

Review

Serotonin biology as a basis for explaining psychedelic drug action

Cory A. Knox¹, Athena Li-Wu¹, and Alex C. Kwan^{1,2,*}¹Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY 14853, USA²Department of Psychiatry, Weill Cornell Medicine, New York, NY 10065, USA*Correspondence: alex.kwan@cornell.edu<https://doi.org/10.1016/j.cub.2026.08.045>**SUMMARY**

Psychedelics exert their effects primarily through the serotonergic system. Like the endogenous neuromodulator, the drugs bind to many serotonin receptor subtypes. However, their receptor selectivity profiles and spatiotemporal patterns of action differ from those of serotonin and vary across compounds. In this review, we summarize studies that have established roles for serotonin in three domains: reward learning, visual processing, and cerebrovascular function. We contrast the neurophysiological and behavioral consequences of endogenous serotonin release with those produced by exogenous psychedelic administration. We propose that several major effects of psychedelics can be understood as perturbations to serotonergic signaling, while also noting some drug actions that remain difficult to explain by existing serotonin biology. Viewing psychedelic drug action through the lens of serotonin provides a mechanistic framework for linking molecular pharmacology to circuit dynamics and behavior.

Introduction

Psychedelics are receiving renewed interest as therapeutics. Numerous clinical trials have demonstrated efficacy of psychedelics for psychiatric disorders, including psilocybin for major depressive disorder¹ and treatment-resistant depression², as well as lysergic acid diethylamide (LSD) for generalized anxiety disorder³. However, long before this re-emergence, there was already intense interest in understanding how psychedelics alter perception, emotion, and cognition. Indeed, some of the earliest neurobiological studies of psychedelic drug action focused on their subjective effects. Yet much of the underlying neurobiology remains unknown. At their core, psychedelics are agonists of serotonin receptors, which suggests that serotonin biology should provide a solid foundation for understanding psychedelic drug action. This perspective is compelling, especially given the extensive literature on how serotonin modulates brain function to shape behavior⁴. In this review, we aim to show that serotonin biology can illuminate how psychedelics work. Psychedelics, in turn, may help dissect principles of serotonin function.

Psychedelics and serotonin: same same but different

Serotonin (5-hydroxytryptamine, or 5-HT) belongs to the chemical class of tryptamines. Several well-studied psychedelics, including psilocin, the active metabolite of psilocybin, and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), are also tryptamines. Other classic psychedelics belong to distinct chemical classes, including the ergoline LSD and the phenethylamine 2,5-dimethoxy-4-iodoamphetamine (DOI), though these compounds still share a common pharmacophore scaffold⁵ (Figure 1A).

A key feature of psychedelics is their polypharmacology⁶. Psychedelic drugs act as agonists at various serotonin receptors, but they differ in their receptor selectivity profiles. One common

way to quantify the differences is through K_i values, which estimate ligand binding affinity to receptors. Here, we tabulated K_i values from the latest characterizations for serotonin⁷ and for psychedelics⁶ (Figure 1B). Although the concept of binding affinity is easy to grasp, empirical K_i values should be interpreted cautiously because they can vary considerably depending on experimental conditions⁸. Moreover, binding of the ligand to receptor does not tell us about the magnitude of downstream signaling within neurons. A more informative metric is the transduction coefficient, a logarithmic parameter that captures both receptor affinity and signaling efficacy to estimate the ability of a ligand to drive a cellular response⁶ (Figure 1C). These comparisons illustrate that both serotonin and psychedelics interact with a broad range of serotonin receptors and many downstream signaling pathways. Importantly, they also highlight how serotonin is a comparatively weak agonist at the 5-HT_{2A} receptor relative to other receptor subtypes. Consistent with this receptor selectivity, a psychoactive dose of psilocybin increased the 5-HT_{2A} receptor occupancy in the cortex from baseline to ~60–70% in humans⁹. Likewise, psilocybin was estimated to produce 50% receptor occupancy at 0.88 mg/kg in the mouse frontal cortex¹⁰. The implication is that endogenous serotonergic signaling reflects a balance of competing influences across multiple 5-HT receptor subtypes (Figure 2A), whereas psychedelics may produce disproportionately strong and unopposed activation of 5-HT_{2A} receptors (Figure 2B).

Although serotonin and psychedelics share many receptor targets, they do not act on an identical set of receptors. One distinction is that psychedelics do not bind to the ionotropic 5-HT_{3A} receptor. In the mouse neocortex, 5-HT_{3A} receptors are expressed selectively in a subset of GABAergic neurons, to the extent that *Htr3a* is used as a defining marker for the cell population that includes vasoactive intestinal peptide- and Reelin-expressing



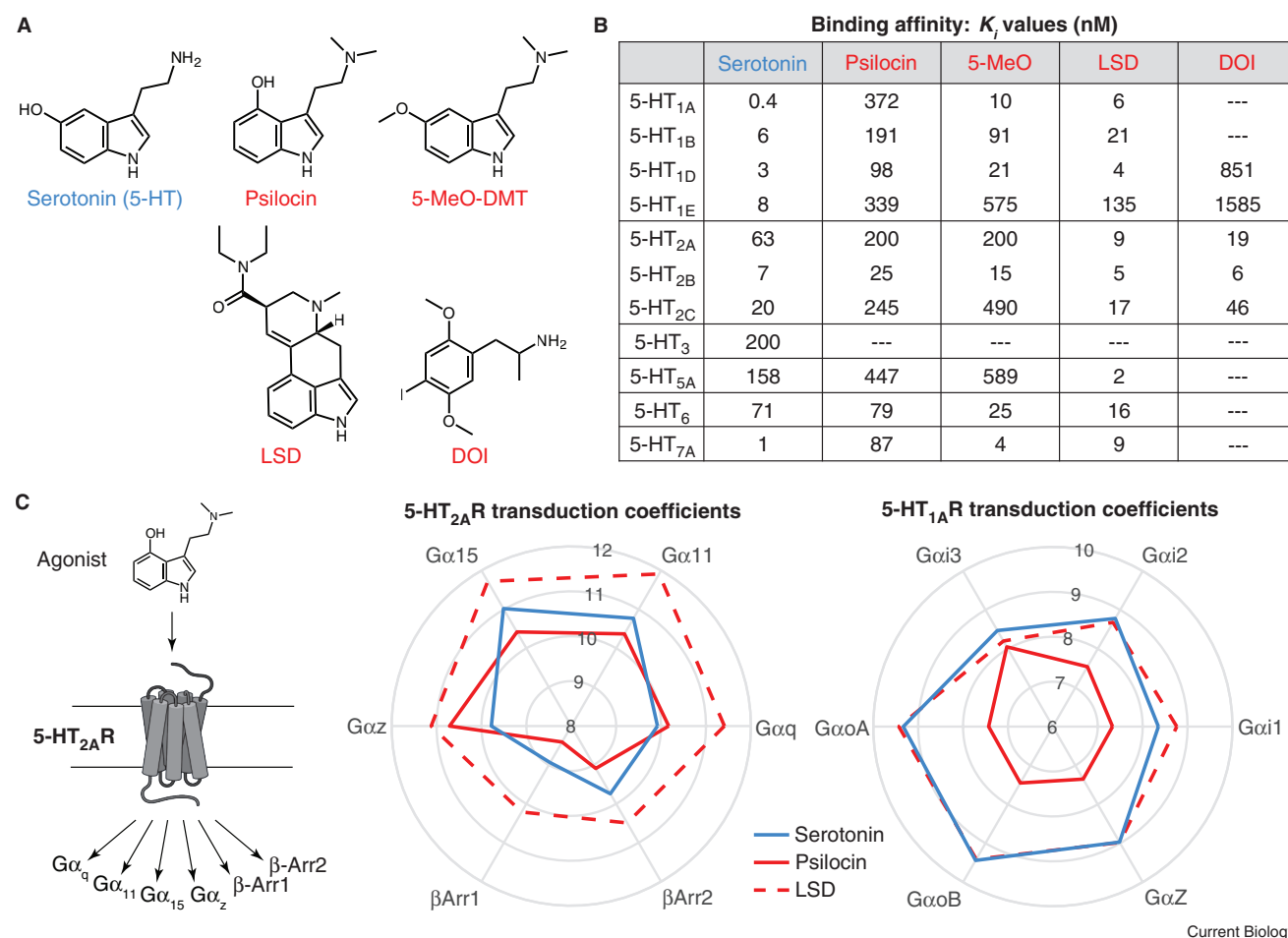


Figure 1. Serotonin receptors as targets for serotonin and psychedelics.

(A) Chemical structures of serotonin and several psychedelics. (B) Binding affinities in terms of K_i values for serotonin, taken from the IUPHAR/BPS Guide to Pharmacology⁷ (CC BY-SA 4.0). Each value is the geometric mean based on the highest and lowest values in the database. K_i values for psilocin, 5-MeO-DMT, LSD, and DOI, taken from Jain *et al.*⁶. K_i values are dependent on the choice of radioligands and other experimental conditions. For details, refer to the original publications. (C) Transduction coefficients for serotonin, psilocin, and LSD at the 5-HT_{2A} and 5-HT_{1A} receptors, taken from Jain *et al.*⁶. Compared to serotonin, LSD has higher transduction coefficients at 5-HT_{2A} while exhibiting similar coefficients at 5-HT_{1A}. By contrast, psilocin shows comparable transduction coefficients at 5-HT_{2A} but substantially lower coefficients at 5-HT_{1A}. Thus, both psychedelics are expected to preferentially bias signaling towards 5-HT_{2A} over 5-HT_{1A} receptor, relative to serotonin.

interneurons¹¹. Whether this feature is conserved across species is debated. One study suggested that the transcript encoding the receptor is largely absent from primate cortical interneurons¹², although subsequent large-scale transcriptomic analyses showed abundant *HTR3A* expression in caudal ganglionic eminence-derived interneurons in the human cerebral cortex¹³. Notwithstanding this caveat, 5-HT₃ receptors are activated by serotonin to rapidly depolarize the interneurons¹⁴. The broad implication is that this can be a mechanism through which serotonin can uniquely influence cortical circuit activity. The converse is also true, where psychedelics can act at receptors not normally targeted by serotonin. For example, LSD additionally acts as an agonist at the dopamine D₁ and D₂ receptors, which contribute to its overall effects in the brain.

It is worth considering the fundamentally different ways in which serotonin and psychedelics reach neural circuits. Serotonin does not enter the brain from the periphery, because it

cannot cross the blood–brain barrier. Instead, the endogenous neuromodulator is produced within the brain by serotonergic neurons, primarily located in the dorsal and median raphe nuclei. Serotonin is synthesized and released from axonal varicosities, supporting a form of transmission that is non-synaptic yet still spatially restricted¹⁵ (Figure 2C). In contrast, psychedelics are typically administered systemically, leading to widespread brain exposure (Figure 2D). The temporal dynamics also differ markedly. Endogenous serotonergic signaling consists of a tonic baseline with superimposed phasic transients (Figure 2E). By comparison, a bolus administration of psychedelics means a rapid onset and then gradual clearance (Figure 2F). For instance, orally administered psilocybin reaches peak plasma concentration in humans after ~2 hours and has an elimination half-life of ~1.5 hours¹⁶. Although there has been speculation that psychedelics such as *N,N*-dimethyltryptamine (DMT) may be produced in the brain, back-of-the-envelope calculations suggest that the

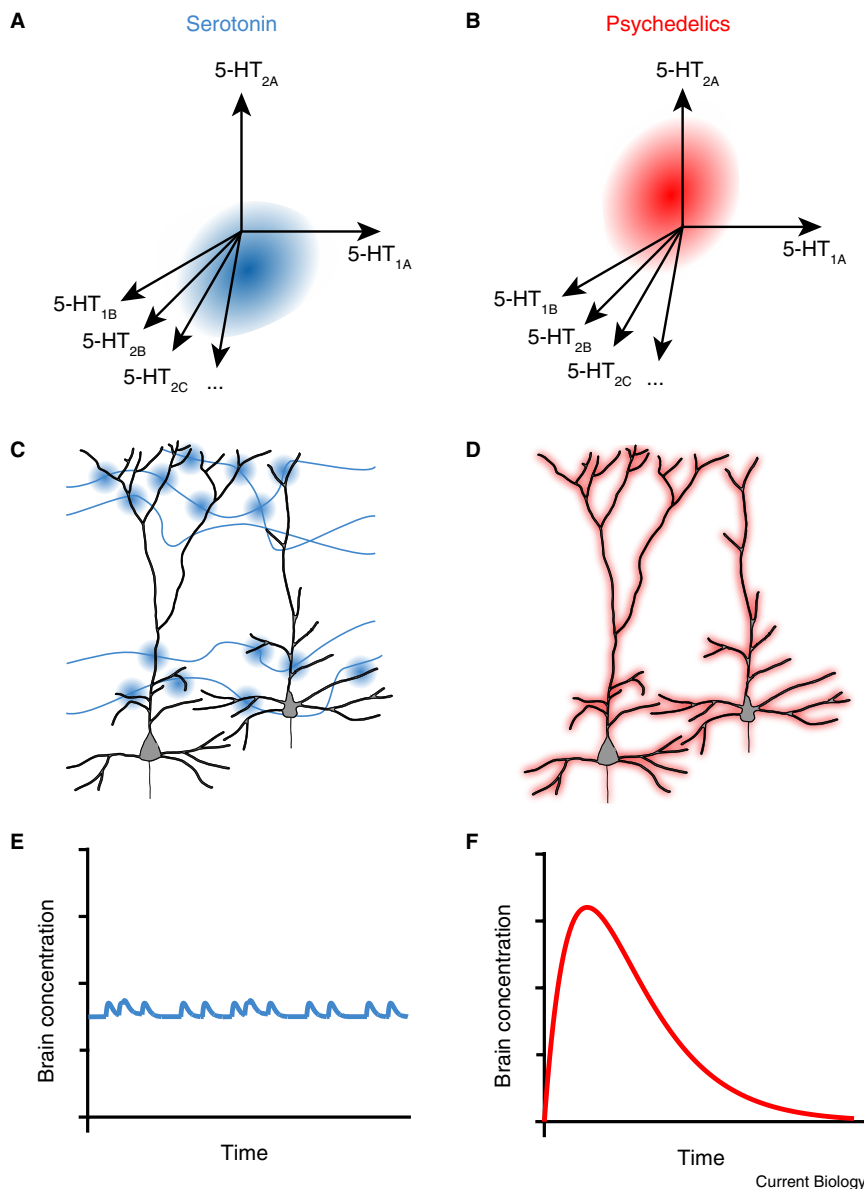


Figure 2. Serotonin and psychedelics differ in receptor engagement, spatial distribution, and temporal dynamics.

(A,B) Endogenous serotonin and psychedelics are expected to produce distinct patterns of 5-HT receptor activation because of their different receptor selectivity profiles. Conceptually, receptor activation can be represented in a multidimensional space in which each axis corresponds to agonism of a serotonin receptor subtype. Serotonin and psychedelics occupy overlapping but distinct subspaces. (C,D) Endogenous serotonergic signaling arises from localized release at serotonergic axon terminals, generating spatially heterogeneous patterns of receptor activation. Systemic psychedelic administration leads to widespread drug exposure. (E,F) Endogenous serotonergic signaling consists of a tonic baseline with superimposed phasic fluctuations. Psychedelics are typically administered at a discrete time point, producing a rapid increase in brain drug concentration followed by gradual clearance.

More recent studies relied on opto-tagging to identify genetically targeted serotonergic neurons²⁰. However, this approach usually does not discriminate between the several subpopulations of serotonergic neurons with distinct molecular and physiological properties²¹ that project to different brain regions²². Other experimental strategies, including optogenetic activation of serotonergic neurons and acute tryptophan depletion, have been used to probe the causal effects of altering serotonergic function. Each approach provides only a partial view of endogenous signaling but has provided valuable insights into the biological function of serotonin.

Serotonin has been implicated in a remarkably long list of physiological and behavioral functions. In agreement with such widespread influence, mice lacking *Tph2*, the enzyme required for serotonin synthesis expressed predominantly

amount, if any, would be far too low to cause psychoactive effects¹⁷. Thus, there are similarities but also numerous key differences between endogenous serotonergic signaling and the actions of psychedelics at the molecular and cellular levels.

Challenges in serotonin research

The study of serotonin has historically been hampered by the lack of tools to directly measure serotonin levels *in vivo*. This roadblock is disappearing with the development of genetically encoded fluorescent sensors for serotonin^{18,19}. Prior to the sensors, a proxy for directly measuring serotonergic signaling has been to record the spiking activity of neurons in the dorsal raphe nucleus, under the assumption that firing correlates with serotonin release at distant axon terminals. Early studies identified putative serotonergic neurons based on broad spike waveforms, slow rhythmic firing, and modulation across sleep–wake states.

within the brain, are viable but exhibit growth retardation along with numerous physiological and behavioral abnormalities in adulthood²³. Some of the proposed functions of the serotonergic system include regulation of the sleep–wake cycle, appetite and energy balance, motor facilitation, memory, and the coordination of defensive behaviors. It is not possible to comprehensively cover the full biology of serotonin here, so we will focus on three areas — reward learning, visual processing, and cerebrovascular function — where decades of work on the serotonin system intersect closely with current efforts to understand the neural mechanisms of psychedelic drugs.

Reward learning — serotonin and cognitive flexibility

There are early clues that serotonin signaling in the brain may relate to reinforcements, particularly the long-term expectation of future rewards. Most of the evidence has come from

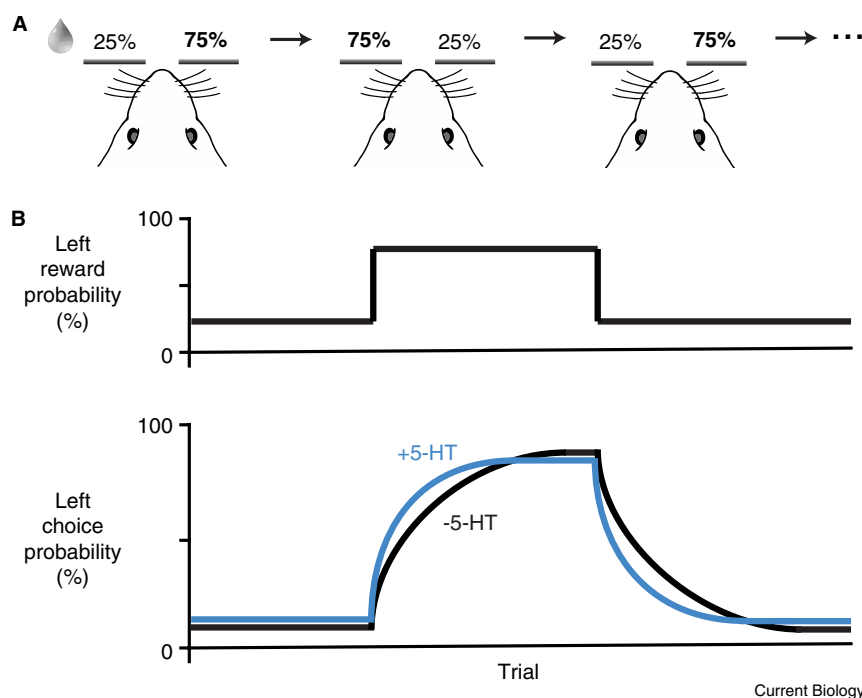


Figure 3. Potential role for serotonin in flexible decision-making.

(A) In an example probabilistic reward reversal task, for each trial, the animal chooses between two options: left or right. Initially, a left choice led to a 25% chance of receiving a water reward, whereas a right choice led to a 75% chance of receiving a water reward. After several dozens of such trials, unbeknownst to the animal, the contingencies would reverse, such that the left reward probability becomes 75% and right reward probability becomes 25%. There can be multiple reversals within a single session. (B) A hypothesized role of serotonin is in regulating the reward learning rate, which allows the animal to adapt more quickly following a reversal.

recordings of serotonergic neurons in the dorsal raphe while the animal is performing a behavioral task. In rhesus monkeys, neurons in the dorsal raphe nucleus encode reward-related information both before and after reward delivery²⁴. Unlike dopamine neurons that are well known to exhibit phasic firing in response to rewards, the dorsal raphe neurons can show either positive or negative modulation by reward size, and many exhibit sustained changes in tonic firing at the onset of a behavioral task trial, suggesting that they encode an ongoing expectation of future rewards rather than just reward prediction errors^{24,25}. These results were corroborated by recordings of serotonergic neurons identified via opto-tagging, where they showed tonic activity changes during inter-trial intervals that track the value of reward or punishment blocks²⁰. Together, the findings have motivated the latest theoretical framework proposing that serotonin encodes the total anticipated reward, using a scheme that accounts for discounting distant outcomes and neural activity adaptations²⁶.

Another way to view the proposed function of serotonin in reward learning is through the lens of uncertainty. In reversal learning paradigms, an animal initially learns that sensory cues or actions are associated with different outcomes. The contingencies are then reversed, introducing an *unexpected uncertainty* in the environment that requires the animal to update the previously learned associations. A more sophisticated version of the paradigm — probabilistic reward reversal — would deliver the outcomes with varying probabilities, also introducing *expected uncertainty* (Figure 3A). Researchers have combined these learning tasks with causal perturbations to investigate the role of serotonin. In one influential study, serotonin depletion in the marmoset prefrontal cortex led to pronounced cognitive inflexibility during reversal learning²⁷. In agreement, silencing serotonergic neurons in mice slowed or disrupted the ability of

mice to flexibly adapt their behavior^{28,29}. The current results are consistent with a hypothesized role for serotonin in enabling quicker adjustments following a change in the environment (Figure 3B).

How might serotonin contribute to cognitive flexibility? Traditional studies of behavioral performance are limited to observable variables, such as the animal's choices and the outcomes of the trials.

More recent approaches use reinforcement learning models to infer latent variables, such as action values, reward prediction errors, and learning rates, that reflect the internal computations guiding behavior. By fitting these models to the animal's choices and outcomes, one study revealed that mice track uncertainty in the environment and dynamically adjust their learning rates to optimize performance while performing a probabilistic reward reversal task²⁸. Notably, the spiking activity of serotonergic neurons correlated with both expected and unexpected uncertainty on a trial-by-trial basis, suggesting that monitoring uncertainty may be an important function of the serotonergic system.

Reward learning — psychedelics and cognitive flexibility

These ideas for serotonin functions have shaped the research of psychedelic drugs, where reversal learning paradigms are also frequently used to probe cognitive flexibility. The results have been intriguing, although not always consistent across studies. In one classic experiment, rats were trained to associate a light or dark corridor with a water reward, and then tested on reversed contingencies shortly after LSD administration³⁰. Higher doses of LSD at 12.5–50 $\mu\text{g/kg}$ accelerated reversal learning, suggesting that the psychedelic acutely enhances behavioral flexibility. This effect was not observed with 2-Br-LSD, the non-hallucinogenic analog. Encouragingly, in humans, LSD administration was also reported to enhance cognitive flexibility in a probabilistic reversal learning task³¹. Most notably, the improvement appeared to be best explained by an increase in reward learning rate, consistent with the idea that serotonergic signaling contributes to our ability to dynamically regulate learning under uncertainty.

However, other rodent studies found either no effect or even impairments in reversal learning acutely after psychedelic administration^{32,33}. Interpretation is complicated by the limitation that

rodent paradigms are often reduced versions of human cognitive tasks, such that there may be multiple strategies that animals can use to solve the simplified task. For example, the intended strategy could be reinforcement learning, but animals may instead perform the task using heuristics, such as switching their choice after a fixed number of errors. The effects of psychedelics on learning are difficult to interpret if we are uncertain about the animal's behavioral strategy. To alleviate this issue, we may use complementary tasks to evaluate the effects of a psychedelic. For example, one study compared the effects of psilocybin on reversal learning and set-shifting paradigms, finding that psilocybin selectively improved performance when rats had to switch between previously learned rules³³. Additionally, we can fit computational models to behavior, using goodness-of-fit to infer the most likely strategy and deviations from model predictions to identify mismatches between assumed and actual behavior.

An open question is whether psychedelics produce longer-lasting effects on cognitive flexibility beyond the acute drug state. Several recent studies showed that psilocybin, DOI, and 25CN-NBOH can improve reversal learning when animals are tested one day or more after drug administration^{34–36}. Intriguingly, the delayed effects depended on whether the animals had the opportunity to reengage with the task after drug administration, suggesting experience-dependent plasticity³⁵. There is likely a complex relationship between psychedelics and cognitive flexibility that depends on the specific drug, behavioral paradigm, and timescale.

Reward learning — other theories

Another influential theory for serotonin function emphasizes its role in suppressing impulsivity and promoting waiting for future rewards. This idea of behavioral inhibition is rooted in the framework that serotonin and dopamine may exert opposing influences on behavior³⁷. Serotonergic neurons increase tonic firing while animals wait for delayed rewards³⁸. Moreover, serotonergic activity decreases immediately before animals give up on waiting, leading to the interpretation that elevated serotonergic signaling promotes patience for future rewards. These ideas are at odds with findings that psychedelics typically disrupt inhibitory control. In rodents, DOI increased premature responses in the 5-choice serial reaction time task when tested 30 minutes after administration³⁹. Similarly, LSD impaired motor response inhibition in a go/no-go task in humans⁴⁰. Although the reasons behind the impulsive actions are unclear, the behavioral effects of serotonin and psychedelics appear, at face value, to point in opposite directions with respect to inhibitory control.

Serotonergic neurons exhibit not only slower tonic changes in firing, but also rapid phasic activity on sub-second timescales that may contribute to learning. For instance, serotonergic neurons show transient firing responses to reward-predicting cues²⁰ and punishment-related stimuli^{20,29}. Such endogenous phasic signaling is likely very different from the sustained pharmacological state produced by psychedelic drugs. During the acute drug state, the exogenous agonists have prolonged engagement with the receptors, which probably masks endogenous phasic signals. In addition, psychedelics strongly suppress the activity of serotonergic neurons within the raphe nuclei⁴¹, which would further blunt endogenous serotonin signaling.

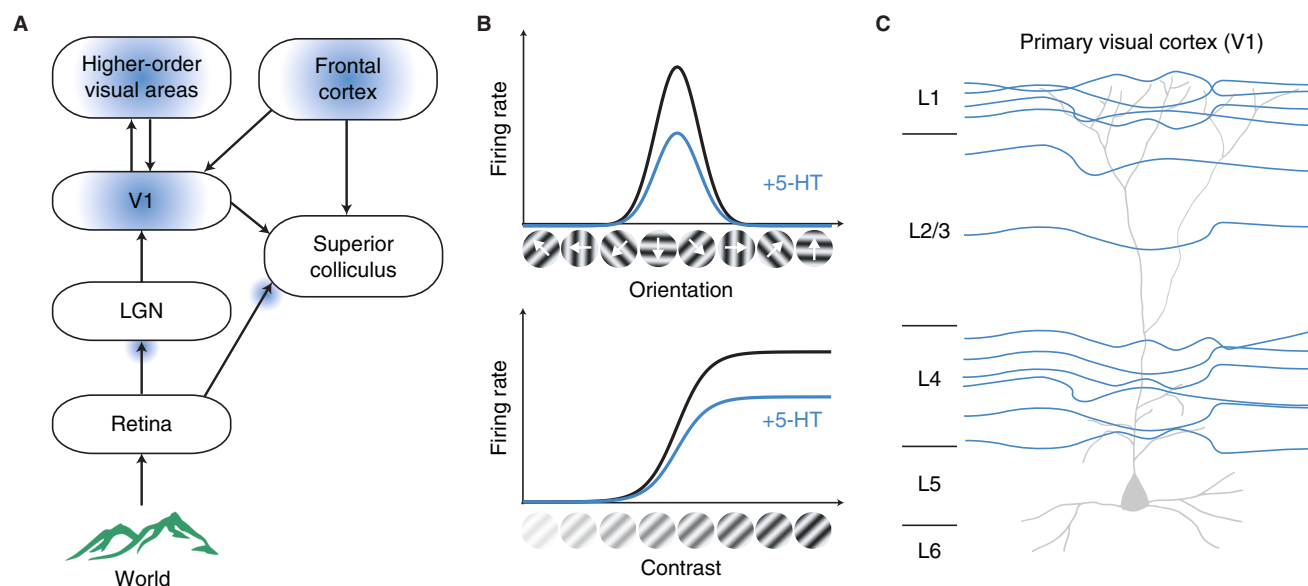
To summarize this section, current findings point to convergent effects for serotonin and psychedelics in cognitive flexibility. Serotonergic activity tracks uncertainty and may dynamically regulate learning rates in changing environments. Psychedelic administration has often been associated with enhanced behavioral flexibility, although the effects may be more nuanced and depend on the specific drug, behavioral paradigm, and timescale under investigation.

Visual processing — suppressing visually evoked responses

Serotonin influences visual processing beginning at the earliest stages of the visual hierarchy (Figure 4A), where its effects are predominantly suppressive⁴². Stimulation of the dorsal raphe nucleus or local serotonin application reduces the spiking activity of neurons in the rat lateral geniculate nucleus^{43,44}. Mechanistically, this suppression is thought to arise from presynaptic 5-HT_{1B} receptors, which attenuate stimulus-evoked glutamate release from retinal ganglion cell axons in the thalamus⁴⁵. Similar 5-HT_{1B} receptor-mediated suppression has been observed in other early visual pathways, such as the projections from retina to superior colliculus⁴⁶. These suppressive effects from endogenous serotonergic signaling are well aligned with the impact of psychedelics in early visual pathways. Indeed, in one of the earliest electrophysiological studies involving psychedelics in 1955, the researchers recorded from cat lateral geniculate nucleus while stimulating the optic tract, finding that thalamic spiking responses were diminished following LSD administration⁴⁷.

In the primary visual cortex, a main effect of serotonin is to lower the gain for visually evoked firing responses. This effect was demonstrated most clearly by experiments combining extracellular single-unit electrophysiology with local microiontophoretic application of serotonin, which have been done in anesthetized rats⁴⁸ and awake macaques⁴⁹. The serotonergic modulation can be effectively described as a multiplicative, downward scaling of the visually evoked responses⁴⁹ (Figure 4B). Therefore, serotonin contributes to gain control, regulating the responsiveness of the visual system to sensory stimuli. Other response properties, such as orientation tuning, spatial frequency selectivity, and stimulus size tuning, were largely unaffected by serotonin. Consistent with these findings, optogenetic stimulation of the dorsal raphe nucleus in mice similarly reduced response gain in the primary visual cortex⁵⁰. Intriguingly, pharmacological blockade experiments suggested a potential division of labor, with 5-HT_{1A} receptors contributing to the reduction of spontaneous activity and 5-HT_{2A} receptors selectively attenuating visually evoked responses⁵⁰.

The modulatory effect of serotonin in the primary visual cortex is again broadly consistent with observations made for psychedelics. Early studies investigated the effects of LSD, delivered either systemically via intravenous injection or locally via iontophoresis, on visual cortical neurons in cats. Although there was a range of effects on the neuronal responses, LSD generally decreased visually evoked activity, particularly when high doses were applied⁵¹. Receptive field structures and tuning properties, including orientation and direction selectivity, were largely unchanged by the psychedelic. Similar findings were reported in a more recent study, showing that systemic administration of



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Figure 4. Effects of serotonin on visual processing.

(A) Illustration of key components within the visual hierarchy influenced by serotonergic neuromodulation (blue shading). In early visual circuits, serotonin suppresses activity in the retinogeniculate and retinotectal pathways via its action on presynaptic 5-HT_{1B} receptor. In the neocortex, serotonin modulates local microcircuits in visual and frontal cortical regions. V1, primary visual cortex; LGN, lateral geniculate nucleus. (B) In the primary visual cortex, serotonin lowers the gain in visually evoked response, which can be observed in orientation tuning curves and contrast response functions. (C) There is a laminar distribution for serotonergic axons, with denser innervations in layers 1 and 4 relative to layers 2/3, 5, and 6. The illustrations in (B) and (C) are based on Seillier *et al.*⁴⁹ (CC BY 4.0) and Morrison *et al.*⁵³ (with permission from J.H. Morrison), respectively.

the psychedelic DOI compressed the dynamic range of visually evoked responses in mouse primary visual cortex by reducing response gain, while sparing basic tuning properties such as orientation selectivity⁵².

Although serotonin and psychedelics appear to exert similar effects on visually evoked responses in the primary visual cortex, the underlying mechanisms remain unclear. The observation that these effects can be achieved by intracortical application of either serotonin or LSD suggests that they must arise at least in part from the local cortical microcircuit. For serotonin, one important clue comes from the organization of serotonergic innervation. In primates, serotonergic fibers have a characteristic laminar profile, with the densest axonal density concentrating in layer 4, the main input layer of primary visual cortex, with additional innervation in the superficial layer 1, but relatively sparse projections to layers 5 and 6⁵³ (Figure 4C). Studies in mice suggest a qualitatively similar organization⁵⁴, though the laminar differentiation is less pronounced than in primates. The laminar organization hints at possibly serotonergic neuromodulation on specific cortical circuit elements at those locations.

Visual processing — the psychedelic effects and potential mechanisms

What about the well-known visual perceptual effects of psychedelics? These percepts are rarely completely imaginary, but instead reflect altered perception to sensory input from the environment. Commonly reported effects include distortions in the perceived size, shape, and angles of objects, as well as exaggerated motion and optical flow⁵⁵. Psychedelics can also evoke vivid geometric patterns resembling lattices, cobwebs, tunnels,

and spirals. In addition, there is synesthesia, in which the visual perception is heightened by stimulation in another sensory modality such as sound. These visual perceptual effects of psychedelics are most certainly mediated by the 5-HT_{2A} receptor. In humans, pretreatment with the 5-HT_{2A} receptor antagonist ketanserin completely eliminated the visual imageries elicited by psilocybin and LSD^{56,57}. Moreover, the occupancy of 5-HT_{2A} receptors in the neocortex closely correlated with the intensity of the subjective experience, which includes perceptual metrics⁹. The extent to which animals may experience perceptual phenomena comparable to those reported by humans is poorly understood. Future studies using cross-species behavioral tasks may help address this question. There are hints that at least some aspects of the psilocin-induced visual distortions may be perceived by rodents⁵⁸.

We can speculate on the circuit-level mechanisms underlying the characteristic visual percepts produced by psychedelics. In early visual pathways, psychedelics dampen the transmission of bottom-up sensory inputs into cortical circuits. This mechanism may contribute to the effects of psychedelics because prolonged sensory deprivation can cause hallucination-like experiences. However, studies with LSD show that visually evoked activity is diminished but not fully abolished, indicating that some bottom-up sensory signals are likely still present under the drug state. More importantly, current findings emphasize the role of presynaptic 5-HT_{1B} receptors in suppressing early visual pathways, whereas the 5-HT_{2A} receptor is essential for the perceptual effects of psychedelics. Therefore, reduced sensory drive into the cortex alone seems insufficient to account for psychedelic visual experiences.

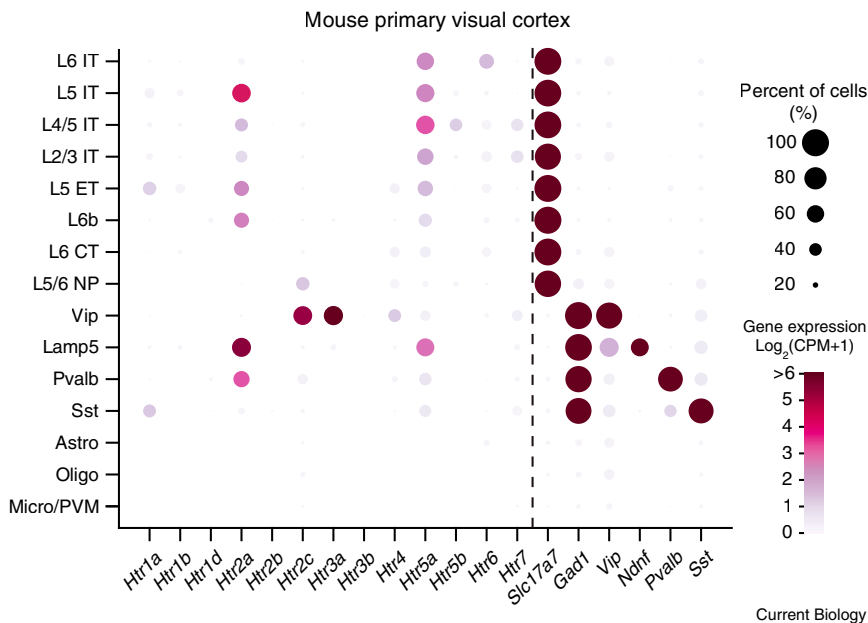


Figure 5. Expression of serotonin receptor transcripts in the mouse primary visual cortex.

Single-cell transcriptomic profiles from the mouse VISp region. *Slc17a7* and *Gad1* are markers of excitatory and GABAergic neurons, respectively. *Vip*, *Ndnf*, *Pvalb*, and *Sst* are markers of subtypes of GABAergic neurons. Circle size denotes the percentage of cells with detectable expression of a gene (>0 reads). Circle color denotes expression level (CPM, counts per million). This figure is adapted from Liao *et al.*⁶¹, using values extracted from Allen Institute SMART-Seq dataset⁶².

Collectively, these various potential mechanisms reduce bottom-up sensory drive and enhance top-down influence, which are consistent with frameworks that conceptualize hallucinations as disruptions in perceptual inference^{68,69}. These frameworks posit that perception depends on the relative weighting of sensory evidence and prior knowledge. Over-reliance on higher-level predictions

Instead, the primary visual cortex may be a key locus for the perceptual effects of psychedelics. 5-HT_{2A} receptors are expressed in both excitatory and inhibitory cortical neurons⁵⁹. To gain insight into the cell type-specific contributions, we previously analyzed expression patterns of serotonin receptor genes^{60,61} using single-cell sequencing datasets from the Allen Institute⁶². In the mouse primary visual cortex, *Htr2a* expression is widespread among excitatory cell types, with particularly high levels in layer 5 intratelencephalic neurons, layer 5 extratelencephalic neurons, and layer 6b neurons (Figure 5). Among GABAergic populations, expression is more selective, with enrichment in *Lamp5*- and *Pvalb*-expressing interneurons. Because parvalbumin-expressing interneurons provide strong perisomatic inhibition, their activation would be expected to suppress spiking output in the excitatory cells. However, perisomatic inhibition is generally thought to produce subtractive rather than multiplicative changes in visually evoked responses⁶³, suggesting that additional circuit mechanisms may be involved.

Another potential mechanism is that psychedelics perturb top-down modulation of sensory processing. Higher-order visual and frontal cortical regions send extensive feedback projections to the primary visual cortex. Aberrant amplification of these signals could contribute to altered perception. Consistent with this idea, psilocybin alters neuronal firing dynamics in regions such as anterior cingulate cortex⁶⁰ and retrosplenial cortex⁶⁴. However, the activity changes are heterogeneous across neurons, and their impact on downstream regions remains to be determined. There is currently stronger evidence suggesting that psychedelics may heighten the dendritic processing of long-range inputs. At the subcellular level, 5-HT_{2A} receptors are preferentially expressed on apical dendrites^{65,66}. Direct agonism of these receptors, perhaps together with the activation of layer 6b neurons that target the apical tufts⁶⁷, may elevate dendritic excitability and increase the responsiveness of pyramidal cells to long-range corticocortical inputs.

rather than current information from external stimuli has been associated with hallucinations and delusions^{70,71}. Neuromodulators may play an important role in regulating this balance. For example, acetylcholine may increase the weight assigned to current sensory evidence⁷², consistent with its ability to elevate signal-to-noise in visual cortical neurons⁷³. Conversely, cholinergic blockade by delirants such as scopolamine can cause hallucinations. Similar processes may operate under psychedelics⁵, as serotonergic mechanisms can reduce the relative weight of sensory input and increase the influence of cortico-cortical signals. Thus, multiple local and long-range circuit mechanisms may work in concert to produce the unique perceptual effects of psychedelics.

Cerebrovascular function — a perspective from migraine treatment

Although serotonin is now widely studied for its roles in the brain, it was first recognized for its vascular properties⁷⁴. In 1948, Irvin Page, Maurice Rapport, and Arda Green were searching for an endogenous constricting substance that could be responsible for hypertension, but instead isolated a contaminating factor in the serum that was later named ‘serotonin’. Subsequently Betty Twarog demonstrated that serotonin is present in the mammalian brain, which opened the door to studying serotonin as a neuromodulator. Thus, from its earliest characterization, serotonin’s vascular and neural identities were intertwined. A similar lineage is evident in the history of psychedelics. While looking for respiratory and circulatory stimulants, Albert Hofmann synthesized LSD from the ergotamine, an ergot alkaloid with vasoconstricting properties and used to treat migraine⁷⁵. Therefore, serotonin and several psychedelics share a common historical and pharmacological connection through the vascular system. For this reason, we will begin by discussing the cerebrovascular effects of serotonin and psychedelics through the lens of migraine therapeutics.

Migraine is characterized by unilateral pulsating headache lasting for hours, often accompanied by nausea and hypersensitivity to light and sound. Serotonergic agonists have been a mainstay of migraine medications, although our understanding of their mechanisms of action has shifted considerably over the years. Early theories postulated vascular dysfunction with serotonin as one of the possible proximate triggers, starting with an initial phase of vasoconstriction followed by a rebound of vasodilation during headaches⁷⁶. However, this vascular theory has since been replaced by recent frameworks emphasizing trigeminal ganglion neurons and their projections to the pia, dura, and large cerebral arteries. The release of neuropeptides such as calcitonin gene-related peptide (CGRP) causes dural and pial vasodilation, as well as activates and sensitizes meningeal nociceptors, contributing to migraine pain.

In this context, serotonin acts as an important modulator because the trigeminal neurons and cranial blood vessels widely express 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors⁷⁷. 5-HT_{1B} and 5-HT_{1D} receptors are the main targets of ergotamines and triptans, two classes of serotonergic drugs for migraine. Agonism of 5-HT_{1B/1D} receptors in the trigeminal ganglion suppresses the release of CGRP from trigeminal afferents^{77–79}. However, for triptans, they are contraindicated for individuals with cardiovascular conditions because of the constriction caused by 5-HT_{1B} receptors on coronary smooth muscle. The 5-HT_{1F} receptor is expressed in the trigeminovascular system but does not produce vasoconstriction. This target allows another class of serotonergic drug, ditans, to inhibit trigeminal CGRP signaling without the vascular liabilities associated with triptans^{77,80}.

Despite the availability of serotonergic drugs and newer therapeutics that directly target CGRP signaling, current treatments remain insufficient for many patients. It was estimated that ~40% of individuals with migraine fail to respond to multiple preventive medications⁸¹. This is where psychedelics have re-emerged with therapeutic potential. Interest in this possibility dates back to the 1960s, when LSD was explored as a prophylactic treatment for migraines⁸². More recently, proof-of-concept studies found that a low dose of psilocybin reduced migraine frequency in the subsequent two weeks^{83,84}. Interestingly, the therapeutic benefit was not correlated with the intensity of the acute subjective experience, suggesting that migraine relief may be mechanistically separable from the hallucinogenic effects of the drug. The interest in psychedelic-based therapeutics is likely fueled in part by the popular use of psilocybin and LSD for alleviating cluster headache, a related disorder with excruciating pain and few treatment options. There is patient-driven use of psychedelics as self-medication for cluster headaches^{85,86}, which motivated recent trials that employed a similar pulse protocol of three low doses of psilocybin delivered 5–7 days apart each^{87,88}. Other drugs are also being tested, including LSD and its non-hallucinogenic analog 2-Br-LSD⁸⁹. Although these preliminary studies are limited by small sample sizes, they highlight renewed interest in psychedelics for migraines and related disorders.

The mechanisms through which psychedelics may prevent and alleviate migraine remain unclear. Because psychedelics exhibit affinity for the same 5-HT_{1B} and 5-HT_{1D} receptors as triptans, they may similarly modulate the trigeminovascular systems

via their direct action on serotonin receptors. However, a key feature that distinguishes psychedelics from conventional migraine and cluster headache treatments is the persistence of effects after only one or a few doses. Notably, although the main target of psychedelics, the 5-HT_{2A} receptor, has often been associated with cranial vasoconstriction, there is currently no approved migraine medications whose therapeutic mechanism is based solely on direct agonism of the 5-HT_{2A} receptor. These observations raised the possibility that additional mechanisms contribute to the beneficial effects of psychedelics, including potential alterations in cerebral blood flow and neurovascular coupling, which we will next discuss.

Cerebrovascular function — cerebral blood flow and neurovascular coupling

There is some evidence that endogenous serotonergic signaling within the brain can influence cerebral blood flow. In anesthetized rodents, electrical or optogenetic stimulation of the dorsal raphe nucleus decreases cerebral blood flow and volume, indicating that activation of the serotonergic pathways produces vasoconstriction^{90,91}. In awake rats, however, similar stimulation paradigms produced more heterogeneous changes, with increases in blood flow in frontal sensorimotor and parietal cortices but decreases in the primary auditory cortex⁹². These results suggest that serotonergic signaling in the brain can alter cerebral circulation, though the direction of the effect may vary depending on brain region and behavioral state.

The acute effects of psychedelics on cerebral blood flow have been studied in humans using the arterial spin labeling technique. Psilocybin lowers the overall amount of blood flow into the brain. After accounting for this global reduction in perfusion, relative increases in blood flow were observed in frontal and limbic regions, relative to parietal and lateral temporal cortex^{93,94}. These results were corroborated by a recent study, further showing that the psilocybin constricts the internal carotid artery⁹⁵. Because psychedelics are administered systemically, it is unclear to what extent these effects reflect changes in endogenous serotonergic signaling, compared to the likely dominant direct effects of drug actions on the vasculature itself.

In addition to their vasoconstrictive effects, psychedelics also appear to alter neurovascular coupling, the process by which changes in neural activity regulate local blood flow. A recent study in awake mice provided compelling evidence for disrupted neurovascular coupling following psychedelic administration⁹⁶. By simultaneously imaging the activity of cortical excitatory neurons and hemodynamic responses, the study revealed that the psychedelic DOI decreased neuronal firing in the retrosplenial and posterior cingulate regions, while hemodynamic responses were reduced in the somatosensory and increased in contralateral auditory cortex. The spatial mismatch between the neural and vascular responses indicates altered neurovascular coupling, which was observed under both sensory-evoked and resting-state conditions. Notably, most of these effects were abolished by a selective 5-HT_{2A} receptor antagonist. Related work further shows that psilocybin may also perturb neurovascular coupling in a 5-HT_{2A} receptor-dependent manner⁹⁷. These findings point to a potentially

underappreciated mechanism for how psychedelics can influence cerebrovascular function.

Although the precise mechanisms remain to be clarified, current findings make it clear that psychedelics can influence the vascular system through multiple pathways. There are important implications. First, much of our current understanding of psychedelic drug action in the human brain comes from functional magnetic resonance imaging, which relies on blood oxygenation level-dependent signals as an indirect proxy for neural activity. However, if psychedelics directly alter cerebral blood flow and disrupt neurovascular coupling, then the imaging signals likely reflect a complex combination of vascular effects, altered coupling, and changes in neuronal activity. Second, although studies are now beginning to illuminate the cerebrovascular effects of psychedelics, the changes have thus far been characterized during acute drug exposure. The timing of these effects contrasts sharply with the potential therapeutic benefits in migraine and cluster headache, which persist after only one or a few administrations. There is an opportunity for future studies to investigate longer-lasting adaptations in cerebrovascular functions due to changes in serotonergic signaling, particularly from psychedelic administration.

Connecting the dots from neuromodulator to therapeutic

A recurring theme across the three domains — reward learning, visual processing, and cerebrovascular function — is the importance of timescale. Several acute effects of psychedelics align closely with functions attributed to serotonin at the minute-to-minute level, including enhanced cognitive flexibility and diminished visual responses. However, psychedelics also produce effects that are distinct from endogenous serotonergic signaling, which usually occur at longer timescale, such as enduring effects in reversal learning and migraine symptoms. To our knowledge, persistent changes have not been clearly established for serotonin. One study hinted at potential long-term effects: chronic administration of the selective serotonin reuptake inhibitor fluoxetine restored ocular dominance plasticity and visual acuity in adult rats subjected to early monocular deprivation, effects normally restricted to a developmental critical period⁹⁸. Because recovery emerged only after chronic treatment, the findings suggest that sustained serotonergic modulation can produce enduring changes. The prolonged effects of psychedelics may be particularly relevant for therapeutic applications. For instance, rigid patterns of thought are associated with chronic stress and depression. Long-lasting enhancements in cognitive flexibility may represent an important component of the therapeutic effects of psychedelics in neuropsychiatric disorders.

We can speculate on why the long-term effects are absent for endogenous serotonergic signaling. One possibility is that serotonin and psychedelics engage different regions of receptor activation space (Figure 2A). Because serotonergic signaling is constrained by its characteristic receptor selectivity profile and spatiotemporal dynamics, there are likely intrinsic boundaries to the potential neuromodulatory states. Neural circuits develop in the continual presence of endogenous serotonin signaling, such that they are tuned to operate within this physiological regime. By contrast, psychedelics may

transiently push neural circuits into neuromodulatory states that are not ordinarily accessible through serotonergic transmission.

By putting the brain in distinct neuromodulatory states, serotonin and psychedelics may evoke different patterns of neural activity. For serotonin, a recent mouse study found that optogenetic stimulation of serotonergic neurons led to region-specific neural responses, which were in line with the regional density of serotonergic axons and distributions of 5-HT₁ and 5-HT₂ receptors⁹⁹. Unsurprisingly, the effects of psychedelics are more closely linked to the 5-HT_{2A} receptor. Whole-brain imaging of c-Fos expression following psilocybin administration revealed that the cortical activation pattern directly correlated with *Htr2a* transcript abundance, but not other 5-HT receptor subtypes¹⁰⁰. Similarly, analyses of human neuroimaging data following LSD administration showed that drug-evoked changes in large-scale brain activity tightly tracked the cortical distribution of 5-HT_{2A} receptors¹⁰¹. The preferential engagement of 5-HT_{2A} receptors and the resulting evoked brain activity patterns may be crucial in shaping drug-induced neural plasticity^{60,64}, with consequences for long-term behavioral changes.

We need more solid frameworks to explain psychedelic drug action. Although several theories have been put forth to explain psychedelic drug action⁵, they are largely descriptive. A challenge will be to develop quantitative models that can test whether the theories are implementable by neural circuits. Early efforts in this direction include mathematical models that can generate the geometric visual hallucinations produced by psychedelics¹⁰². More recently, artificial neural networks have emerged as a promising approach for modeling psychedelic-like states. One particularly powerful example used a computational architecture consisting of separate bottom-up and top-down pathways. In wake mode, the network would receive external input, whereas in sleep mode it could generate and train from internal representations. Remarkably, when the model was set to operate in an intermediate regime that lies between sleep and wake modes, it produced outputs resembling visual hallucinations: images that did not correspond to any training examples, yet preserved the statistical structure of the images¹⁰³.

Conclusion

Taken together, the literature suggests that many hallmark effects of psychedelics arise from their interactions with the brain's serotonergic system. However, there are also important distinctions between psychedelics and endogenous serotonin signaling, particularly in the long timescale. The differences are likely due to the distinct receptor affinities, pharmacokinetics, and spatial patterns of engagement produced by psychedelics. Ultimately, framing psychedelics within the broader context of serotonin biology provides a solid foundation for understanding how these drugs alter neural activity and behavior.

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