamatergic neurotransmission as well as their long-lasting effects on structural and functional neuroplasticity in the cortex. We propose that the neurobiological changes leading to the acute and sustained effects of psychedelics might be distinct, which could provide opportunities for engineering compounds with optimized safety and efficacy profiles.

INTRODUCTION

Classic serotonergic psychedelics are defined as psychoactive small molecules that produce acute effects on perception, mood, and cognition by activating serotonin 2A receptors (5-HT_{2A}Rs) (1). Psychedelic drugs have long been used by humans recreationally, therapeutically, and as part of cultural and spiritual traditions (2). This class of compounds includes molecules from the tryptamine, phenethylamine, and ergoline chemical families such as psilocin, 2,5-dimethoxy-4-iodoamphetamine (DOI), and lysergic acid diethylamide (LSD) (3) (**Figure 1*a***). While the acute effects of psychedelics on subjective experience are well known, these substances also produce long-lasting changes in neural circuits relevant to depression and other neuropsychiatric diseases (4). Recent clinical trials have revealed that psychedelics may possess both rapid and sustained therapeutic effects for patients with mood, anxiety, and substance use disorders (5–9).

Because of their intense mind-altering effects and promising therapeutic potential, there has been a dramatic resurgence of research into the neuropsychopharmacological effects of psychedelics. Currently, it is unclear whether psychological or neurobiological effects mediate the therapeutic properties of psychedelics (for an overview of the current debate with examples, see 10, 11). However, it is clear that psychedelics have profound effects on neuronal physiology due to their activation of specific receptors located within various circuits across the brain. These molecular-, cellular-, and circuit-level effects may directly contribute to the therapeutic properties of psychedelics and, at the very least, result in the profound subjective experiences characteristic of this class of compounds. Here, we review preclinical literature demonstrating that psychedelics regulate major neuronal physiological processes such as neurotransmission, neuroplasticity, and cell survival. By integrating what is known about psychedelic drug action at the molecular, cellular, and circuit levels, we aim to stimulate new hypotheses about how these compounds may modulate key neuronal functions both acutely and in the long term.

THE PHARMACOLOGY OF PSYCHEDELICS

The three major structural classes of psychedelics each possess unique polypharmacological profiles (**Figure 1*b***). Ergolines are the least selective class of psychedelics with high affinities for serotonin, dopamine, histamine, adrenergic, and sigma receptors. In general, tryptamines have high affinity for most serotonin receptors, while phenethylamines tend to be more selective for the 5-HT_2 family. A common feature of all classic psychedelics is that they potently activate 5-HT_2Rs. Rodent drug discrimination studies have revealed a strong correlation with 5-HT_2R binding affinity (12), and administration of the 5-HT_2R antagonist ketanserin has been shown to block subjective, cognitive, and mood-related effects of psychedelics in humans (13–19).

Of the three 5-HT_2R subtypes, the 5-HT_{2A}R has been found to be critically important for many of the effects induced by psychedelics. Drug discrimination studies revealed that the affinities of 5-HT_2R antagonists for 5-HT_{2A}Rs, rather than 5-HT_{2C}Rs, correlated better with their abilities to block the effects of LSD (20). Moreover, occupancy of 5-HT_{2A}Rs correlates well with the intensity of subjective experiences induced by psychedelics (21). Human hallucinogenic potencies correlate exceptionally well with potencies in the mouse head-twitch response (HTR) assay, and 5-HT_{2A}R knockout (KO) (22), but not 5-HT_{2C} KO (23), completely abrogates psychedelic-induced HTR.

Some evidence suggests that cortical 5-HT_{2A}Rs play a key role in the HTR (22), but given that 5-HT_{2A}Rs are expressed widely throughout the brain, it has been challenging to determine which brain regions are critical for the many effects of psychedelics. A variety of studies in both humans and rodents have established particularly high densities of 5-HT_{2A}Rs in layer 5 of the cortex and in the claustrum (24–27) (**Figure 1*c*,*d***), but key differences between species do exist.

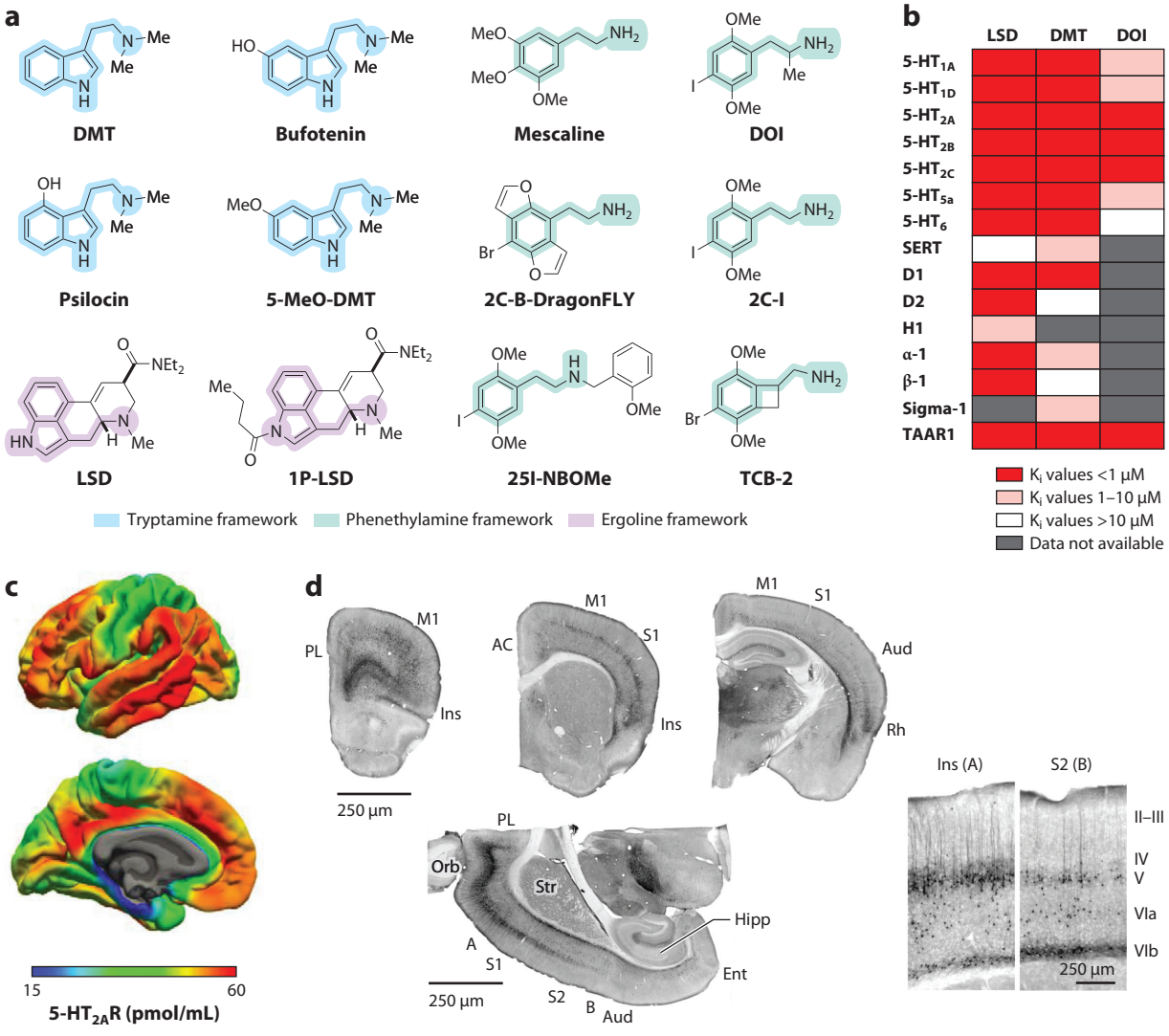

Figure 1

Polypharmacology of psychedelics. (*a*) Structures of several psychedelic drugs with tryptamine, phenethylamine, and ergoline primary pharmacophores highlighted. Panel adapted with permission from Reference 3; copyright 2022 Springer Nature. (*b*) Radioligand binding profiles for prototypical members of the ergoline (LSD), tryptamine (DMT), and phenethylamine (DOI) families. Colored boxes indicate K_i values using either agonist or antagonist radioligands, where K_i represents the inhibition constant describing the binding affinity of a ligand for a receptor (the smaller the K_i, the greater the binding affinity). Data obtained from the Psychoactive Drug Screening Program K_i Database with the exception of TAAR1 data. Data for TAAR1 were taken from Reference 59, with red boxes indicating >50% activation of rat TAAR1 following 1 μM treatment. (*c*) Radioligand binding to 5-HT_{2A}Rs across the human brain. Panel adapted with permission from Reference 27 (CC BY 4.0). (*d*) Expression of 5-HT_{2A}Rs in the mouse brain. Panel adapted with permission from Reference 25 (CC BY 4.0). Abbreviations: 5-HT_{2A}R, serotonin 2A receptor; AC, anterior cingulate cortex; Aud, auditory cortex; DMT, *N*,*N*-dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; Ent, entorhinal cortex; Hipp, hippocampus; Ins, insular cortex; LSD, lysergic acid diethylamide; M1, primary motor cortex; Orb, orbital cortex; PL, prelimbic cortex; Rh, rhinal cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SERT, serotonin transporter; Str, striatum; TAAR1, trace amine–associated receptor 1.

In humans, expression of 5-HT_{2A}Rs is higher in the prefrontal and visual cortices rather than the motor and somatosensory cortices (**Figure 1*c***), whereas rodents exhibit a more pronounced anterior to posterior expression gradient (**Figure 1*d***).

The 5-HT_{2A}R is a G protein–coupled receptor (GPCR) that typically activates G_q signaling. That leads to a cascade of events including activation of phospholipase C, hydrolysis of phosphatidylinositol-4,5-bisphosphate into inositol trisphosphate and diacylglycerol, and release of Ca^{2+} stores from the endoplasmic reticulum, ultimately activating CAMKII, protein kinase C, and MAPK pathways. Psychedelics have been primarily shown to activate these pathways in non-neuronal cells heterologously expressing 5-HT_{2A}Rs (28–30), though these pathways are operative in neurons as well (31). Psychedelics increase inositol monophosphate accumulation in cortical cultures (32), and unpublished work suggests that psilocin can increase the firing rates of 5-HT_{2A}R-expressing cortical neurons in a G_q-dependent manner (33). However, activation of 5-HT_{2A}Rs and canonical downstream signaling does not necessarily lead to hallucinogenic effects, as several nonhallucinogenic agonists of the 5-HT_{2A}R have been discovered including lisuride, 6-fluoro-*N*,*N*-diethyltryptamine, tabernanthalog, ariadne, and IHCH-7079, among others (34–41). Structural biology studies suggest that hallucinogenic and nonhallucinogenic agonists may induce distinct confirmations of the 5-HT_{2A}R, leading to their disparate effects (35). Moreover, a novel biosensor that couples 5-HT_{2A}R conformation to a fluorescence signal is capable of differentiating between hallucinogenic and nonhallucinogenic ligands (42).

Currently, very little is known about how biased agonism at the 5-HT_{2A}R might impact the effects of psychedelics. Psychedelic-related behaviors induced by LSD are dependent on β-arrestin 2 (43), while those induced by DOI are not (44). Moreover, DOI can still produce an HTR in G_q KO mice (45). Other forms of functional selectivity might be operative, including location bias (32) and the activation of distinct heterodimeric complexes. The 5-HT_{2A}R is known to form complexes with a variety of GPCRs that may alter its function, including metabotropic glutamate, dopamine, cannabinoid, and serotonin receptors (46–49). Importantly, psychedelics have been shown to impact neuronal function in a manner reliant on such heterodimers (50–52).

Although evidence for 5-HT_{2A}R activation in the subjective effects of psychedelics is substantial, to the best of our knowledge, no psychedelic has been described that completely lacks 5-HT_{2B}R or 5-HT_{2C}R agonism, leaving open the question of how these receptors might contribute to the various effects of psychedelics. A role for 5-HT_{2B}Rs in the psychoactive effects of psychedelics has been largely dismissed owing to low 5-HT_{2B}R expression in the central nervous system compared to 5-HT_{2A}Rs and 5-HT_{2C}Rs (53). However, 5-HT_{2B}Rs have been shown to play a key role in compound-induced release of serotonin (54) and thus have the potential to modulate the effects of psychedelics. Expression of 5-HT_{2C}Rs is much higher in the central nervous system (53), and they are likely to play major roles in the actions of psychedelics. Moreover, 5-HT_{2C}Rs are posttranscriptionally edited, leading to several functionally distinct isoforms found in various brain regions (55, 56).

Outside of the 5-HT_2 family of receptors, psychedelics target a wide variety of other neuroreceptors including 5-HT_1Rs, trace amine–associated receptors (TAARs), and sigma-1 receptors (**Figure 1*b***), among others. Activation of 5-HT_{1A} autoreceptors on neurons of the raphe nucleus by LSD decreases their firing rate (57). Furthermore, 5-HT_{1B}R and 5-HT_{1D}R agonism could explain the propensity for psychedelics to induce vasoconstriction given that 5-HT_{1B} and 5-HT_{1D} receptors are known targets for the antimigraine triptan drugs (58), and triptans are structurally related to tryptamine-based psychedelics like *N*,*N*-dimethyltryptamine (DMT). Some psychedelics, like DMT, act as agonists at TAARs (59) and sigma-1 receptors (60). While DMT has been hypothesized to be an endogenous ligand for the sigma-1 receptor, its binding affinity for that target (>1 μM) is unremarkable (60). Recent work suggests that psychedelics

may directly bind to the receptor tyrosine kinase TrkB, serving as positive allosteric modulators of brain-derived neurotrophic factor (BDNF) signaling (61).

EFFECTS OF PSYCHEDELICS ON GENE AND PROTEIN EXPRESSION

Gene microarray experiments have demonstrated that a single dose of LSD only regulates a very small number of genes in the brain, but many of them have been implicated in plasticity processes (62). Indeed, many psychedelics have relatively modest effects on gene expression despite their long-lasting effects on neuronal functions. Psychedelics have consistently been shown to increase the expression of immediate early genes like *c-Fos*, *arc*, *egr-1*, and *egr-2*, and these effects are absent in 5-HT_{2A}R KO mice or following pretreatment with a 5-HT_2R antagonist (22, 63–68). Recent whole-brain mapping of c-Fos following an acute dose of psilocybin showed dramatic increases in c-Fos induction in the prefrontal cortex (PFC), claustrum, amygdala, thalamus, lateral habenula, and hippocampus, with decreased c-Fos in the raphe nuclei (69). The degree of c-Fos induction was best correlated with messenger RNA (mRNA) transcript levels of N-methyl-D-aspartate (NMDA) receptor subunits and the 5-HT_{2A}R. Interestingly, brain-wide expression of c-Fos following psilocybin administration shared many similarities to that of the dissociative anesthetic ketamine.

Both hallucinogenic and nonhallucinogenic agonists of the 5-HT_{2A}R can increase expression of various immediate early genes in the somatosensory cortex in a 5-HT_{2A}R-dependent manner, albeit with unique transcriptional fingerprints (63). Unlike LSD, lisuride does not upregulate *egr-1* or *egr-2* expression (22). Both compounds increase *c-Fos* expression, but the magnitude of response appears to be greater for LSD (22). While LSD induces *c-Fos* in the PFC, hippocampus, and midbrain of rats, it only increases *arc* expression in the PFC (62), suggesting that particular immediate early gene-related pathways might be circuit-specific.

While psychedelic-induced *c-Fos* expression is 5-HT_{2A}R-dependent (22, 64, 68), upregulation of this immediate early gene occurs in cells not expressing 5-HT_{2A}Rs (65). One mechanistic explanation is that BDNF or glutamate release may be a critical mediator of psychedelic-induced changes in cortical microcircuit activity. Indeed, DOI dose-dependently increases cortical *bdnf* mRNA while decreasing hippocampal *bdnf* mRNA in a 5-HT_{2A}R-dependent manner (70), and increases in cortical *arc* mRNA levels following DOI administration are abolished with the inducible KO of BDNF (71). Induction of *bdnf* expression in the cortex and claustrum is also blocked by $mGlu_{2/3}$ receptor agonism and potentiated in the medial PFC by $mGlu_{2/3}$ receptor antagonism (72). Furthermore, an $mGlu_{2/3}$ receptor agonist and an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist abrogated DOI-induced *c-Fos* expression in the medial PFC (73, 74), implicating glutamate signaling in psychedelic-induced immediate early gene (IEG) expression. Interestingly, different signal transduction pathways downstream of 5-HT_{2A}R activation might lead to distinct gene expression responses. In cultured cortical neurons, *arc*, *bdnf*, and *egr-2* were upregulated following DOI administration in both a MAPK- and CAMKII-dependent manner, whereas DOI-induced upregulation of *c-Fos* and *egr-1* was specifically dependent on CAMKII and MAPK signaling, respectively (75).

In addition to IEGs and *bdnf*, psychedelics also increase the expression of key pre- and postsynaptic proteins. In pigs, a single dose of psilocybin led to long-lasting increases in the presynaptic protein SV2A in both the PFC and hippocampus (76). In the PFC of rodents, psilocybin also had a marked effect on postsynaptic structures, increasing the expression of *Psd95* (77) and dose-dependently increasing the synthesis of NMDA receptor subunits (78). Moreover, proteomic analysis of human cerebral organoids following treatment with 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) or LSD revealed increased expression of proteins involved in structural and functional neuroplasticity (79, 80).

Psychedelics can also produce long-lasting changes in the neuronal epigenome that may explain the enduring effects of psychedelics. A single systemic administration of DOI increased the enhancer level of genes associated with structural and functional neuroplasticity persisting at least 7 days post-administration (81). Repeated (7-day) administration of LSD significantly increased the methylation level of CpG sites of genes related to neuronal development, growth, and morphology, as well as neuronal death and survival mechanisms (82). In the same study, LSD primarily upregulated the synthesis of proteins involved in synaptic plasticity and microtubule polymerization (essential for neuronal structure), while downregulating the synthesis of proteins that regulate receptor-mediated endocytosis.

EFFECTS OF PSYCHEDELICS ON STRUCTURAL NEUROPLASTICITY

Psychedelic drugs have recently been classified as psychoplastogens, small molecules that produce therapeutic effects by rapidly promoting structural and functional neuroplasticity (83). In cortical cultures, psychedelics have been shown to increase the size of dendritic growth cones, promote the growth of new neurites, increase dendritic spine density, and alter spine morphology (84–89) (**Figure 2*a***). Moreover, only short stimulation periods are required to induce long-lasting changes in cortical neuron growth (90). Psychedelic-induced spine growth is likely associated with synaptogenesis given that colocalization of pre- and postsynaptic markers is also increased following treatment (84).

The first in vivo evidence for psychedelic-induced neuroplasticity was obtained from Golgi-Cox staining 24 h after a single systemic administration of DMT to rats, where treatment with DMT increased spine density in the PFC to a comparable extent as ketamine (84). Subsequently, single doses of DOI and 5-MeO-DMT were shown to increase dendritic spine density in the PFC of mice 24 h after administration (32, 81) (**Figure 2*b***). Similar results following DOI treatment were observed in the somatosensory cortex using two-photon in vivo imaging (34). Repeated (7-day) systemic administration of LSD increased dendritic spine density in the PFC of wild-type mice and in animals exposed to 15 days of chronic restraint stress (91). However, chronic intermittent dosing of DMT over several weeks resulted in spine retraction in female but not male rats (92), suggesting that overstimulation of cortical neuron growth pathways may lead to homeostatic changes curtailing growth.

Longitudinal in vivo imaging of cortical neurons following a single dose of psilocybin revealed significant increases in dendritic spine density in the cortex that persisted for at least one month (93) (**Figure 2*c***). Interestingly, the magnitude of the effect was greater in female mice. Similar long-lasting effects have been observed following a single dose of 5-MeO-DMT (94). Two-photon imaging studies using psilocybin, DOI, and 5-MeO-DMT have all demonstrated that psychedelics increase the rate of spine formation but have little to no effect on the rate of spine elimination (34, 93, 94).

The effects of psychedelics on structural plasticity are dependent on 5-HT_{2A}R signaling, as 5-HT_2R antagonists block psychedelic-induced increases in dendritic branching and dendritic spine density in culture (84, 88). In vivo, 5-MeO-DMT and DOI promote robust spine growth in wild-type mice, but these effects are not observed in 5-HT_{2A}R KO animals (32, 81). While 5-HT_{2A}Rs exist on the plasma membrane, a large population is localized to intracellular compartments within cortical neurons. This intracellular pool plays a critical role in psychedelic-induced neuroplasticity, and location bias can potentially explain why polar, membrane-impermeable 5-HT_{2A}R agonists like serotonin cannot promote cortical neuron growth (32).

Although the mechanism of psychedelic-induced neuroplasticity has not been fully elucidated, several clues are beginning to emerge (95). In addition to 5-HT_{2A}R activation, the

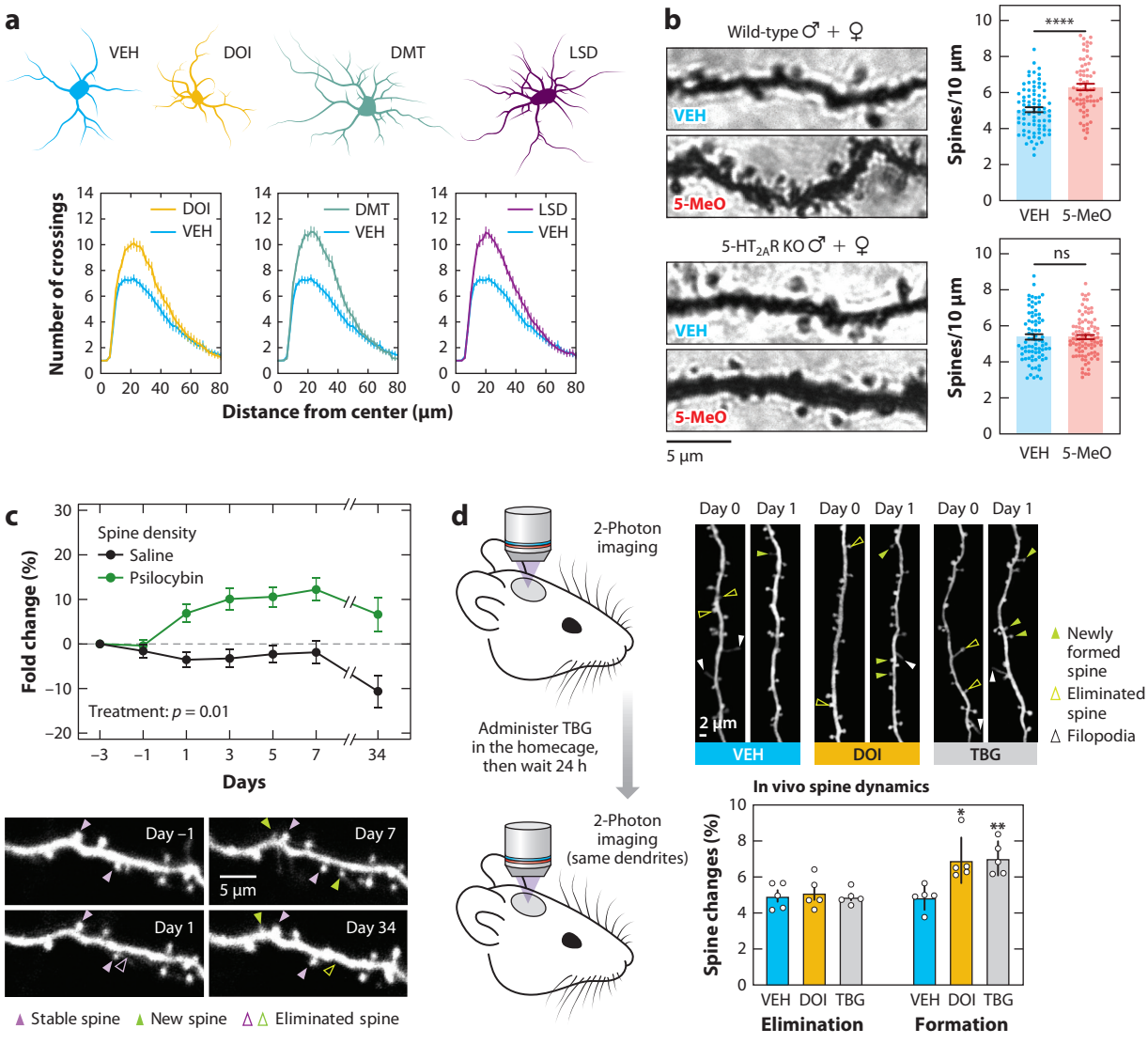

Figure 2

Psychedelics promote structural neuroplasticity. (*a*) DOI, DMT, and LSD promote dendritogenesis in vitro. Dendrite tracings and Sholl plots are shown. Panel adapted with permission from Reference 84; copyright 2018 Elsevier. (*b*) 5-MeO-DMT (5-MeO) increases dendritic spine density in the prefrontal cortex of wild-type but not 5-HT_{2A}R KO mice. **** = $p < 0.0001$. Panel adapted with permission from Reference 32; copyright 2023 AAAS. (*c*) Psilocybin produces long-lasting changes in dendritic spine density in vivo. Panel adapted with permission from Reference 93; copyright 2021 Elsevier. (*d*) DOI, and the nonhallucinogenic 5-HT_{2A}R agonist TBG, increase dendritic spine formation in the primary sensory cortex as measured by 2-photon imaging in vivo. * = $p < 0.05$, ** = $p < 0.01$. Panel adapted with permission from Reference 34. Abbreviations: 5-HT_{2A}R, serotonin 2A receptor; 5-MeO-DMT, 5-methoxy-*N*,*N*-dimethyltryptamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DMT, *N*,*N*-dimethyltryptamine; KO, knockout; LSD, lysergic acid diethylamide; ns, not significant; TBG, tabernanthalog; VEH, vehicle.

psychoplastogenic effects of psychedelics also require TrkB, mammalian target of rapamycin (mTOR), and AMPA receptor signaling (84, 90). Proteomics experiments demonstrated that LSD treatment upregulated the mTOR pathway in human brain organoids (80), and mTOR activation in excitatory pyramidal cells of the cortex is essential for repeated (7-day) LSD administration to produce prosocial effects (96). Given that mTOR is the downstream effector of the canonical signaling pathway initiated by TrkB activation, these data again implicate BDNF-TrkB signaling in the effect of psychedelics on structural neuroplasticity. Intriguingly, a recent report found that LSD and psilocin might serve as positive allosteric modulators of BDNF signaling by directly binding to TrkB (61).

Although the psychoplastogenic effects of psychedelics require 5-HT_{2A}R activation, they do not appear to be directly coupled to hallucinations. Evidence continues to mount suggesting that nonhallucinogenic agonists of the 5-HT_{2A}R may have therapeutic potential (34–36, 39, 40, 97). Some of these compounds have been shown to promote cortical neuron growth in a 5-HT_{2A}R-dependent manner (34, 36, 38). The nonhallucinogenic 5-HT_{2A}R agonist tabernanthalog was shown to increase neuritogenesis and dendritic spine formation in cultured cortical neurons, and two-photon in vivo imaging revealed that its psychoplastogenic properties were comparable to those of the hallucinogen DOI (34) (**Figure 2*d***). Follow-up studies revealed that a single dose of tabernanthalog rescued cortical pyramidal neuron spine loss following unpredictable mild stress. More than 30% of tabernanthalog-induced spines were formed near sites where stress had induced spine loss, and ~30% of tabernanthalog-induced spines survived for 12 days (98). The effects of tabernanthalog on spine growth are in sharp contrast to those of the traditional antidepressant fluoxetine, as a single dose of fluoxetine did not produce any measurable changes in spine density and did not rescue stress-induced behavioral deficits (98). Like tabernanthalog, the nonhallucinogenic 5-HT_{2A}R agonist lisuride has been shown to promote dendritic spine growth following an insult that resulted in spine retraction (97). As cortical atrophy is a hallmark of many neuropsychiatric diseases (99), the long-term effects of psychedelics and nonhallucinogenic psychoplastogens on cortical neuron growth could have important implications for the treatment of numerous conditions.

EFFECTS OF PSYCHEDELICS ON NEURONAL SURVIVAL AND NEUROGENESIS

Psychedelics have been consistently shown to regulate the expression and synthesis of cell survival–related genes and proteins in the cortex, including serum glucocorticoid kinase, inhibitor of nuclear factor kappa B-α (IκB-α), and nuclear factor-kappa B (NF-κB) (62, 77, 100). While DOI significantly increased IκB-α mRNA in the somatosensory cortex in a 5-HT_{2A}-dependent manner (63), LSD-induced changes in serum glucocorticoid kinase and IκB-α expression were unaffected by 5-HT_{2A} receptor antagonism (100), suggesting that different psychedelics may regulate cell survival via distinct mechanisms.

Prolonged (6-day) exposure to DOI prevented kainate- and H_2O_2-induced excitotoxic and oxidative insults, respectively, in cultured cortical neurons by promoting mitochondrial biogenesis and reducing reactive oxygen species levels (101). Interestingly, serotonin and DOI shared a common mechanism for driving neuroprotective effects, involving 5-HT_{2A} receptor-dependent activation of sirtuin 1, a master regulator of mitochondrial function. These data imply a physiological role of 5-HT_{2A}R activation in regulating neuronal mitochondria-driven bioenergetics and offer a potential mechanism by which some psychedelics can promote cell survival.

Importantly, DMT can bind to the sigma-1 receptor (60), a receptor localized to the endoplasmic reticulum–mitochondria interface where it ensures delivery of inositol trisphosphate

(IP_3)-dependent Ca^{2+} ions released from intracellular stores to mitochondria to regulate cell survival processes (102). The sigma-1 receptor is also known to functionally modulate BDNF expression and secretion (102) and transactivate TrkB receptors (103, 104). BDNF promotes the survival of neurons produced via neurogenesis (105), and BDNF-TrkB-Akt signaling is an established neuroprotective and prosurvival signaling cascade (106). It is therefore possible that at least some psychedelics regulate cell survival mechanisms via sigma-1 receptor activation. Indeed, DMT prevented human induced pluripotent stem cell–derived cortical neuronal cell death in response to severe hypoxic stress and promoted cell survival following focal ischemia in mice in a manner dependent on sigma-1 receptor expression (107, 108).

With respect to neurogenesis, the effects of psychedelics have been mixed. Intracerebroventricular administration of 5-MeO-DMT induced neurogenesis in the dentate gyrus of rodents just 15 min after injection, and these newborn neurons exhibited increased dendritic arbor complexity when compared to those not stimulated by 5-MeO-DMT (109). Conversely, acute administration of DOI and LSD had no effect on hippocampal neurogenesis (110), while psilocybin and 25I-NBOMe decreased hippocampal neurogenesis (111). Interestingly, 5-HT_2R blockade by ketanserin decreased hippocampal progenitor cell turnover following acute treatment, while chronic treatment increases the turnover (110). Repeated (4-day) systemic injection of 5-MeO-DMT induced hippocampal neurogenesis that was blocked by a sigma-1 receptor antagonists, but not by 5-HT_{2A}R or 5-HT_{1A}R antagonists (112).

Clearly, sigma-1 and 5-HT_{2A} receptors play important roles in the effects of psychedelics on neuronal survival and neurogenesis; however, whether these mechanisms are mutually exclusive or inherently linked to each other is unknown. For example, 5-HT_{2A}R-mediated G_q signaling may play a role in calcium ion (Ca^{2+}) release from intracellular stores that the sigma-1 receptor then funnels to mitochondria to regulate bioenergetics and facilitate cell survival mechanisms.

EFFECTS OF PSYCHEDELICS ON NEURONAL ACTIVITY

Psychedelics have profound acute and long-lasting functional effects on a variety of neuronal populations. Stimulation of rat cortical slices with DOI was shown to enhance the occurrence of late excitatory postsynaptic currents (EPSCs) in layer 5 pyramidal neurons in a 5-HT_{2A}R-dependent manner (113), an effect that was blocked by NR2B-selective antagonists (114). Furthermore, DOI increased the amplitude of evoked excitatory postsynaptic potentials (EPSPs) in layer 5 pyramidal neurons (115). Bath application of DOI also increases the frequency of spontaneous EPSPs in layer 5 pyramidal neurons, and this effect is suppressed by $mGlu_{2/3}$ agonism (116). Enhanced excitatory neurotransmission in cortical slices has also been observed following treatment with 2,5-dimethoxy-4-bromoamphetamine (DOB) and was blocked with 5-HT_2R antagonists (117). In vivo, 5-MeO-DMT increases cortical pyramidal neuron firing rate and burst activity following systemic administration (118).

In addition to excitatory neurons in the cortex, psychedelics also acutely impact the function of inhibitory and monoaminergic neurons. The 5-HT_{2A}R is expressed in both glutamatergic and γ-aminobutyric acid (GABA)-ergic neurons in the cortex (119, 120). In slices from the piriform cortex, both DOI and LSD increased the firing rate of interneurons, and the effect was blocked by a 5-HT_2R antagonist (121). In the locus coeruleus of rats, mescaline, 2,5-dimethoxy-4-methylamphetamin (DOM), and LSD decreased and increased the spontaneous and evoked activity of neurons, respectively (122). These effects are blocked by 5-HT_2R antagonists and appear to be mediated by locus coeruleus afferents, as iontophoretic application onto cell bodies in the locus coeruleus did not produce the same effects.

In the raphe, psychedelics can dramatically suppress the firing of serotonergic neurons, but these effects are only observed following treatment with psychedelics that have substantial

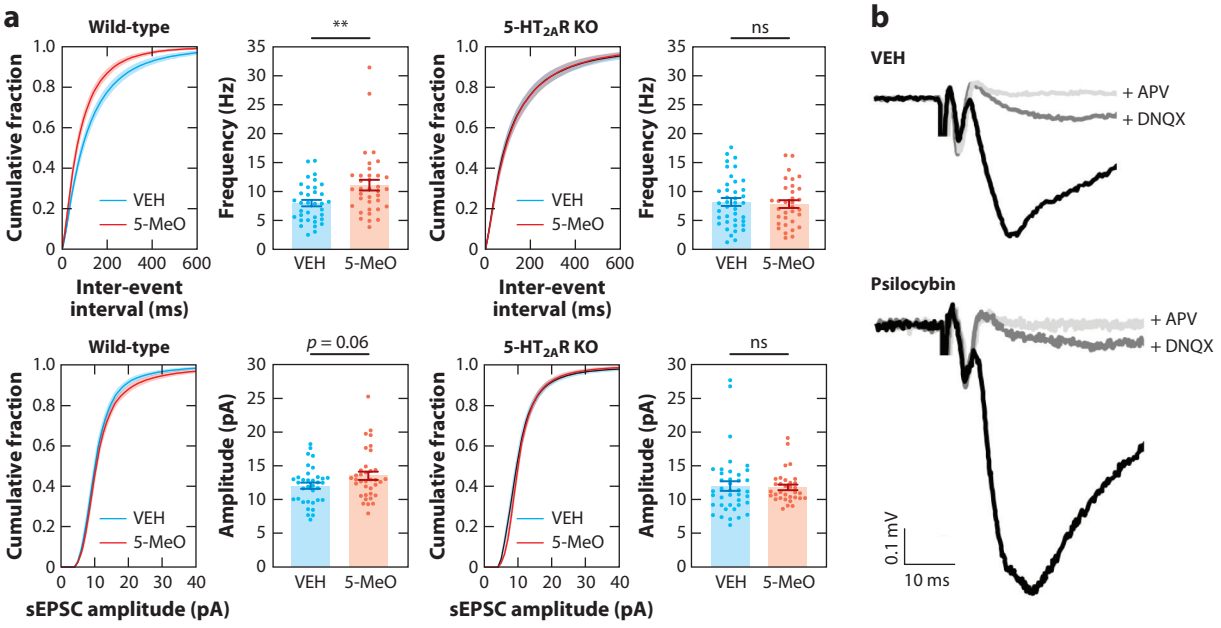

Figure 3

Psychedelics impact neuronal activity. (*a*) 5-MeO-DMT (5-MeO) increases cortical sEPSCs in wild-type, but not 5-HT$_{2A}$R KO mice. Panel adapted with permission from Reference 32; copyright 2023 AAAS. ** = $p < 0.01$. (*b*) Psilocybin increases hippocampal slice EPSPs. Panel adapted with permission from Reference 126; copyright 2021 NAS. Abbreviations: 5-MeO-DMT, 5-methoxy-*N*,*N*-dimethyltryptamine; APV, 2-aminophosphonovaleric acid; DNQX, 6,7-dinitroquinoxaline-2,3-dione; EPSP, excitatory postsynaptic potential; KO, knockout; ns, not significant; sEPSC, spontaneous excitatory postsynaptic current; VEH, vehicle.

5-HT$_{1A}$R activity (123–125). The 5-HT$_{1A}$R might also play a role in the effects of LSD on the firing rate of neurons of the ventral tegmental area (VTA), though the mechanism is more complex. Dose-response studies demonstrated that LSD decreased the firing rate of dopaminergic neurons in the VTA via a mechanism involving activation of 5-HT$_{1A}$, D$_2$, and TAAR$_1$ receptors (57).

A unique property of psychedelics is their ability to produce changes in neuronal function that last long after the compounds have been cleared from the body. Systemic administration of DMT to rats increased both the amplitude and frequency of spontaneous EPSCs in cortical pyramidal neurons measured by ex vivo electrophysiology 24 h after dosing (84). Similar results have been observed following administration of 5-MeO-DMT to wild-type mice, and these changes in functional plasticity were absent in 5-HT$_{2A}$R KO mice (32) (**Figure 3*a***). Similarly, psilocybin increased the frequency of miniature EPSCs in layer 5 pyramidal neurons 24 h following systemic administration (93). In general, effects on EPSC frequency seem quite robust, whereas effects on EPSC amplitude are more modest (32, 84, 93).

In addition to their long-lasting effects on EPSCs, psychedelics have also been found to have additional effects on cortical neuron function. A single systemic administration of DOI significantly enhanced cortical long-term potentiation in slices collected 24 h post-administration (81), while repeated (7-day) LSD administration increased the burst activity of PFC pyramidal neurons and potentiated the excitatory response of DOI and the AMPA receptor agonist, quisqualate (96). Importantly, the effects of repeated dosing of LSD were dependent on mTOR activation. Outside of the cortex, systemic administration of psilocybin to mice that had been exposed to chronic stress

led to the strengthening of intrahippocampal synapses measured 3 days later (126) (**Figure 3*b***). Currently, it is unclear whether hippocampal plasticity induced by psychedelics is a result of direct action on hippocampal cells or an indirect effect from hippocampal afferents.

EFFECTS OF PSYCHEDELICS ON NEUROTRANSMITTER/ NEUROMODULATOR RELEASE

Microdialysis studies have indicated that a number of psychedelics increase glutamate release in the PFC via 5-HT_{2A}R activation, including LSD, DOM, DOI, 25I-NBOMe, and psilocybin (78, 127–129). Moreover, glutamate release appears to be a direct effect of cortical neuron stimulation, as intracortical administration of psychedelics reproduces the glutamate release observed following systemic administration (128). Changes in excitatory neurotransmission following psilocybin administration are reflected in enhanced cortical glucose metabolism as measured in humans using [^{18}F]fluorodeoxyglucose positron emission tomography (130, 131). Psychedelic-induced neuroplasticity has been hypothesized to involve glutamatergic transmission in the cortex; however, it is unclear whether a large glutamate burst is necessary to induce cortical structural plasticity, and it is unknown if nonhallucinogenic psychoplastogens increase glutamate levels in the cortex to a comparable extent as psychedelics (95).

Psilocybin and DOI may regulate cortical microcircuits by activating 5-HT_{2A}R-expressing GABAergic interneurons and increasing GABA release in the PFC (78, 132). Psilocybin appears to regulate long-range cortical-subcortical circuits by rapidly increasing GABA release in the thalamus and increasing GABA levels in the PFC after 140 min (78). The delayed release of cortical GABA may indicate that psilocybin impacts plasticity mechanisms that then facilitate delayed changes in neuronal circuit activity. Furthermore, ayahuasca ingestion by rats increased 5-HT and GABA release in the hippocampus, and increased 5-HT, GABA, and noradrenaline release in the amygdala (133).

Systemic administration of psilocybin in rats rapidly increased dopamine release in the PFC (78), suggesting that psilocin regulates a known top-down neurocircuit involving 5-HT_{2A}R-expressing pyramidal neurons that project to and activate mesocortical dopaminergic VTA neurons. Indeed, activation of 5-HT_{2A}Rs in the PFC by DOI increases mesocortical dopaminergic signaling (134), and 25I-NBOMe dose-dependently increases dopamine in the frontal cortex (129). DOI and psilocin also activate mesolimbic dopaminergic VTA neurons, increasing dopamine release in the nucleus accumbens (135, 136). While increased mesolimbic dopamine is typically associated with the addictive potential of drugs, LSD induces much higher c-Fos expression in the nucleus accumbens when compared to the highly addictive drugs cocaine and morphine (137), suggesting that distinct mechanisms may regulate addictive liability.

CIRCUIT-LEVEL EFFECTS OF PSYCHEDELICS

Although 5-HT_{2A}Rs are expressed broadly throughout the brain, layer 5 of the cortex and the claustrum are two brain regions with the highest densities (25). Given the extensive role the cortex plays in sensory processing and top-down control of various subcortical regions also involved in sensory processing, 5-HT_{2A}R-dependent changes in cortical function have been hypothesized to mediate the subjective effects that constitute the classic psychedelic experience. Though it is much harder to study due to its anatomy, the claustrum is likely to also play a key role in the effects of psychedelics. This enigmatic region was famously hypothesized by Crick and Koch to be the seat of consciousness (138) due to its vast interconnectivity with the cortex and subcortical structures involved in sensory processing (139, 140). In humans, the claustrum is the most

interconnected brain structure per volume (141), supporting a role for the claustrum in binding sensory information from across the cortex to form a unified conscious experience.

Given 5-HT_{2A}R expression patterns, it is unsurprising that psychedelics can dramatically impact network activity across the cortex. Treatment with DOI or 5-MeO-DMT decreased the amplitude of low-frequency (0.3–4 Hz) oscillations in the cortex, and the effects were blocked by 5-HT_{2A}R antagonists (118, 142). The two drugs appear to have opposite effects on high-frequency oscillations in the cortex, with DOI and 5-MeO-DMT reducing and increasing gamma power in rodents, respectively (143, 144). Psilocybin also decreased the power of low-frequency bands in the cortex of rats, while potentially increasing gamma power (145). Another study found that DOI reduced local field potential power across a wide frequency range (146). Unlike DOI, 25C-NBOMe seems to increase the power of high-frequency oscillations (120–150 Hz) in the cortex of rats, an effect blocked by a 5-HT_2R antagonist (147). Electroencephalography studies in freely moving rats have revealed that psilocin, LSD, mescaline, and DOB—compounds representing the tryptamine, ergoline, and phenethylamine classes of psychedelics—all decreased spectral power in the 1–40 Hz frequency range (148).

Disruption of cortical oscillations might be directly related to the effects of psychedelics on cortical neuron excitability. Several studies have observed that psychedelics induce bidirectional modulation of cortical neuron function with approximately one-third of the cells in the cortex being excited, one-third being inhibited, and one-third being unaffected (118, 142). Interestingly, excitatory neurons in V1 of the mouse cortex with low or high firing rates were enhanced or suppressed, respectively, following DOI exposure (146). Similar observations have been made in V1 of cats and nonhuman primates (149, 150). The effect is likely determined by whether or not a neuron expresses 5-HT_{2A}Rs, as recent unpublished work using a tdTomato reporter for 5-HT_{2A}R expression has shown that psilocin directly activates 5-HT_{2A}R-expressing layer 5 pyramidal neurons in the cortex (33). Importantly, ketamine also appears to suppress cortical neurons that are normally active and activate those that are typically inactive (151). Thus, this switch in cortical neuron activity may represent a general feature of hallucinogenic drugs.

CONCLUSION AND UNANSWERED QUESTIONS

Psychedelics produce profound effects on nervous system function by activating 5-HT_{2A}Rs and several other targets (**Figure 4**). While the acute effects of these drugs on perception have long been appreciated, their sustained effects are now being investigated to explain how they can produce long-lasting therapeutic responses after only a single administration. Many questions remain about the mechanisms of psychedelics, including why biological sex seems to impact both their acute and sustained effects. For example, female mice appear to be more sensitive to psychedelics in both the HTR assay (38, 152) and in measures of structural neuroplasticity (93). It is unclear if sex hormones modulate responses to psychedelics or if differences in receptor expression patterns across the brain underlie the distinctions observed between males and females.

Perhaps the most important unanswered questions about the mechanisms of psychedelics are related to which circuits mediate the various behavioral effects associated with this class of small molecules. Currently, we do not know which circuits are involved in hallucinogenic behaviors such as the HTR and which mediate long-lasting beneficial responses relevant to treating depression, post-traumatic stress disorder, and substance use disorder. It is quite possible that these circuits are distinct, and modern optogenetic, chemogenetic, and gene knockout tools should enable their elucidation. If the circuits mediating the hallucinogenic and therapeutic effects of psychedelics are distinct, it should be possible to engineer targeted therapeutics with improved efficacy and safety profiles.

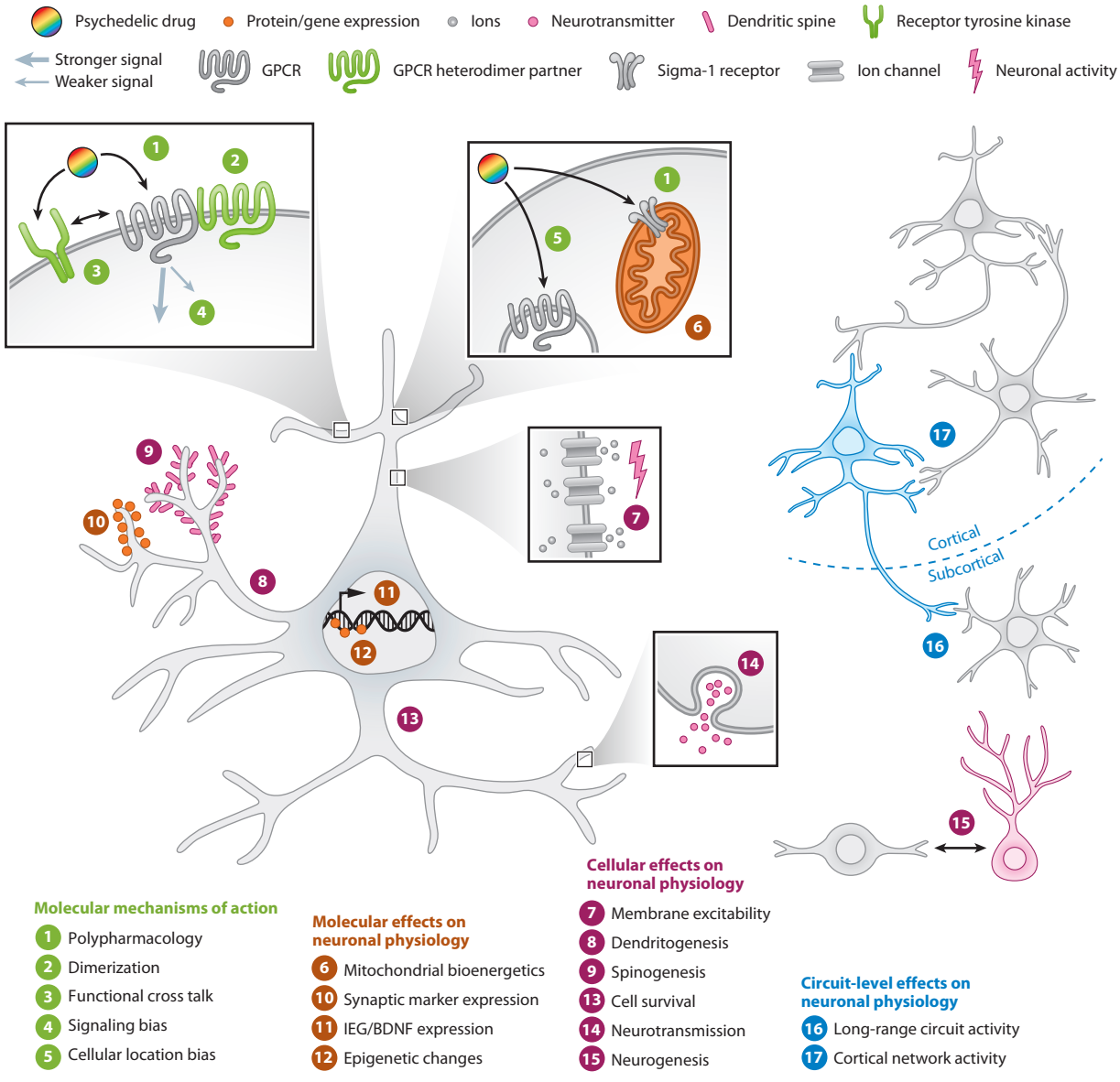

Figure 4

Schematic overview of the putative molecular mechanisms of psychedelic drug action as well as the molecular-, cellular-, and circuit-level effects of psychedelics on neuronal physiology. Abbreviations: BDNF, brain-derived neurotrophic factor; GPCR, G protein–coupled receptor; IEG, immediate early gene.

DISCLOSURE STATEMENT

D.E.O. is a cofounder of Delix Therapeutics, Inc., serves as the Chief Innovation Officer and Head of the Scientific Advisory Board, and has sponsored research agreements with Delix Therapeutics. Delix Therapeutics was not involved in the conceptualization, design, decision to publish, or preparation of this manuscript. C.J.H. is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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