nature neuroscience

Review Article

https://doi.org/10.1038/s41593-022-01177-4

The neural basis of psychedelic action

Received: 7 December 2021

Accepted: 6 September 2022

Published online: 24 October 2022

Check for updates

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Psychedelics are serotonin 2A receptor agonists that can lead to profound changes in perception, cognition and mood. In this review, we focus on the basic neurobiology underlying the action of psychedelic drugs. We first discuss chemistry, highlighting the diversity of psychoactive molecules and the principles that govern their potency and pharmacokinetics. We describe the roles of serotonin receptors and their downstream molecular signaling pathways, emphasizing key elements for drug discovery. We consider the impact of psychedelics on neuronal spiking dynamics in several cortical and subcortical regions, along with transcriptional changes and sustained effects on structural plasticity. Finally, we summarize neuroimaging results that pinpoint effects on association cortices and thalamocortical functional connectivity, which inform current theories of psychedelic action. By synthesizing knowledge across the chemical, molecular, neuronal, and network levels, we hope to provide an integrative perspective on the neural mechanisms responsible for the acute and enduring effects of psychedelics on behavior.

Psychedelics have captured the imagination of neuroscientists since the early 20th century[1], as they are molecules that can profoundly bend sensory processing, alter cognition and produce intense subjective experiences. The abilities of psychedelic drugs to modulate perceptual states provide powerful tools for probing the human mind. Psychedelics are also molecules that afford potential benefits to individuals diagnosed with a wide range of neuropsychiatric disorders, including depression, anxiety and substance-use disorders[2–4]. Unlike current treatment options, only one or a few sessions of psychedelic-assisted psychotherapy have been reported to yield durable reductions of symptoms in phase II clinical trials. For these reasons, psychedelics hold promise to transform neuroscience and psychiatry. Psychedelic research flourished in the 1950s and 1960s, when lysergic acid diethylamide (LSD) and psilocybin were synthesized for pharmacological and behavioral research and were readily available. Controlled substance laws enacted in the 1970s led to a hiatus lasting several decades, but now there is renewed scientific interest in understanding psychedelics and their effects on the brain and body.

This Review article focuses on the neuroscience of psychedelics. We will begin with chemistry, move to receptors and molecular signaling and finish with recent insights into how psychedelics modulate neurons and neural circuits. Because the emphasis is on basic neurobiology, we will set the stage with only brief descriptions of the behavioral effects and clinical relevance of psychedelics (Box 1) and preclinical assays for evaluating psychedelics in animal models (Box 2), which have been covered by other excellent reviews[5–8]. Our aim is to connect multiple levels of investigation to provide both an integrative and in-depth perspective on this topic. We will address questions such as how knowledge at the chemical and molecular levels may accelerate psychedelic-related drug discovery and whether neuronal and network

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https://doi.org/10.1038/s41593-022-01177-4

BOX 1

Brief overview of behavioral effects and therapeutic potentials

The term 'psychedelic', from the Greek for mind-manifesting, was coined in 1956 by Humphrey Osmond, who chose the term because 'it is clear, euphonious, and uncontaminated by other associations'[146]. Acutely, psychedelic drugs generate perceptual distortions, psychological experiences and labile moods[147,148]. The effects are often accompanied by imaginary percepts akin to hallucinations; hence 'hallucinogens' is another term used in the scientific literature to refer to molecules that include psychedelics. Some psychedelic users experience a reduced sense of self-referential awareness, a subjective feeling termed 'ego dissolution'. In 2006, an influential study by Roland Griffiths and colleagues reported that psilocybin can evoke mystical-type experiences that impart personal meaning and spiritual significance[149]. The peak intensity of such an experience is associated with a level of 10–20 μg l^{-1} psilocin in plasma, which corresponds to ~60% occupancy of serotonin 2A (5-HT_{2A}) receptors in the neocortex of humans[32]. There are noted variations in how individuals respond to the same dose of a psychedelic. Set and setting, which refers to a person's internal state and external environment, may influence the psychedelic-induced subjective experience. Intriguingly, the intensity of mystical-type experience has been reported to correlate with therapeutic efficacy[150].

It was recognized early that psychedelics may have therapeutic potential for treating mental illnesses. There is a rich history of experimentation with compounds such as LSD for alcoholism and psychiatric distress[151], although these early studies lacked the rigor of current clinical trial designs. Recent trials have focused on psilocybin-assisted psychotherapy, starting with a few pilot studies demonstrating improvements in depression and anxiety in individuals with terminal cancer[150,152,153]. Subsequently, randomized phase II trials demonstrated a reduction of symptoms following psilocybin-assisted psychotherapy for major depressive disorder and treatment-resistant depression[2,3]. The results of these trials are notable for their relatively large effect sizes and enduring benefits lasting up to several weeks or months, although these remain to be confirmed in multisite, large-scale clinical trials. Psilocybin and other psychedelics have also shown value for overcoming substance-use disorders[4]. In parallel, although ketamine and MDMA are not considered to be psychedelic, their progressions through clinical trials (ketamine for depression[154] and MDMA for post-traumatic stress disorder[155]) are part of a paradigm shift in psychiatry to leverage substances with acute psychoactive effects to induce long-term benefits for individuals with psychiatric disorders.

mechanisms can lead to unified theories explaining psychedelic action. We will complement discussion of recent results with historical findings that are often ignored in the current explosion of research activity. The goal of this review is to synthesize the field's current knowledge and to highlight open questions that could spark further investigations into the neural basis of psychedelic action.

Chemistry of psychedelics

All classical psychedelics are derived from a primary pharmacophore consisting of an aromatic group separated from a basic amine by a two-carbon linker (Fig. 1a). When protonated, the basic nitrogen engages a key aspartate residue ($D155^{3.32}$) in the binding pocket of the 5-HT_{2A} receptor, while the aromatic group makes important hydrophobic contacts with other residues in the protein[9,10]. A two-carbon linker length appears to provide optimal spacing between these functional groups for activation of 5-HT_{2A} receptors. Shortening the linker length by one carbon converts the 5-HT_{2A} receptor agonist *N*,*N*-dimethyltryptamine (DMT) into the 5-HT_{2A} receptor antagonist gramine[11,12], while increasing the distance between the aromatic group and basic amine can reduce affinity[13]. The specific identity of the aromatic group in the primary pharmacophore divides psychedelics into two broad structural families. Tryptamines possess a C3-substituted indole, while phenethylamines are characterized by a phenyl group. Ergolines, often considered as a distinct group, can be viewed chemically as a specialized case of tryptamines because the DMT pharmacophore is embedded within the ergoline framework.

Comparing the conformationally flexible substituted tryptamines, such as psilocin and bufotenin, and rigidified ergolines, such as LSD, shows that rigidification of a primary pharmacophore can often increase affinity or potency (that is, the amount of drug necessary to bind to or activate a receptor) by easing entropic penalties to binding, and this may be one of the reasons that LSD is a particularly potent psychedelic with respect to its ability to activate the 5-HT_{2A} receptor and elicit associated behavioral responses. Potencies of the more flexible tryptamines are highly dependent on secondary contacts in the binding pocket, and, thus, tryptamine substitution can have a dramatic impact on potency. Typically, 4- and 5-substituted tryptamines are more potent than their 6- and 7-substituted congeners[14]. Like tryptamines, the potencies of phenethylamines can be modulated by both substitution and scaffold rigidification. The 2,4,5-trisubstitution pattern appears to be more favorable than the 3,4,5-trisubstitution pattern, as compounds such as 2C-I and 2C-B are much more potent than mescaline[13]. Potency can be further improved by conformationally restricting the ethylamine group or the methoxy substituents as in the cases of (*R*)-TCB-2 (ref. [15]) and 2C-B-dragonFLY[16], respectively. In addition to rigidification strategies involving the aromatic ring, the potency of phenethylamines can be improved by structural modifications that promote additional secondary interactions with the 5-HT_{2A} receptor or prevent metabolism. In the case of *N*-benzylated compounds, such as 25I-NBOMe, potency is likely to be enhanced because the benzyl group appended to the basic nitrogen can engage a deep secondary binding pocket in the 5-HT_{2A} receptor[9]. In the case of (*R*)-2,5-dimethoxy-4-iodoamphetamine ((*R*)-DOI), simple addition of a methyl group α to the basic amine yields amphetamine-like structures that are more resistant to oxidative deamination by monoamine oxidase[17]. Similar effects have been observed for α-methyltryptamines[18]. The stereochemistry of the α-methyl group is important, with the *R* and *S* enantiomers of α-methylphenethylamines (that is, amphetamines) and α-methyltryptamines being the more potent optical isomers, respectively[18,19]. While LSD is classified here chemically as a tryptamine derivative, it is interesting to note that the (*R*)-amphetamine substructure is embedded within the ergoline scaffold, making LSD a hybrid structure that contains the key elements of both psychedelic structural families (Fig. 1b).

A hallmark of psychedelics is their pharmacokinetic properties and high brain penetrance. Many psychedelics adhere to the 'rule of three' (that is, the molecular weight is <300 Da, calculated logarithm of the partition coefficient (ClogP) is ≤3, the number of hydrogen-bond acceptors is ≤3 and the number of hydrogen-bond donors is ≤3)[20] and exhibit excellent CNS multiparameter optimization scores[21], as they are small, relatively hydrophobic and possess few hydrogen-bond donors and acceptors. These physical properties enable psychedelics to cross the blood–brain barrier easily and rapidly, leading to high brain-to-plasma ratios[22]. Although tryptamine psychedelics bear substantial structural similarities to serotonin and have high affinity for many of the same receptors, the pharmacological properties of

https://doi.org/10.1038/s41593-022-01177-4

BOX 2

Behavioral assays for evaluating psychedelics in animal models

Subjective experience in humans is assessed through self-reports and questionnaires, which cannot be applied to animals. In preclinical research, the main assays for evaluating psychedelics are drug discrimination and head-twitch response[5,8]. For drug discrimination, animals are trained for many weeks to distinguish between a psychoactive substance (for example, LSD) and vehicle by indicating their response via lever presses. On test day, the experimenter can determine the extent to which a test drug can substitute for the reference psychedelic. For head-twitch response, several species, including mice, rats and rabbits, exhibit high-frequency side-to-side head movements following the administration of a psychedelic drug. These assays have predictive validity because potencies in drug discrimination in rats[33] and head-twitch response in mice[34] correlate exceptionally well with hallucinogenic potencies in humans across a panel of several dozen distinct molecules. A difference between the assays is that the head-twitch response is an innate behavior, whereas drug discrimination is learned and requires animal training. Moreover, drug discrimination allows finer classification of molecules because a drug may act on multiple receptors that collectively contribute to the interoceptive stimulus. A partial substitution in drug discrimination is possible and would indicate that the test and reference compounds share some but not all features. However, it has been noted that these assays have certain pitfalls[156,157], and ultimately it is important to recognize that these behavioral readouts in animal models are surrogate measures that cannot capture the full spectrum and nuances of the human experience.

serotonin differ substantially from those of psychedelics. While some of these differences can be attributed to how serotonin engages various residues in the binding pocket of the 5-HT_{2A} receptor[23], another major factor is pharmacokinetics. Serotonin is a very polar molecule that cannot easily cross non-polar membranes. In fact, the majority of serotonin in the body is produced in the gut, and its high polarity ensures that peripherally produced serotonin cannot readily access the brain[24]. By contrast, methylation of serotonin produces bufotenin and 5-methoxy-DMT (compounds that are substantially more hydrophobic and thus capable of crossing the blood–brain barrier[22]). It is interesting to note that psychedelics with greater lipophilicity and/or pK_a values closer to physiological pH tend to be more potent[25]. The pK_a of mescaline is 9.56, while the pK_a of LSD is 7.8 (ref. [26]). Thus, compared to LSD, a substantially lower proportion of mescaline molecules exists in the deprotonated state that is capable of passively diffusing across the non-polar blood–brain barrier. This property, in addition to mescaline's very weak partial agonism of 5-HT_{2A} receptors, contribute to its low potency in vivo. The importance of pharmacokinetics in the actions of psychedelics is perhaps best illustrated by comparing psilocin and bufotenin. These compounds are constitutional isomers and differ only in the position of their phenolic hydroxyl groups (4- and 5-positions for psilocin and bufotenin, respectively). While these compounds exhibit comparable 5-HT_{2A} receptor potencies and efficacies in vitro[23], their in vivo effects are drastically different. In contrast to bufotenin, psilocin is orally bioavailable and readily crosses the blood–brain barrier because it can form an intramolecular hydrogen bond that improves lipophilicity by lowering the pK_a of its amino group[27].

Several psychedelics are natural products produced by plants and fungi, but others are non-natural structures conceived by humans (Fig. 1a). While some psychedelics can be obtained directly from natural sources, most are produced via de novo chemical synthesis from simple starting materials. Although LSD is a non-natural compound, it is derived from the natural product lysergic acid through semisynthesis. Recent advances in synthetic biology have enabled the reconstitution of biosynthetic pathways in organisms such as yeast and *Escherichia coli*, and these techniques have the potential to enable large-scale production of several psychedelics and psychedelic precursors, such as psilocybin and lysergic acid[28,29].

Receptors and molecular signaling

In humans, pretreatment with the 5-HT_2 receptor antagonist ketanserin diminishes, in a dose-dependent manner, the ability of psilocybin[30] and LSD[31] to alter subjective experience. The occupancy of 5-HT_{2A} receptors in the brain relates closely to the intensity of the psychedelic effect[32]. These human data are corroborated by animal studies, which showed that human hallucinogenic potencies and potencies in rodent drug discrimination assays scale with 5-HT_{2A} binding affinity[33]. Moreover, a strong correlation has been observed between human hallucinogenic potencies and potencies in the mouse head-twitch response[34], which is abolished in 5-HT_{2A} receptor-knockout mice[35,36]. Together, the evidence is overwhelming that the 5-HT_{2A} receptor is crucial for the psychedelic effect. However, there are species differences that can affect the properties of 5-HT_{2A} receptors. For example, primate and pig 5-HT_{2A} receptors possess a serine at residue 242 in the binding pocket, whereas the rat and mouse receptors have an alanine at this position. Mutagenesis studies have demonstrated that an S242A mutation can drastically increase the dissociation rate of LSD[9].

Notwithstanding the importance of 5-HT_{2A} receptors, psychedelics have a complex pharmacology with actions on many other biogenic amine G-protein-coupled receptors[8,37]. LSD, for instance, is a high-affinity agonist for most of the 14 distinct human 5-HT receptors and has potent agonist activity at D1, D2, D3 and D4 dopamine and α1- and α2-adrenergic receptors[37]. In rodents, the actions of LSD at D2 receptors have been postulated to mediate the relatively prolonged drug effects[38], while its actions at D4 and 5-HT_{5A} receptors may underlie select behavioral actions[39,40]. Likewise, psilocin is a potent agonist at many serotonin receptors[41], and actions at the 5-HT_{1A} receptor have been observed in humans[42]. It is currently unknown which of these receptors mediate the potential therapeutic actions of psychedelics, although recent studies in rodents and humans suggest that 5-HT_{2A} receptors may not be the sole determinants[42–44]. Many psychedelic drugs (including LSD and psilocin) also have high affinities for 5-HT_{2B} and 5-HT_{2C} receptors[9,45–47]. The actions at 5-HT_{2B} receptors are especially problematic as it is now well established that 5-HT_{2B} agonists, when chronically administered, cause potentially life-threatening cardiac valvulopathy[8,48]. Although valvulopathy has not yet been sufficiently evaluated, there have been reports among individuals who have used 3,4-methyl enedioxy methamphetamine (MDMA) chronically[49] due to 5-HT_{2B} receptor activation[50].

Downstream of 5-HT_{2A} receptors, 5-HT_{2A} agonists in general[51,52] and psychedelics[53,54] in particular activate G_q-like G proteins to enhance the hydrolysis of phosphatidylinositol-4,5-bisphosphate (Fig. 2a). This leads to the mobilization of intracellular Ca^{2+} by released inositol trisphosphate and the activation of protein kinase C via diacylglycerol[51,52]. Other signaling pathways at 5-HT_{2A} receptors include activation of arrestin translocation[9,46,47,55] and arachidonic acid release[56]. Actions at both G_q- and arrestin-signaling pathways have been implicated in the behavioral effects of various psychedelics, although in vivo evidence is sparse[57–59]. Some investigators have noted activity of mouse 5-HT_{2A} receptors at an apparent G_i-mediated response for regulating arachidonic acid release[60].

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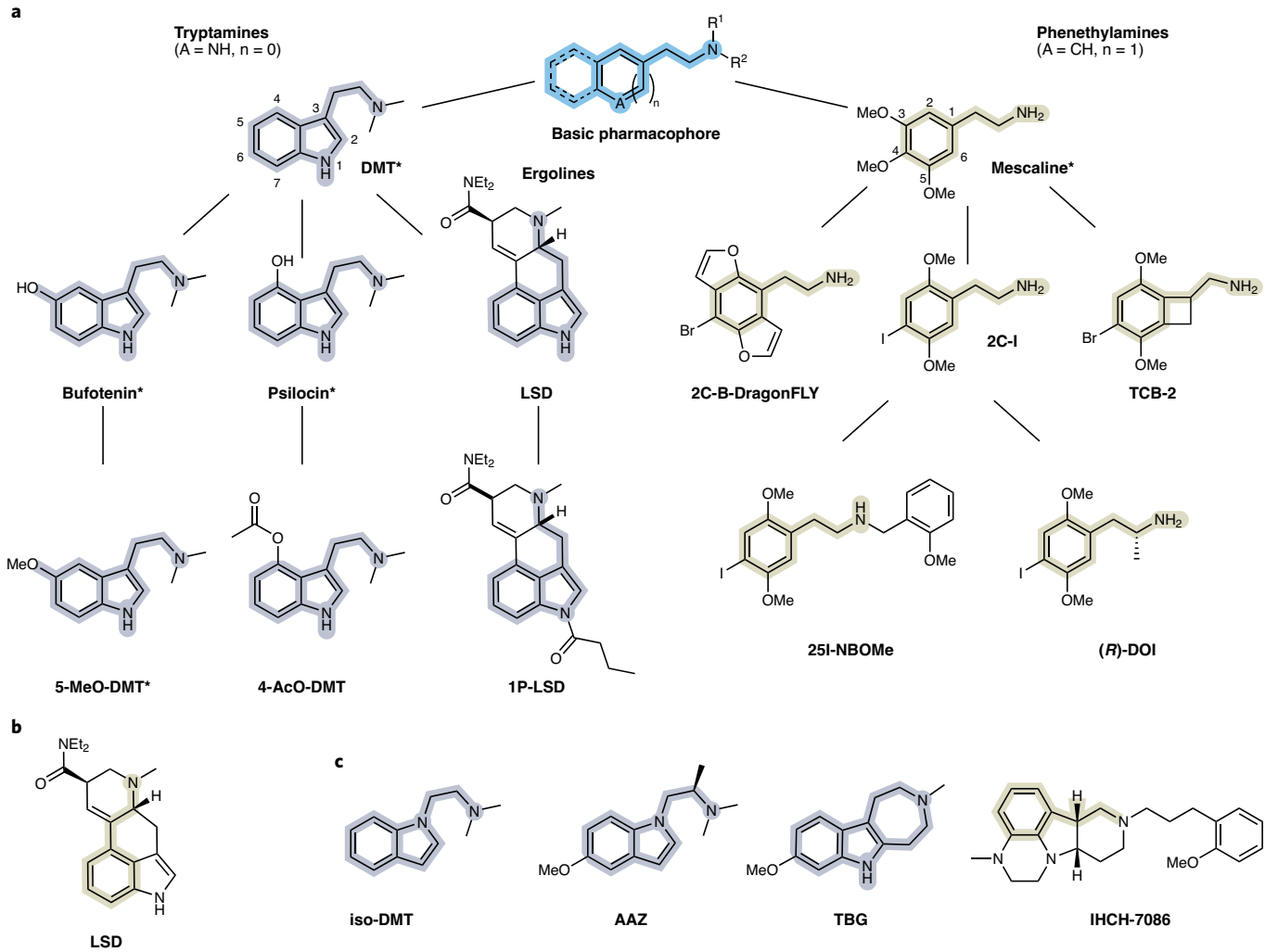

Fig. 1 | Chemical phylogeny of psychedelics. a, The basic psychedelic pharmacophore is highlighted in blue. Tryptamine and phenethylamine pharmacophores are highlighted in gray and yellow, respectively. Ergolines (LSD and 1-propionyl-D-LSD (1P-LSD)) can be viewed chemically as a specialized case of tryptamines. Branches indicate structurally related compounds. Natural products are indicated with asterisks. 5-MeO-DMT, 5-methoxy-DMT; 4-AcO-DMT, 4-acetoxy-DMT. **b**, LSD has the phenethylamine substructure (yellow) embedded and thus contains the key elements of both psychedelic structural families. **c**, Structures of non-hallucinogenic psychedelic analogs with therapeutic potential, which may contain the tryptamine-like (gray) or phenethylamine-like (yellow) pharmacophore. TBG, tabernanthalog.

Although the molecular details responsible for psychedelic drug actions at 5-HT_{2A} receptors have been elusive for many decades, recent breakthrough studies via X-ray diffraction and cryoelectron microscopy have provided crystal structures of psychedelic-bound serotonin receptors (Fig. 2b). The first study by Wacker and colleagues[47] of LSD complexed with the 5-HT_{2B} receptor was largely validated by a second report[9] demonstrating that LSD interacts with 5-HT_{2A} receptors via a variety of hydrophobic, ionic and other factors[9]. The results were further supported by additional structural biology results, including an inverse agonist-stabilized crystal structure of a complex of 5-HT_{2A} receptors with the psychedelic drug 25-CN-NBOH along with the active nucleotide-free G_q hetereotrimer[9]. The availability of these relatively high-resolution structures of 5-HT_{2A} and other relevant receptors[61] promises to produce novel insights into the molecular details of psychedelic drug action.

Integrating chemical and molecular mechanisms to discover new compounds

Molecular advances have led to a surge of medicinal chemistry efforts, which seek to use computational modeling and structure–activity relationships to engineer psychedelic-based therapeutics.

The structure of psilocybin often serves as a starting point for these efforts, and although psilocybin is one of the most commonly studied psychedelics in clinical trials, it is not responsible for producing hallucinogenic effects. In fact, psilocybin is rapidly dephosphorylated in vivo and serves as a prodrug for psilocin[62]. Compared to psilocin, psilocybin exhibits higher chemical stability in the solid state and has a longer shelf life; although not published, this fact is well known among researchers in the field. Whereas clandestine labs have attempted to use prodrugs of psychedelics, such as 4-acetoxy-DMT and 1-propionyl-D-LSD[41,63] (Fig. 1a), to circumvent controlled substance laws, pharmaceutical companies have become interested in psychedelic prodrugs as a means to improve oral bioavailability or modify pharmacokinetic properties. The duration of a psychedelic-induced subjective experience could be a key parameter in the optimization of psychedelic-assisted psychotherapy. Psychedelics that produce hallucinogenic effects of shorter durations are likely to be more cost-effective and more scalable to implement at a clinic, given that contact time with medical professionals can be minimized[64]. However, this idea depends crucially on the assumption that the duration of the acute psychedelic effect can be manipulated without affecting efficacy, which has not yet been convincingly demonstrated in humans.

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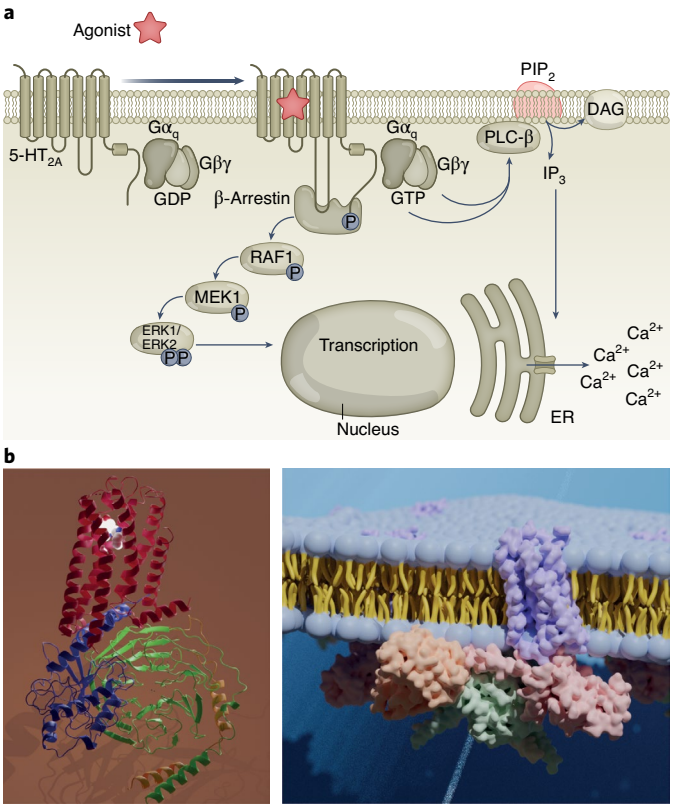

Fig. 2 | The 5-HT$_{2A}$ receptors and molecular signaling pathways. a, Intracellular signal transduction pathways. Downstream of the 5-HT$_{2A}$ receptor, activation of heterotrimeric G proteins and subsequent intracellular signaling (Ca^{2+} release and diacylglycerol (DAG) production) synergistically activate additional downstream effects, which ultimately lead to altered neuronal firing; PIP_2, phosphatidylinositol-4,5-bisphosphate; PLC-β, phospholipase C-β; ER, endoplasmic reticulum; IP_3, inositol trisphosphate. **b**, Left, structure of the 5-HT$_{2A}$ receptor; right, model of the 5-HT$_{2A}$ receptor signaling complex in the membrane.

Parallel efforts to improve the scalability of psychedelic-like therapeutics have focused on engineering compounds that lack hallucinogenic or perceptual effects but maintain sustained therapeutic efficacy after a single dose[64]. Presumably, these compounds could be administered at home, obviating the need for costly in-clinic supervision, as is currently required for psychedelics and other intoxicating compounds, such as ketamine. Initial work in this area has focused on developing non-hallucinogenic entities (also referred to as non-hallucinogenic psychoplastogens[65]), such as isoDMT[66], tabernanthalog[67] and AAZ-A-154 (ref.[12]), by slightly modifying the structures of known hallucinogenic compounds (Fig. 1c). On this front, the availability of high-resolution structures of 5-HT$_{2A}$ receptors in complex with psychedelics promises to accelerate the search for novel psychedelic and non-hallucinogenic 5-HT$_{2A}$ agonists. For example, in silico design is beginning to yield potentially non-hallucinogenic 5-HT$_{2A}$ receptor ligands, such as IHCH-7086 (ref. [10]; Fig. 1c). The search has been boosted by recent ultra-large-scale computational studies of hundreds of millions[68] to billions[69] of compounds, which have demonstrated the relative ease of discovering new chemotypes for many G-protein-coupled receptors.

What properties are desirable for novel psychedelic-based compounds? Such novel chemical matter may have enhanced selectivity toward 5-HT$_{2A}$ receptors and therefore fewer off-target actions. Selective agonists would also represent useful tools for clarifying the role of 5-HT$_{2A}$ and other receptors in the hallucinatory and therapeutic actions of psychedelics. It should be possible to identify and optimize chemotypes with biased signaling profiles preferring G_q versus arrestin versus other potential signaling pathways to determine which of these pathways are physiologically and therapeutically relevant. Finally, developing psychedelic-like drugs devoid of 5-HT$_{2B}$ agonism is essential for therapeutic interventions that envision chronic dosing. Overall, efforts are aimed at leveraging functional selectivity to maximize efficacy, safety and tolerability.

Neurons and circuits modulated by psychedelics

Psychedelics modify neural activity dynamics by activating various receptors. Specifically, 5-HT$_{2A}$ receptor agonism increases neuronal excitability through multiple mechanisms, including membrane depolarization, diminished afterhyperpolarization and reduced spike frequency adaptation[70]. However, some psychedelics also bind to other receptors with opposing functional consequences; for example, tryptamines, such as psilocin and 5-methoxy-DMT, have affinities for 5-HT$_{1A}$ receptors, which act to decrease neuronal excitability[70,71]. The relative abundance and subcellular distribution of the receptor subtypes will therefore dictate the overall effects of psychedelics on the electrical activities of a neuron[72].

Acute effects

The effects of psychedelics on neurophysiology have been well studied in a few brain regions. In the prefrontal cortex, 5-HT$_{2A}$ receptors are primarily postsynaptic[73] and highly enriched in the apical dendrites of deep-layer pyramidal neurons[74,75] (Fig. 3a). The localization pattern suggests that psychedelics should increase dendritic excitability and induce excitatory postsynaptic potentials, as has been shown for serotonin[76]. However, the impact of psychedelics in vivo is likely to be more complex because cortical microcircuits contain multiple subpopulations of pyramidal neurons and subtypes of GABAergic neurons. These cell types express different amounts of 5-HT$_{2A}$ and other serotonin receptors[72,77,78], which are reflected in their heterogeneous responses to serotonin neuromodulation[79]. In agreement with this, following systemic administration of DOI, frontal cortical neurons in vivo showed varied changes in firing rates across the neuronal population in the rat medial frontal cortex[80].

The visual pathway has been a focus of neurophysiologists who are motivated by the hallucinogenic property of psychedelics. In one of the earliest studies, single-unit activities were recorded from the optic tract, lateral geniculate nucleus and visual cortex of anesthetized cats[81]. LSD was found to decrease neuronal firing in the lateral geniculate nucleus in response to optic tract stimulation. In the visual cortex, although the overall effect is also suppressive, individual neurons' responses to psychedelics are heterogeneous; some cells increase spiking, whereas others decrease or exhibit no change[82]. A more recent, systematic investigation corroborated these spiking activity differences and further indicated that feature tuning is intact, but surround suppression is reduced, in mice after the administration of DOI[83] (Fig. 3b), hinting at erroneous processing of contextual information. These results suggest that psychedelics suppress sensory inputs at multiple points along the central visual pathway.

Psychedelics also exert pronounced effects of firing activity in select subcortical nuclei, with the dorsal raphe as a prime example. The dorsal raphe is the largest serotonergic nucleus in the brain. In a series of elegant studies spanning more than 20 years, Aghajanian and colleagues found that intravenous administration of LSD can lead to a near-complete cessation of firing in the dorsal raphe within 1–2 min, and that firing returns to baseline after 20–30 min in anesthetized rats[84] (Fig. 3c). This effect is specific for psychedelics, with comparable effects being evoked by psilocin, DMT, mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM)[85]. By contrast, compounds such as atropine, scopolamine and phencyclidine do not have appreciable effects on raphe unit firing[85]. Psychedelic-induced cessation of spiking activity arises from local mechanisms within the dorsal raphe, probably through somatodendritic 5-HT$_{1A}$ receptors[86]. Initially, it was thought that the strong effects on raphe activity may be

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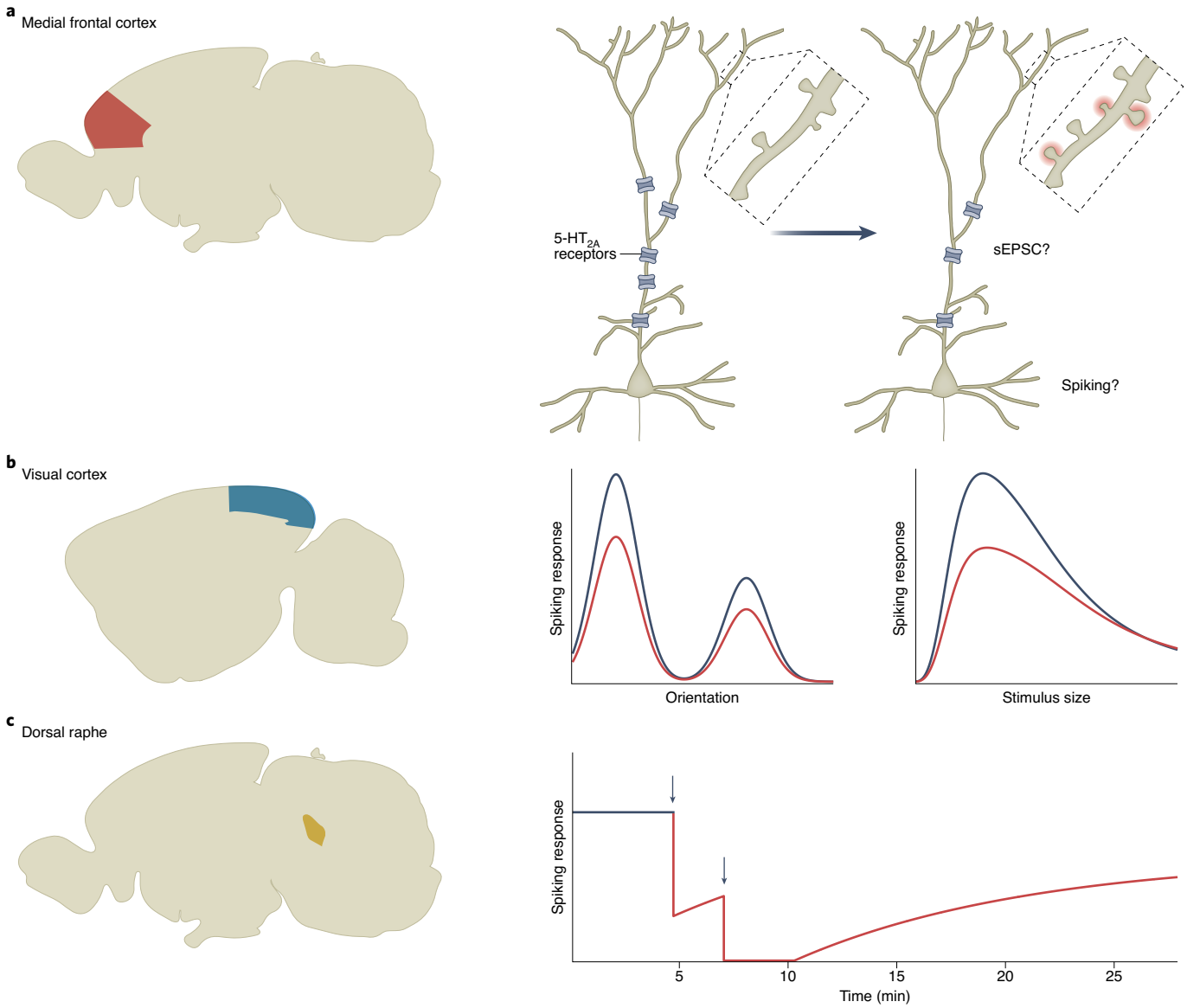

Fig. 3 | Regional differences in psychedelic action on neurophysiology. a, In the medial frontal cortex (red), psychedelics are thought to acutely increase dendritic excitability owing to the dendritic localization of 5-HT_{2A} receptors, but the overall effect on postsynaptic currents and spiking activity in vivo remains unclear. On the days following administration, psychedelics cause receptor internalization (resulting in fewer receptors being expressed) and promote the formation of new dendritic spines. sEPSC, spontaneous excitatory postsynaptic current. **b**, In the primary visual cortex (blue), psychedelics reduce visually evoked spiking activity (right). Orientation tuning remains intact, but surround suppression is reduced (middle); black, baseline; red, after drug administration. **c**, In the dorsal raphe (yellow), systemic or local administration of psychedelics causes a cessation of spiking activity; black, baseline; red, after drug administration; black arrows, times of drug infusion. The schematics are based on data from Shao et al.[44] for **a**, Michaiel et al.[83] for **b** and Aghajanian et al.[85] for **c**.

responsible for the acute behavioral effects of psychedelics. However, subsequent studies in freely moving animals argued against this possibility, because LSD's effects on raphe firing do not display tolerance[87] and are not aligned with behavioral changes[88]. It remains unclear which brain regions are responsible for the acute subjective effects in humans and which specific neural circuits mediate the head-twitch response in mice. In addition to the prefrontal cortex, visual cortex and dorsal raphe, psychedelics have been reported to alter synaptic neurotransmission and spiking activities in the hippocampus[43,89], locus coeruleus[90] and numerous other cortical and subcortical locations[91].

Longer-term effects

The acute effects of psychedelics on molecular signaling and neuronal firing are precursors to long-term modifications in the brain. Indeed, analysis of mRNA transcripts shows that 90 min after a single dose of LSD in rodents, there are several-fold increases in the expression of immediate early genes associated with plasticity, such as *Fos*, *Arc* and *Egr2* in the neocortex[36,92]. Further neural adaptation may rely on the upregulation of neurotrophic factors, such as brain-derived neurotrophic factor, which has been reported in some brain regions following the administration of psychedelics[93]. More comprehensive profiling of the transcriptional impact of psychedelics is underway, adding cell-type and epigenetic information[78,94].

One enduring consequence of psychedelic administration is structural neural plasticity. In primary neuronal cultures, bath application of psychedelics can alter spine size[95], increase spine density[96] and promote the proliferation of dendrites[97]. Structural remodeling has likewise been observed in tissues ex vivo[94,97] and in the intact brain in vivo for psilocybin and other psychedelic analogs[44,67,98]. In one recent study, longitudinal two-photon microscopy was used to track dendritic

spines in the mouse medial frontal cortex[44]. The results showed that a single dose of psilocybin led to a rapid increase in spine density and size within 24 h (Fig. 3a). Strikingly, spine density remained elevated for up to 1 month after the initial administration, which could potentially underlie the long-lasting beneficial effects that follow psilocybin administration. It is worth noting that structural remodeling has also been observed in primary culture[99] and in the medial frontal cortex after a single dose of the fast-acting antidepressant ketamine[100], potentially via acute actions on dendritic excitability[101]. However, ketamine is primarily an NMDA receptor antagonist. It is still unknown how ketamine and psychedelics, which engage distinct receptors, converge onto seemingly related structural plasticity processes at the neuronal level[72,102]. Studies with direct comparisons of multiple compounds[99,103] will be helpful to address this important question.

Networks involved in psychedelic actions

Psychedelic-induced changes in neuronal activity manifest in spontaneous and task-evoked activations of brain regions at the network level. The impact of psychedelics can be observed in the living human brain by using neuroimaging methods, such as positron emission tomography, single-photon emission computed tomography, functional magnetic resonance imaging, electroencephalography (EEG) and magnetoencephalography. In the first neuroimaging studies of psychedelics, effects of mescaline and psilocybin were assessed using ^{18}F-fluorodeoxyglucose positron emission tomography to measure glucose metabolism and single-photon emission computed tomography to assess cerebral blood flow[104,105]. Across the entire neocortex, psilocybin administration is associated with increased metabolism[105] but reduced blood flow[106]. However, after adjusting for global changes, there is relative hypermetabolism in prefrontal cortical areas and hypometabolism in subcortical and occipital brain regions[105]. Similar regional differences in cerebral blood flow were confirmed by a subsequent arterial spin labeling study[107]. Collectively, these results demonstrate differential responses in associative and sensory cortical regions under the influence of psychedelics.

Another approach to assess the effects of psychedelics on neural architecture is to investigate the functional connectivity between or within brain networks, which refers to covarying activities across regions. Unfortunately, it has been challenging to compare results across studies because there are various measures of functional connectivity, with some of them sensitive to preprocessing methods. Nevertheless, there are a couple of consistent findings. First, psilocybin acutely reduces the activity and functional connectivity within association networks, including the default-mode network[106,108–110], which consists of medial prefrontal cortex, posterior cingulate cortex and parietal regions and is thought to be activated when people are at rest and focused on internal mental processes. Further analyses using data-driven approaches, such as global brain connectivity, reveal that, while disintegrating the connectivity in associative brain regions, psilocybin and LSD concurrently induce hyperconnectivity between sensory brain regions[108,111]. Second, it has repeatedly been shown that LSD increases thalamocortical functional connectivity, in particular between the thalamus and sensory regions as part of the somatomotor network[108,112]. These changes are corroborated by effective connectivity, deduced from dynamic causal modeling, which highlights increases in thalamic connectivity to the posterior cingulate cortex and decreases to the temporal cortex[113]. Concurrent neuroimaging and pharmacological blockade confirm that the LSD-induced changes in functional network configuration rely on binding to 5-HT$_2$ receptors[108].

An exciting development in neuroscience is the availability of high-resolution atlases of gene expression and receptor binding across the entire brain. For instance, the Allen Institute for Brain Science applied in situ hybridization and single-cell sequencing approaches to map transcript levels of all genes in the brain[114]. These data have enabled exploratory analyses to correlate gene expression with drug-evoked functional magnetic resonance imaging signals in humans[108,111], which highlight the importance of 5-HT$_{2A}$ receptors and potentially dopamine and glutamate receptors in shaping region-specific responses to LSD and psilocybin. Another notable advance is a protein density map of serotonin receptors and the serotonin transporter in humans[115]. These large-scale genomic and proteomic datasets open avenues for incorporating molecular and receptor information into biophysically based computational models[116–118], with the aims of capturing and predicting how psychedelics interact within the constraints of the neural architecture to modulate activity dynamics.

While detailed network-level measurements of acute psychedelic effects are starting to emerge, longitudinal studies that can relate to enduring behavioral changes remain scarce. Comparisons of before versus after psilocybin administration revealed changes in resting-state network configurations that are detectable for at least 1 week after a single dose exposure[119–122]. Therefore, there are hints of enduring changes in brain networks, but the prolonged effects and their clinical relevance remain understudied. Part of the challenge is the need to address inter- and intraindividual variations in psychedelic action. So far, it has been shown that an individual's baseline functional connectivity influences the magnitude of psilocybin-induced changes on network activation[111]. Additionally, baseline availability of 5-HT$_{2A}$ receptors predicts the intensity and duration of the acute subjective experience[123]. A better understanding of the time course and heterogeneity of network-level effects will facilitate precision medicine approaches for psychedelic-assisted psychotherapy.

Integrating neuronal and network mechanisms to inform theories of psychedelic action

Building on current knowledge of the neuronal and network mechanisms, different theories have been proposed to explain psychedelic action in the brain. We will highlight the cortico–striato–thalamocortical (CSTC) model[124], the relaxed beliefs under psychedelics and the anarchic brain (REBUS) model[125], the strong prior (SP) model[126] and the cortico–claustro–cortical (CCC) model[127].

The CSTC model suggests that psychedelics alter information processing in the brain by stimulating 5-HT$_{2A}$ receptors located within cortico–striato–thalamic loops, resulting in a disruption of thalamic gating[124]. Consequently, an increase in feedforward information may underlie the acute subjective effects experienced under the influence of psychedelics (Fig. 4a). This model is supported by behavioral measures of impaired sensorimotor gating in humans after administration of psilocybin and LSD[128,129]. Additionally, the model agrees with neuroimaging measures of increased thalamocortical functional connectivity[108,112] and synchronization of cortical sensory regions[108,111,130].

The REBUS model postulates that psychedelics enhance bottom–up flow of sensory inputs, while reducing the precision of prior beliefs, expectations and past experiences that normally constrain neural processing[125] (Fig. 4b). The collective effect is predicted to increase entropy in neural dynamics[125]. Empirical evidence for this model hinges on the findings from neuroimaging of a disintegration of association networks, including the default-mode network[106,109]. More complex neural signals can be observed with magnetoencephalography and EEG after the administration of LSD, psilocybin and DMT[131,132]. Furthermore, frequency domain analyses can be used to estimate the directionality of signal propagation from multielectrode EEG recordings, which suggest that DMT weakens α-band oscillatory neural signals flowing in the top–down direction while potentiating the bottom–up signals[133].

However, the REBUS model is at odds with various neurophysiological and behavioral results, which instead favor the SP model. Specifically, recordings in animals showed mostly reduced stimulus-evoked spiking activity in the visual cortex[81,83]. Moreover, it is well known that perceptions are often not altered by vivid stimuli, but rather hallucinations can occur for healthy humans under sensory deprivation in complete darkness[134]. These results suggest that the psychedelic

https://doi.org/10.1038/s41593-022-01177-4

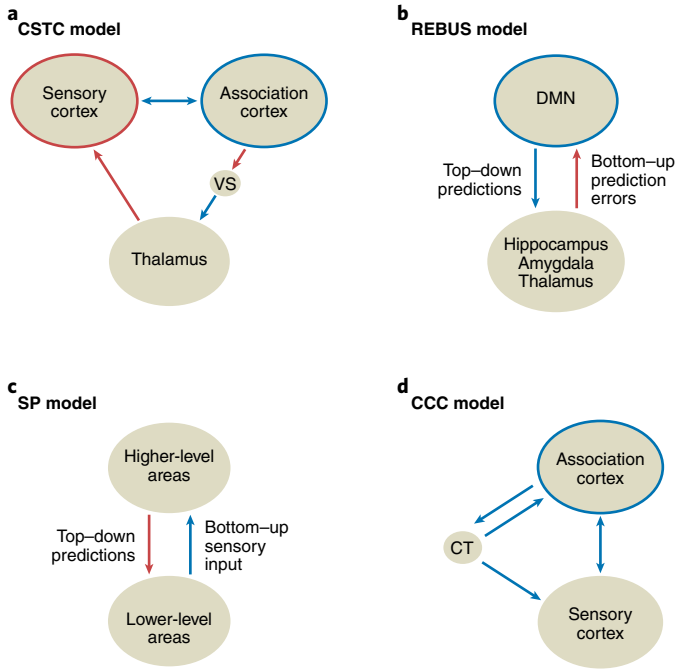

Fig. 4 | Network-level models of psychedelic action. a, The CSTC model focuses on altered thalamic gating and subsequent changes in sensory versus association processing induced by psychedelics[108,124]. **b**, The REBUS model posits increased bottom–up signaling, concurrent with a disintegration of association cortices and reduced top–down predictions, which are postulated to underlie psychedelic-induced effects[125]. **c**, The SP model suggests that psychedelic experiences arise from a reduction of bottom–up sensory inputs and an aberrant reliance on top–down expectations. This model does not make predictions about specific anatomical substrates[126]. **d**, The CCC model centers on disrupted claustrum activity and functional connectivity, leading to a desynchronization of cortical networks[127]. Red arrows indicate increased functional connectivity/control, blue arrows indicate decreased functional connectivity/control, red circles indicate increased integration and blue circles indicate decreased integration. VS, ventral striatum; CT, claustrum.

experience may arise from reduced bottom–up sensory inputs coupled with aberrant reliance on top–down expectations, which constitute key features of the SP model[126] (Fig. 4c). Indeed, recent studies of conditioning-induced hallucinations data have provided evidence for such heightened dependence on inappropriate beliefs[135].

Beyond the cortico–striato–thalamic loops, other recurrent networks in the brain may be involved, such as the CCC pathway. In one model[127], psychedelics were suggested to disrupt communication between the prefrontal cortex and claustrum by aberrantly driving prefrontal inputs and/or activating the claustrum (Fig. 4d), which impairs the coordinated responses of association networks to changing task demands. The involvement of the claustrum has been suggested on the basis of the high density of 5-HT_{2A} receptors[5] and is supported by a recent study showing reduced functional connectivity between the claustrum and cortical networks after a low dose of psilocybin[136].

It should be appreciated that the various models arise from different explanatory focuses. The CSTC and CCC models emphasize implementation, highlighting altered circuits without relying heavily on psychological implications. By contrast, SP is a theory of perceptual and cognitive processes that give rise to hallucinations, which is computational in nature and agnostic to implementation in the brain. SP may be reconciled with REBUS if the hypothesized weakened low-level beliefs eventually culminate in stronger extraperceptual beliefs, although more precise definitions of priors and beliefs will be helpful for comparing and testing these models. Ultimately, a unified model of psychedelic action should build on the growing body of knowledge at the neuronal and network levels and be tethered firmly to both implementation- and computation-based explanations.

Open questions

Accumulating evidence in humans and rodents strongly suggests that activation of the 5-HT_{2A} receptor is primarily responsible for the hallucinogenic effects of psychedelics. These receptors and their downstream signaling pathways may also mediate some of the therapeutic effects observed following psychedelic administration, considering that the 5-HT_{2A} receptor is a common target shared by all psychedelic compounds. However, no clinical study to date has explicitly tested the molecular basis of the potential therapeutic effects of psychedelics in humans, whether through antagonist pretreatment or comparison with a non-hallucinogenic 5-HT_{2A} agonist. In rodents, it remains debatable whether psychedelic-evoked neural plasticity requires functional 5-HT_{2A} receptors. On the one hand, pretreatment with ketanserin did not affect psilocybin-evoked structural remodeling[43,44], although this manipulation does not block all 5-HT_{2A} receptors in the rodent brain[137]. On the other hand, other data indicate that the 5-HT_{2A} receptor is essential for structural plasticity[94,97], but these studies relied on in vitro preparations or constitutive knockout mice in which neurodevelopment could be affected.

Another important caveat to consider is that many, if not all, psychedelics also potently activate the closely related 5-HT_{2C} receptor. This receptor is highly expressed in the brain and is known to regulate the function of mesolimbic dopaminergic neurons, making it an ideal therapeutic target for several neuropsychiatric disorders[138]. Complicating matters further, multiple isoforms of the 5-HT_{2C} receptor exist due to post-transcriptional RNA editing[139]. Unfortunately, we currently lack pharmacological tools that can adequately differentiate between 5-HT_{2A} and 5-HT_{2C} receptors. To the best of our knowledge, there are no potent 5-HT_{2A} receptor agonists that either lack affinity for 5-HT_{2C} receptors or exhibit 5-HT_{2C} receptor antagonism. Moreover, a truly selective 5-HT_{2A} receptor antagonist has not yet been identified[140]. This dearth of selective pharmacological tools impedes our ability to achieve a full mechanistic understanding of psychedelic drug action.

In addition to psychedelics, other drugs, such as psychostimulants (including amphetamine and cocaine), can induce changes in dendritic architecture. A key difference is that psychostimulant-induced alterations occur after repeated exposure over several weeks[141]. Another difference is that increases in spine density and dendritic branching after psychostimulant administration are more pronounced in striatal regions, such as the nucleus accumbens, although they can also be detected in the medial frontal cortex and hippocampus. Other chronic exposures, such as long-term diazepam treatment, can lead to a loss of cortical dendritic spines[142]. Therefore, although various drugs can modify the density of dendritic spines, they differ in specific parameters such as duration of treatment and affected brain regions. Finding out those specific characteristics unique to psychedelic-induced neural plasticity will be important, particularly if we want to leverage structural remodeling as a biomarker for drug discovery.

The roles of cell types in driving the neural responses to psychedelics remain to be clarified. Many of the neurophysiological recordings were performed during a time when the diversity of cell types was less appreciated than it currently is. For example, in the frontal cortex, major classes of GABAergic neurons (including subtypes expressing parvalbumin, somatostatin and other markers) express varying amounts of different serotonin receptor subtypes[72,78] and therefore should have distinct responses to psychedelics. Similarly, although the dorsal raphe nucleus is known for containing serotonergic neurons, those cells only constitute 30–50% of the population in this region, and the remainder of the population consists of glutamatergic, GABAergic, dopaminergic and other peptidergic neurons that also express subtypes of serotonin receptors[143]. The local circuit interactions that

shape the neural activity dynamics induced by psychedelic compounds are largely unknown.

Taking a step back, an even greater gap in our current knowledge of psychedelics is linking causally these neurobiological actions to the compounds' behavioral effects. Among the potential multitude of receptor targets, plasticity processes and cell types involved, it is not understood which of these mechanisms drive the beneficial effects seen in clinical trials. Without this fundamental understanding, we lack a foundation to guide optimal dosing and identify individuals who are likely to respond positively to psychedelics.

Looking ahead

What can we look forward to in the next decade for psychedelic research? A major question in the field is the extent to which the subjective experience may be separable from potential therapeutic effects[144,145]. The question can be reframed at the molecular level by asking whether the acute and long-lasting effects arise from activating the same receptors and/or the same intracellular signaling pathways. We may expect answers soon as more receptor structures become available, and the function of select signaling pathways are tested via genetic manipulations in preclinical species. Furthermore, the distribution of receptors and degree of biased agonism will vary across cell types and neural circuits, which must also play a role in shaping the effects of psychedelics. Current studies have focused on a few brain regions, but we can anticipate systematic investigations of psychedelic effects on dendritic excitability and spiking dynamics across the entire brain using optical imaging and large-scale electrophysiological recordings. It is not obvious whether the same or different neural circuits are responsible for psychedelics' various perceptual, cognitive and therapeutic effects. In particular, the contribution of subcortical brain regions remains underappreciated. Such neurophysiological insights will complement the gene expression and receptor binding atlases to lay a foundation for more realistic computational models of psychedelic action. For neuroimaging, high-quality, well-powered studies through individualized, repeated sessions could provide further insights into the fine-grained changes in different brain regions and relate them to psychiatric conditions. After all, most modern psychedelic research shares a common goal, which is to find mechanistic explanations for how psychedelics impact human behavior. By integrating across levels and delving deep to understand the neural basis of psychedelic action, we hope to one day leverage the ability of these molecules to shape and heal minds.

Data availability

Not applicable.

Code availability

Not applicable.

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Acknowledgements

A.C.K. thanks N. Savalia, P. Davoudian and P. Corlett and D.E.O. thanks L. Dunlap, H. Warren and D. Nichols for helpful conversations. A.C.K. was supported by the Yale Program in Psychedelic Science, an One Mind - COMPASS Rising Star Award, and NIH/NIMH grants R01MH121848 and R01MH128217. D.E.O. was supported by NIH/NIDA grant R01DA056365, NIH/NIGMS grant R01GM128997 and the Camille and Henry Dreyfus Foundation. B.L.R. was supported by grants from NIH/NIMH, NIH/NIDA, DARPA and the Michael Hooker Distinguished Professorship.

Competing interests

A.C.K. is a member of the Scientific Advisory Board of 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. D.E.O. is a cofounder of Delix Therapeutics, Inc., and serves as the Chief Innovation Officer and Head of the Scientific Advisory Board. K.H.P. is currently an employee of Boehringer Ingelheim GmbH & Co. KG. B.L.R. is a member of the Scientific Advisory Board of Septerna Pharmaceuticals and Escient Pharmaceuticals. These duties had no influence on the content of this article.

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Peer review information *Nature Neuroscience* thanks Javier Gonzalez-Maeso, Gitte Knudsen, and Charles Nichols for their contribution to the peer review of this work.