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LOST FOUNDATIONS: NARRATIVE REVIEW

Dorsal Raphe Revisited: A Systems Neuroscience Lens on Psychedelic Drug Action

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Abstract

Psychedelics rose to prominence in the 1960s, around the same time when neurobiologists identified the midbrain raphe as the brain's primary source of serotonin. It is therefore no surprise that early studies on classical psychedelics like *d*-lysergic acid diethylamide (LSD) focused on their effects within this brainstem nucleus. This review traces the arc of discovery: from the initial report in 1968 that LSD suppresses the firing of serotonergic neurons in the rat midbrain raphe, through more than 15 years of intensive work dissecting the pharmacology and receptor mechanisms. Early hypotheses erroneously suggested the serotonergic neurons as potential drivers of the acute hallucinogenic effects, but the conceptual framework gradually shifted after relating neural activity to behavior. We conclude this brief commentary by revisiting these early findings in light of current knowledge of the serotonergic circuits. Collectively, the pioneering studies laid the foundation for thinking about how psychedelics act on the brain through the lens of neurophysiology.

Keywords: serotonin, LSD, receptors, inhibition, neuromodulation, electrophysiology

Prologue

For 4 years, I sat next to George Aghajanian during the weekly seminars in Yale's Department of Psychiatry, and not once did we talk about psychedelics. It was not that we did not talk about science. In fact, we spent plenty of time discussing his fruitful collaboration with Ron Duman to understand the effects of ketamine on synaptic plasticity. But like many young scientists, I had no clue at that time that George had spent two decades studying how psychedelics act on the midbrain raphe. I only rediscovered his series of papers after my own lab began research on psilocybin a few years later. In retrospect, his research, along with that of his contemporaries, represents the formative years of applying systems neuroscience approaches to study psychedelic drug action. They were grappling with the very questions that we continue to ask today: Which are the essential cell types and brain regions for psychedelics' acute subjective effects? Are there biomarkers that can distinguish hallucinogenic compounds? How do the different receptors interact to give rise to the overall drug action? This early pursuit was marked by persistence, doubt, and continual revision of hypotheses. This is a body of work that I have come to admire, as it is the precursor to today's efforts to understand how psychedelics shape neural circuits.

The Backdrop: The Link Between Psychedelics to Serotonin

Serotonin, initially named as enteramine, was identified from the serum during efforts to find substances for treating hypertension (for a recount of serotonin's discovery, see ref.).[1] It was soon determined analytically to be 5-hydroxytryptamine (5-HT)[2] and be present in brain tissues.[3] The structural similarity between serotonin and psychedelics prompted early speculation about their relationship. Initial experiments in rat uterus and rabbit ear preparations showed that *d*-lysergic acid diethylamide

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(LSD) competes with serotonin, leading to the suggestion that LSD antagonizes serotonin at "one of the two types of tryptamine receptors."[4] This gave rise to the proposal that LSD might act as an "antimetabolite," interfering with serotonin function in the brain.[5] However, subsequent work revealed that the relationship was more nuanced, with psychedelics possessing potentially both serotonin-like and "antiserotonin" properties in these early bioassays.[6]

A more direct link between LSD and serotonin was demonstrated by Daniel Freedman, who showed that LSD produces a small but significant transient increase in serotonin levels in the rat brain.[7] This effect was accompanied by a mirrored decrease in 5-hydroxyindoleacetic acid, the main metabolite of serotonin.[8] Although several explanations were proposed, including LSD binding to sequester serotonin or inhibiting monoamine oxidase activity, a more compelling possibility was that serotonin levels may rise because serotonergic neurons become inactive, cease to release serotonin, and cause a buildup at the terminals. Or in Freedman's words, there could be an "interference of LSD with the storage or release mechanisms, or both." This hypothesis became testable following another key discovery that serotonin-containing neurons in the brain are concentrated in the dorsal and median raphe nuclei.[9]

The Discovery: LSD Suppresses the Firing of Raphe Neurons

George Aghajanian completed his premedical studies at Cornell University, followed by medical school and a psychiatry residency at Yale University. His early interest in psychedelics was evident in his work investigating tolerance to LSD and mescaline by measuring the behavioral effects of repeated injections in rats.[10] Colleagues described him as having "independence, resourcefulness, and technical aptitude."[11] After 2 years of service in the Army Medical Corps, he returned to Yale in 1965 as an Assistant Professor at the then newly founded Connecticut Mental Health Center. Young and fearless, he moved into the emerging field of electrophysiology.

In a seminal study,[12] Aghajanian inserted tungsten microelectrodes into the caudal midbrain of rats under chloral hydrate anesthesia. He recorded neural activity for 5–10 min before administering LSD at a dose of 100 μg/mL either intraperitoneally or intravenously via the tail vein. Of 32 units recorded, 17 stopped firing, 3 increased firing, and 12 showed no change after LSD. The cessation of firing was found in units when the electrode was placed near the midline of the dorsal and median raphe nuclei (Fig. 1A and B). Most of these suppressed units exhibited slow and steady firing with a biphasic spike waveform, presumed to be signatures for serotonergic neurons at the time and confirmed years later via selective lesions or antidromic stimulation. The LSD-induced change in spiking activity was reversible: at 200 μg/kg, firing ceased within 1–2 min of intravenous (i.v.) injection or within 5 min of intraperitoneal (i.p.) injection and did not return to the baseline for at least 20–30 min. By titrating the dose, they found a threshold of 25–50 μg/kg, which still reduced firing, and after which activity began to recover within 5 min (Fig. 1C).

> *"I thought the activity of these [midbrain raphe] neurons may be very important in determining what their function was. I had no background in electrophysiology. In a neighboring lab, I got a postdoc from John Flynn who was at Yale. We got him interested in starting some studies of this nature which we did at night because we did not tell John Flynn that we were doing this... The hypothesis was that based on Danny Freedman's finding that LSD raises the levels of serotonin but decreases its metabolites, I hypothesized that it might be inhibiting the firing of serotonergic neurons. The transmitter would build up and the metabolites would go down. We did the first experiment one night in winter of 1967, and the first experiment worked. Nine out of ten or ninety-five out of a hundred of my hypotheses do not pan out but that one did, so I became a confirmed electrophysiologist from that time," George Aghajanian said.*[14]

The Follow-Up: A Highly Specific and Direct Effect of Psychedelics

Over the next several years, Aghajanian and colleagues sought to determine how specific this effect was for classical psychedelics versus other classes of drugs. One early question was whether the effect of LSD on the midbrain raphe could be due to its stimulant action, as LSD has effects beyond its hallucinogenic properties. The contribution from the stimulant aspect was ruled out when they found that many raphe neurons increased firing after the injection of amphetamine (0.5–1 mg/kg).[15] Moreover, after testing a wider range of compounds, the specificity of this phenomenon was further supported, because *N,N*-dimethyltryptamine (DMT) and, to a lesser degree, 2-bromo-LSD, inhibited raphe units,[13] whereas atropine, scopolamine, phencyclidine, and chlorpromazine had no effect.[13]

How do psychedelics influence the firing of raphe neurons? The drugs may act directly on raphe neurons, or they may act on other brain regions to indirectly influence activity in the midbrain raphe. To distinguish between these possibilities, Aghajanian and colleagues made recordings using multibarreled micropipettes, which allowed them to load different barrels with different drugs, such that the compounds could be ejected in succession to test their effects on neural activity. In anesthetized rats, they used the microiontophoresis technique to locally apply LSD and found that raphe neurons reduced firing.[16] Interestingly, firing in the midbrain raphe was also suppressed by serotonin, and the inhibitory effects of LSD and serotonin

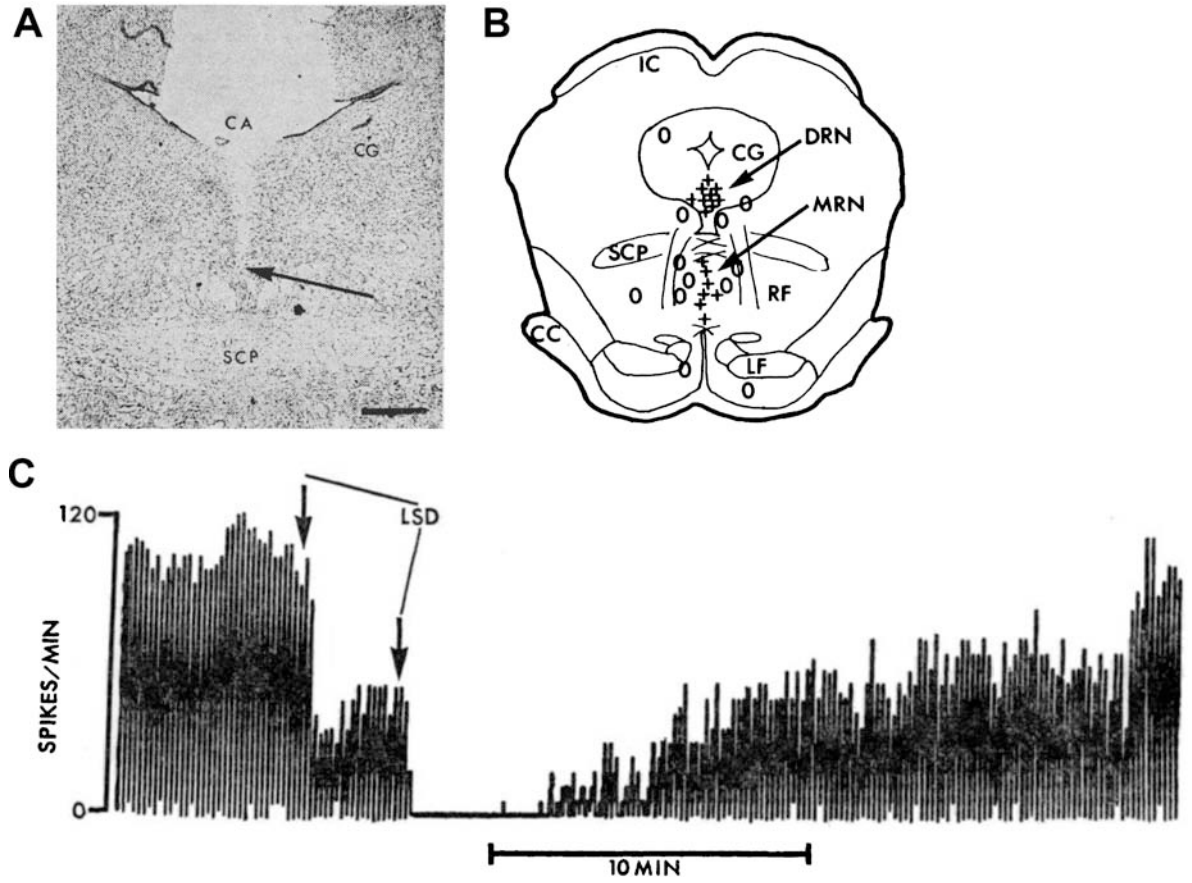

Fig. 1. LSD suppresses the firing of serotonergic neurons in the rat raphe. **(A)** Histology showing a tip of an electrode tract (arrow) in the midbrain raphe. Scale bar = 0.5 mm. **(B)** Summary of electrode site and unit response to LSD. +, sites at which units suppressed firing after LSD. 0, sites at which units did not respond or increased firing after LSD. **(C)** A single unit in the raphe responds to two doses of LSD (10 μg/kg i.v. and 5 μg/kg i.v.). Panels **(A)** and **(B)** are adapted from Aghajanian et al.[12] Panel **(C)** is adapted from Aghajanian et al.[13] CC, cerebral crus; CG, central gray; DRN, dorsal raphe nucleus; IC, inferior colliculus; LF, longitudinal fasciculus; LSD, *d*-lysergic acid diethylamide; MRN, median raphe nucleus; SCP, decussation of superior cerebellar peduncle.

were additive.[16] This clever experiment demonstrated unequivocally that the suppression of firing was due to the psychedelic's direct action on the midbrain raphe. Furthermore, the results indicated that LSD mimics serotonin, rather than acting as a purported "antimetabolite."

The microiontophoresis approach greatly increased the throughput of experiments because multiple drugs can be tested within a single preparation. Psilocin, DMT, and bufotenine were found to suppress the firing of raphe units,[17] as did 5-methoxytryptamine and 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT).[18] In contrast, 2-bromo-LSD, the nonhallucinogenic analog of LSD, failed to fully inhibit raphe unit firing when administered at similar doses.[19] These findings led Aghajanian and colleagues to write that "LSD and indoleamine hallucinogens such as psilocin and DMT produce their hallucinogenic effects by acting preferentially upon presynaptic 5-HT receptors located on or near the soma of serotonergic neurons in the raphe nuclei."[17] The hypothesis was that visual hallucinations may come from the loss of serotonergic signaling in the visual and limbic regions. Relatedly, it was speculated that the changes in raphe neuron activity might be a biomarker that can predict the hallucinogenic potency of a compound in humans.[18]

The Debate: Could the Dorsal Raphe Be the Trigger for Hallucinogenic Effects?

Barry Jacobs, who earned a doctoral degree in psychology from the University of California, Los Angeles, and completed a postdoctoral fellowship at Stanford University,

started his research career studying sleep and wakefulness, including recording unit activity from the amygdala of freely moving cats.[20] In 1972, he joined the Department of Psychology at Princeton University, where his interests expanded to psychedelics, perhaps in part due to the similarities between dreams and drug-induced hallucinations.[21] Until then, a major caveat of the studies was that all the data came from anesthetized or immobilized animals. The anesthetic typically used was chloral hydrate, which was shown to alter various physiological responses of serotonergic neurons.[22] To address this issue, Jacobs and colleagues developed the adult female cat as a model for studying the behavioral effects of psychoactive drugs. By testing the escalating doses of LSD from 10 to 100 μg/kg, they noted that the drug elicited behaviors such as limb flicking, abortive grooming, investigatory or play activity, and what was described as hallucinatory-like behavior that included visually tracking nonexistent objects or hissing and pouncing at imagined targets[23] (Fig. 2A).

When Jacobs and colleagues proceeded to record from the midbrain raphe in freely moving cats under the influence of LSD, they made several important observations.[25] First, the timing of neural and behavioral effects of LSD did not match. At a dose of 50 μg/kg, LSD-induced limb flicks persisted for over 8 h, whereas suppression of raphe activity lasted only about 3 h (Fig. 2B). Second, at lower doses, raphe unit activity had only a mild reduction, yet the cats still displayed substantial changes in behavior (Fig. 2B). Third, it was well known that psychedelics exhibit tolerance and cross-tolerance, where behavioral effects would diminish over repeated exposure to the drugs.[26] However, LSD continued to suppress raphe activity on the second day of dosing even when behavioral effects were greatly reduced (Fig. 2C). Similar dissociations between neural responses in the raphe and behavioral effects were observed with other psychedelics, including psilocin, 5-MeO-DMT, 2,5-dimethoxy-4-methylamphetamine (DOM), and mescaline in the freely moving cat model,[27,28] echoing earlier findings in rats.[29] By relating the drug-induced changes in neural activity with ongoing behavior, these results indicate that the alterations in the midbrain raphe are unlikely to underpin the acute subjective experience.

Although Jacobs and colleagues presented some of the most direct evidence challenging the serotonin hypothesis of psychedelic drug action, there were other studies in

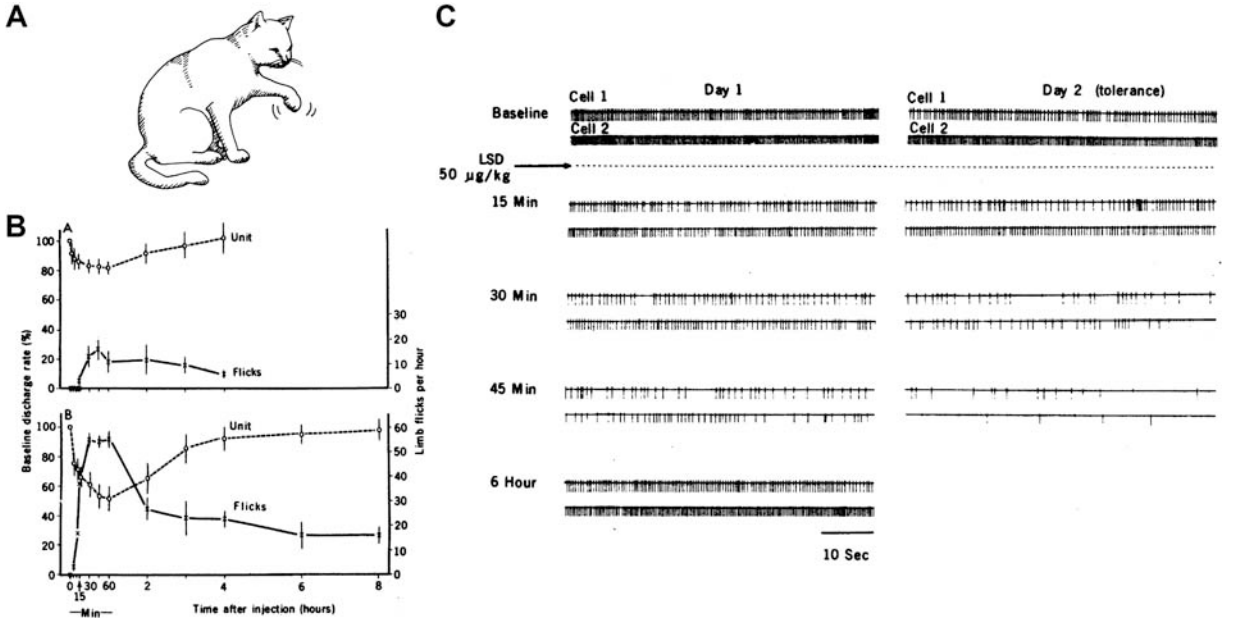

Fig. 2. Effects of LSD in the freely moving cats model argue against the serotonin hypothesis of psychedelic drug action. **(A)** Illustrations of the limb flick exhibited by cats acutely following LSD administration. **(B)** When a low dose of LSD was administered, limb flicks occurred despite only a modest decrease in unit activity in the raphe (top row). When a higher dose of LSD was administered, limb flicks remained elevated 6–8 h after injection, when the drug-induced suppression of raphe unit activity had mostly subsided (bottom row). **(C)** When LSD was administered on consecutive days, the drug elicited little to no behavior on the second dose but continued to robustly suppress unit activity in the raphe. Panel **(A)** is adapted from Jacobs and Trulson.[24] Panels **(B)** and **(C)** are adapted from Trulson and Jacobs.[25]

parallel that pointed in the same direction. For instance, if psychedelics exerted their acute behavioral effects through actions on the midbrain raphe, then ablation of serotonergic neurons or depletion of serotonin should render the drugs ineffective; however, empirical results did not support this prediction.[30,31] Taken together, it was becoming obvious that although the effect of psychedelics on the dorsal raphe was both pronounced and specific, this was not the primary driver of the acute subjective experience.

The Mechanism: 5-HT_{1A} Receptor on the Serotonergic Neurons

What is the receptor basis for psychedelics' effect in the midbrain raphe? It was known early that serotonin was highly effective at displacing radiolabeled LSD, suggesting that the target of the drug was a 5-HT receptor.[32] By the late 1970s, subtypes of serotonin receptors were identified, including what are now recognized as the 5-HT_1 and 5-HT_2 receptor families.[33] Radioligand binding studies revealed dense labeling of the 5-HT_{1A} receptor in the midbrain raphe.[34,35] Selective 5-HT_{1A} receptor agonists, such as buspirone and ipsapirone, were shown to produce dose-dependent suppression of dorsal raphe activity in anesthetized rats.[36–38] The advent of *in vitro* recording of dorsal raphe neurons in brain slices[39,40] allowed for further mechanistic studies, showing that 5-HT_{1A} receptor agonism causes downstream activation of an inwardly rectifying potassium conductance.[41,42] All the data converged to pinpoint the 5-HT_{1A} receptor as the target mediating the psychedelic-induced suppression of raphe activity.

In contrast, blockade of the 5-HT_{2A} receptor with ketanserin did not affect the suppressive effects of serotonin or LSD on raphe activity *in vivo*.[43,44] In parallel, accumulating evidence indicated that a compound's hallucinogenic potency correlates closely with its affinity for the 5-HT_{2A} receptor.[45] Further confirmation came when it was shown that pretreatment with 5-HT_{2A} receptor antagonists abolished the psychedelic's behavioral effects in the cat.[44] Years later, the same manipulation also worked to block the acute subjective experience in humans.[46] Together, these findings demonstrate that while the 5-HT_{2A} receptor is not essential for mediating drug effects in the dorsal and median raphe nuclei, it is critical for the acute subjective experience. Thus, at the receptor level, the evidence further reinforces that the hallucinogenic effect does not originate from the midbrain raphe.

The Pivot: Shifts in Research Directions

I am retelling discoveries that had also been chronicled by the investigators themselves, whose detailed accounts reflect the concepts, methods, and assumptions of their era.[47,48] "One difference between the way things were in the 60s when I got started and now—there were very little knowledge about brain systems at the time. It would take years for any finding to be developed and understood, but now things happen very quickly. . . In one way it makes me envious that the knowledge base is so much greater and the tools one has to work with are so much better than they were. One way that I would not be envious is, starting out now, have a tougher road with greater competition. There are so many more people in the field. When I was starting out, there was hardly anyone doing what I was doing. A young investigator comes up with some novel finding, and in no time at all, ten other labs would be doing it, and they may get lost in the shuffle," George Aghajanian remarked about research at that time.[14]

In the subsequent years, both George Aghajanian and Barry Jacobs shifted their research trajectories away from studying psychedelic drug action on the midbrain raphe. Aghajanian turned his attention to the 5-HT_{2A} receptor that underpins the acute subjective effects of psychedelics. His lab showed that LSD and 2,5-dimethoxy-4-iodoamphetamine (DOI) are partial agonists at cortical 5-HT_{2A} receptors.[49] Moreover, in the neocortex, psychedelics such as DOI can recruit synapses more broadly by increasing glutamate spillover,[50] enhance recurrent network activity,[51] and increase the levels of brain-derived neurotropic factor,[52] thereby providing an early hint that these compounds may promote neural plasticity. He would go on to find that serotonin increases excitatory postsynaptic currents in the apical dendrites of layer 5

Fig. 3. A portrait of George Aghajanian in the Aghajanian Library at the Connecticut Mental Health Center. The smaller photo in the lower right corner was George Aghajanian (right) with Ronald Duman (left) and Georgia Miller (center). The photo was taken by the author of this article.

pyramidal neurons via 5-HT_{2A} receptors[53] and then collaborated with Ron Duman to show that ketamine promotes structural neural plasticity in deep-layer pyramidal neurons[54] (Fig. 3). Jacobs, meanwhile, continued to study the midbrain raphe but broadened his scope to investigate how the activity of serotonergic neurons relates to physiological processes such as the sleep-wake cycle, morphine exposure, and auditory or visual stimuli. He eventually applied the same approach to dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus coeruleus.[55]

The Reappraisal: Current Knowledge and Future Directions

The original discovery has now been replicated with newer methods, showing up, for example, as psilocybin-induced decreases in immediate early gene expression in

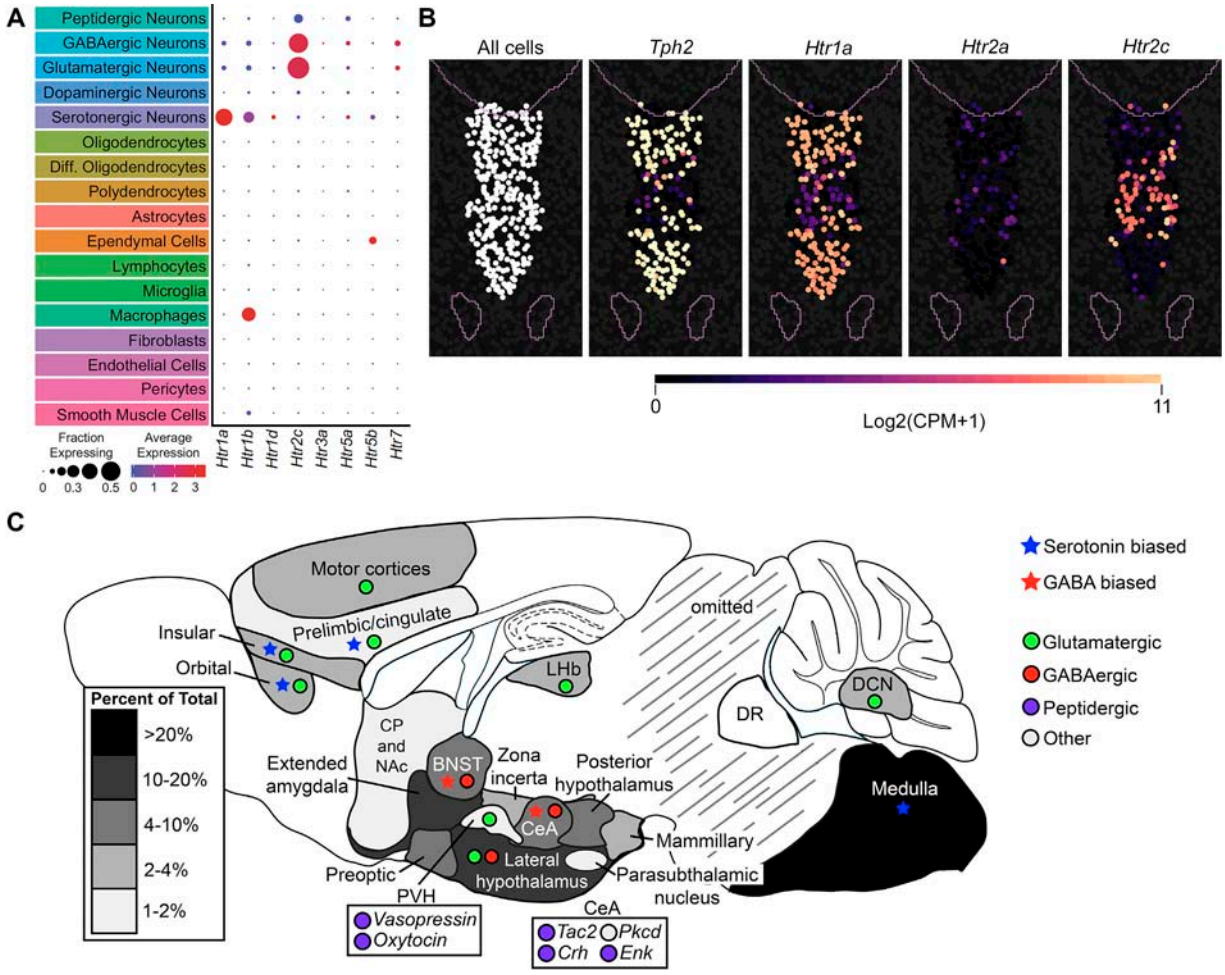

Fig. 4. Receptor expression and long-range inputs in the dorsal raphe. **(A)** Dot plot for the expression of genes encoding different subtypes of serotonin receptor in various cell classes in the mouse dorsal raphe. The color of each dot indicates the mean expression level. The size of each dot indicates the fraction of cells expressing the gene. **(B)** Spatial distribution of all cells in the mouse dorsal raphe, along with the transcript levels for *Tph2*, *Htr1a*, *Htr2a*, and *Htr2c* in the region. *Tph2* encodes tryptophan hydroxylase 2, a marker of serotonergic neurons. The visualizations were obtained from the publicly available data at the Allen Brain Cell Atlas. **(C)** This illustration shows regions that provide >1% of the total inputs to the mouse dorsal raphe, as determined by monosynaptic rabies viral tracing. The percentage of total input is color-coded in gray-scale. Stars indicate if the inputs were preferential for serotonergic or GABAergic neurons in the dorsal raphe. The circle indicates the neurotransmitters expressed by the input regions. Panel **(A)** is adapted from Huang et al.[63] Panel **(B)** is adapted from the data portal at Allen Institute based on Yao et al.[65] Panel **(C)** is adapted from Weissbourd et al.[66] CPM, counts per million.

the dorsal nucleus raphe and the central linear nucleus raphe.[56] In another example, psilocybin reduces the number of serotonergic neurons with spontaneous somatic calcium transients in the dorsal raphe nucleus of zebrafish.[57] The phenomenon and, more broadly, the action of psychedelics may be considered in light of current knowledge of serotonin biology.[58] Although early studies also examined several regions enriched in serotonergic innervations, such as the locus coeruleus[59] and facial motor nucleus,[60] many brain regions and cell types remain unexplored. How may the broader serotonergic system respond to psychedelics?

At the level of local circuits, the application of serotonin to the dorsal raphe produces inhibitory postsynaptic currents in serotonergic neurons,[61] implicating local GABAergic cells in the regulation of raphe activity. Advances in genomics and transcriptomics have clarified the full complement of 5-HT receptor subtypes[62] and revealed that serotonergic and GABAergic neurons in the mouse dorsal raphe preferentially express 5-HT_{1A} and 5-HT_{2C} receptors, respectively[63,64] (Fig. 4A). There are few *Htr2a* transcripts relative to *Htr1a* and *Htr2c* in the mouse dorsal raphe[65] (Fig. 4B). Comparable data from human tissue are currently lacking, and there may be species differences in the cell-type-specific expression of 5-HT receptor subtypes.[67] In terms of physiology, a selective 5-HT_{2C} receptor agonist was sufficient to inhibit the activity of serotonergic neurons, presumably by driving the local GABAergic cells.[68] However, follow-up work demonstrated that administration of LSD or DOI followed by a 5-HT_{2C} receptor antagonist did not prevent suppression of serotonergic units in the rat dorsal raphe, which instead persisted until a 5-HT_{1A} receptor antagonist was applied.[69] One very recent study likewise confirmed the role of 5-HT_{1A} receptors and further suggested that 5-HT_{2B} receptors may play a role.[70] These results remain in favor of the 5-HT_{1A} receptor being the dominant mechanism underlying psychedelic-induced suppression in the raphe, while bringing to light additional influences via the 5-HT_{2B} and 5-HT_{2C} receptors and local inhibitory interneurons. The complexity highlights the emerging appreciation of polypharmacology in psychedelic drug action.[71] Understanding the convergent effects arising from the interactions among different serotonin receptors is an important area for future investigation.[72]

At the level of long-range circuits, serotonergic and GABAergic neurons in the dorsal raphe receive inputs from various cortical and subcortical regions[66,73,74] (Fig. 4C). On the output side, serotonergic neurons are not a homogeneous population, but can be divided into subsystems with distinct projection targets that subserve different behavioral functions.[75] It will be fruitful to revisit how psychedelics act in the dorsal raphe, given the latest understanding of the serotonergic system. A key open question is whether psychedelics may induce lasting plasticity in the local and long-range circuits organized around the dorsal raphe. Psychedelics such as psilocybin can induce persistent structural plasticity in other brain regions such as the medial frontal cortex.[76,77] Given the pronounced acute effects of psychedelics on dorsal raphe activity, it is plausible that plasticity also occurs within the serotonergic system, though precisely how it manifests remains to be determined.

Epilogue

Looking back, the story is as much about the evolution of systems neuroscience as it is about psychedelic drug action. What started in the late 1960s as an idea for testing how LSD alters the firing of serotonergic neurons has grown into a rich framework for understanding the receptor, cellular, and circuit mechanisms of psychedelic drug action.[78] While the field have transitioned from single-unit recordings to more sophisticated methods like high-density electrophysiology, cellular-resolution optical imaging, and molecular and genetic tools, we continue to ask similar questions that motivated George Aghajanian, Barry Jacobs, and their contemporaries. Once a starting point for curiosity, the midbrain raphe may yet reemerge as a vital node in our pursuit to understand the acute and long-term effects of psychedelics on neural circuits in the brain.

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Authors' Contributions

A.C.K.: Writing—original draft, review and editing.

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References

1. Whitaker-Azmitia PM. The discovery of serotonin and its role in neuroscience. Neuropsychopharmacology 1999;21(2 Suppl):2S–8S; doi: 10.1016/S0893-133X(99)00031-7
2. Rapport MM. Serum vasoconstrictor (serotonin) the presence of creatinine in the complex; a proposed structure of the vasoconstrictor principle. J Biol Chem 1949;180(3):961–969; doi: 10.1016/s0021-9258(19)51208-X
3. Twarog BM, Page IH. Serotonin content of some mammalian tissues and urine and a method for its determination. Am J Physiol 1953;175(1):157–161; doi: 10.1152/ajplegacy.1953.175.1.157

4. Gaddum JH, Hameed KA. Drugs which antagonize 5-hydroxytryptamine. Br J Pharmacol Chemother 1954;9(2):240–248; doi: 10.1111/j.1476-5381.1954.tb00848.x
5. Woolley DW, Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. Proc Natl Acad Sci U S A 1954;40(4):228–231.
6. Shaw E, Woolley DW. Some serotoninlike activities of lysergic acid diethylamide. Science 1956;124(3212):121–122; doi: 10.1126/science.124.3212.121
7. Freedman DX. Effects of LSD-25 on Brain Serotonin. J Pharmacol Exp Ther 1961;134(2):160–166; doi: 10.1016/s0022-3565(25)26146-8
8. Rosecrans JA, Lovell RA, Freedman DX. Effects of lysergic acid diethylamide on the metabolism of brain 5-hydroxytryptamine. Biochem Pharmacol 1967;16(10):2011–2021; doi: 10.1016/0006-2952(67)90313-9
9. Dahlstrom A, Fuxe K. Evidence for the existence of monoamine-containing neurons in the central nervous system. Acta Physiol Scand 1965;62(232):1–55; doi: 10.1111/j.1748-1716.1964.tb04028.x
10. Freedman DX, Aghajanian GK, Ornitz EM. Patterns of tolerance to lysergic acid diethylamide and mescaline in rats. Science 1958;127(3307):1173–1174; doi: 10.1126/science.127.3307.1173
11. Lambe EK. George Aghajanian (1932–2023). Nat Neurosci 2023;26(12):2046–2047; doi: 10.1038/s41593-023-01502-5
12. Aghajanian GK, Foote WE, Sheard MH. Lysergic acid diethylamide: Sensitive neuronal units in the midbrain raphe. Science 1968;161(3842):706–708; doi: 10.1126/science.161.3842.706
13. Aghajanian GK, Foote WE, Sheard MH. Action of psychotogenic drugs on single midbrain raphe neurons. J Pharmacol Exp Ther 1970;171(2):178–187.
14. Hollister L, Ban TA. An Oral History of Neuropsychopharmacology: The First Fifty Years, Peer Interviews Volume Two: Neurophysiology. American College of Neuropsychopharmacology; 2011.
15. Foote WE, Sheard MH, Aghajanian GK. Comparison of effects of LSD and amphetamine on midbrain raphe units. Nature 1969;222(5193):567–569; doi: 10.1038/222567a0
16. Aghajanian GK, Haigler HJ, Bloom FE. Lysergic acid diethylamide and serotonin: Direct actions on serotonin-containing neurons in rat brain. Life Sci I 1972;11(13):615–622; doi: 10.1016/0024-3205(72)90153-1
17. Aghajanian GK, Hailgler HJ. Hallucinogenic indoleamines: Preferential action upon presynaptic serotonin receptors. Psychopharmacol Commun 1975;1(6):619–629.
18. de Montigny C, Aghajanian GK. Preferential action of 5-methoxytryptamine and 5-methoxydimethyltryptamine on presynaptic serotonin receptors—Comparative iontophoretic study with Lsd and serotonin. Neuropharmacology 1977;16(12):811–818; doi: 10.1016/0028-3908(77)90142-3
19. Aghajanian GK. LSD and 2-bromo-LSD: Comparison on effects on serotonergic neurones and on neurones in two serotonergic projection areas, the ventral lateral geniculate and amygdala. Neuropharmacology 1976;15(9):521–528; doi: 10.1016/0028-3908(76)90102-7
20. Jacobs BL, McGinty DJ. Amygdala unit activity during sleep and waking. Exp Neurol 1971;33(1):1–15; doi: 10.1016/0014-4886(71)90097-5
21. Jacobs BL. Dreams and hallucinations - common neurochemical mechanism mediating their phenomenological similarities. Neurosci Biobehav R 1978;2(1):59–69; doi: 10.1016/0149-7634(78)90007-6
22. Heym J, Steinfels GF, Jacobs BL. Chloral hydrate anesthesia alters the responsiveness of central serotonergic neurons in the cat. Brain Res 1984;291(1):63–72; doi: 10.1016/0006-8993(84)90651-6
23. Jacobs BL, Trulson ME, Stern WC. An animal behavior model for studying the actions of LSD and related hallucinogens. Science 1976;194(4266):741–743; doi: 10.1126/science.982043
24. Jacobs BL, Trulson ME. Mechanisms of action of LSD. Am Sci 1979;67(4):396–404.
25. Trulson ME, Jacobs BL. Dissociations between the effects of LSD on behavior and raphe unit activity in freely moving cats. Science 1979;205(4405):515–518; doi: 10.1126/science.451617
26. Appel JB, Freedman DX. Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia 1968;13(3):267–274; doi: 10.1007/BF00401404
27. Trulson ME, Jacobs BL. Effects of 5-methoxy-N,N-dimethyltryptamine on behavior and raphe unit activity in freely moving cats. Eur J Pharmacol 1979;54(1–2):43–50; doi: 10.1016/0014-2999(79)90406-0
28. Trulson ME, Heym J, Jacobs BL. Dissociations between the effects of hallucinogenic drugs on behavior and raphe unit activity in freely moving cats. Brain Res 1981;215(1–2):275–293; doi: 10.1016/0006-8993(81)90507-2
29. Trulson ME, Ross CA, Jacobs BL. Lack of tolerance to the depression of raphe unit activity by lysergic acid diethylamide. Neuropharmacology 1977;16(11):771–774; doi: 10.1016/0028-3908(77)90135-6
30. Appel JB, Lovell RA, Freedman DX. Alterations in the behavioral effects of LSD by pretreatment with para-chlorophenylalanine and alpha-methyl-para-tyrosine. Psychopharmacologia 1970;18(4):387–406; doi: 10.1007/BF00402765
31. Appel J, Sheard M, Freedman D. Alterations in the behavioral effects of LSD by midbrain raphe lesions. Commun Behav Biol Part A 1970;5:237–241.
32. Farrow JT, Van Vunakis H. Binding of d-lysergic acid diethylamide to subcellular fractions from rat brain. Nature 1972;237(5351):164–166; doi: 10.1038/237164a0
33. Peroutka SJ, Snyder SH. Multiple serotonin receptors: Differential binding of [3H]5-hydroxytryptamine, [3H]lysergic acid diethylamide and [3H] Spiroperidol. Mol Pharmacol 1979;16(3):687–699; doi: 10.1016/s0026-895x(25)13812-1
34. Marcinkiewicz M, Verge D, Gozlan H, et al. Autoradiographic evidence for the heterogeneity of 5-HT1 sites in the rat brain. Brain Res 1984;291(1):159–163; doi: 10.1016/0006-8993(84)90664-4
35. Pazos A, Palacios JM. Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 1985;346(2):205–230; doi: 10.1016/0006-8993(85)90856-x
36. VanderMaelen CP, Matheson GK, Wilderman RC, et al. Inhibition of serotonergic dorsal raphe neurons by systemic and iontophoretic administration of buspirone, a non-benzodiazepine anxiolytic drug. Eur J Pharmacol 1986;129(1–2):123–130; doi: 10.1016/0014-2999(86)90343-2
37. Sprouse JS, Aghajanian GK. Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT1A and 5-HT1B agonists. Synapse 1987;1(1):3–9; doi: 10.1002/syn.890010103
38. Sprouse JS, Aghajanian GK. (-)-Propranolol blocks the inhibition of serotonergic dorsal raphe cell firing by 5-HT1A selective agonists. Eur J Pharmacol 1986;128(3):295–298; doi: 10.1016/0014-2999(86)90782-x
39. Mosko SS, Jacobs BL. Recording of dorsal raphe unit activity *in vitro*. Neurosci Lett 1976;2(4):195–200; doi: 10.1016/0304-3940(76)90014-8
40. VanderMaelen CP, Aghajanian GK. Electrophysiological and pharmacological characterization of serotonergic dorsal raphe neurons recorded extracellularly and intracellularly in rat brain slices. Brain Res 1983;289(1–2):109–119; doi: 10.1016/0006-8993(83)90011-2
41. Aghajanian GK, Lakoski JM. Hyperpolarization of serotonergic neurons by serotonin and LSD—studies in brain-slices showing increased K+ conductance. Brain Res 1984;305(1):181–185; doi: 10.1016/0006-8993(84)91137-5
42. Williams JT, Colmers WF, Pan ZZ. Voltage- and ligand-activated inwardly rectifying currents in dorsal raphe neurons in vitro. J Neurosci 1988;8(9):3499–3506; doi: 10.1523/JNEUROSCI.08-09-03499.1988
43. Lakoski JM, Aghajanian GK. Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. Neuropharmacology 1985;24(4):265–273; doi: 10.1016/0028-3908(85)90130-3
44. Heym J, Rasmussen K, Jacobs BL. Some behavioral effects of hallucinogens are mediated by a postsynaptic serotonergic action: Evidence from single unit studies in freely moving cats. Eur J Pharmacol 1984;101(1–2):57–68; doi: 10.1016/0014-2999(84)90030-x
45. Glennon RA, Titeler M, McKenney JD. Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 1984;35(25):2505–2511; doi: 10.1016/0024-3205(84)90436-3
46. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, et al. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 1998;9(17):3897–3902; doi: 10.1097/00001756-199812010-00024
47. Jacobs BL, Heym J, Rasmussen K. Action of hallucinogenic drugs at postsynaptic serotonergic receptors. Psychopharmacol Bull 1982;18(3):168–172.
48. Aghajanian GK, Marek GJ. Serotonin and hallucinogens. Neuropsychopharmacology 1999;21(2 Suppl):16S–23S; doi: 10.1016/S0893-133X(98)00135-3
49. Marek GJ, Aghajanian GK. LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT2A receptors on interneurons in rat piriform cortex. J Pharmacol Exp Ther 1996;278(3):1373–1382.
50. Lambe EK, Aghajanian GK. Hallucinogen-induced UP states in the brain slice of rat prefrontal cortex: Role of glutamate spillover and NR2B-NMDA receptors. Neuropsychopharmacology 2006;31(8):1682–1689; doi: 10.1038/sj.npp.1300944

51. Lambe EK, Aghajanian GK. Prefrontal cortical network activity: Opposite effects of psychedelic hallucinogens and D1/D5 dopamine receptor activation. Neuroscience 2007;145(3):900–910; doi: 10.1016/j.neuroscience.2006.12.048
52. Vaidya VA, Marek GJ, Aghajanian GK, et al. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J Neurosci 1997;17(8):2785–2795.
53. Aghajanian GK, Marek GJ. Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology 1997;36(4–5):589–599; doi: 10.1016/s0028-3908(97)00051-8
54. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010;329(5994):959–964; doi: 10.1126/science.1190287
55. Jacobs BL, Fornal CA. Activity of serotonergic neurons in behaving animals. Neuropsychopharmacology 1999;21(2 Suppl):9S–15S; doi: 10.1016/S0893-133X(99)00012-3
56. Davoudian PA, Shao LX, Kwan AC. Shared and distinct brain regions targeted for immediate early gene expression by ketamine and psilocybin. ACS Chem Neurosci 2023;14(3):468–480; doi: 10.1021/acschemneuro.2c00637
57. Braun D, Rosenberg AM, Rabaniam E, et al. High-resolution tracking of unconfined zebrafish behavior reveals stimulatory and anxiolytic effects of psilocybin. Mol Psychiatry 2024;29(4):1046–1062; doi: 10.1038/s41380-023-02391-7
58. Ligneul R, Mainen ZF. Serotonin. Curr Biol 2023;33(23):R1216–R1221; doi: 10.1016/j.cub.2023.09.068
59. Rasmussen K, Aghajanian GK. Effect of hallucinogens on spontaneous and sensory-evoked locus coeruleus unit activity in the rat: Reversal by selective 5-HT2 antagonists. Brain Res 1986;385(2):395–400; doi: 10.1016/0006-8993(86)91090-5
60. McCall RB, Aghajanian GK. Hallucinogens potentiate responses to serotonin and norepinephrine in the facial motor nucleus. Life Sci 1980;26(14):1149–1156; doi: 10.1016/0024-3205(80)90654-2
61. Pan ZZ, Colmers WF, Williams JT. 5-HT-mediated synaptic potentials in the dorsal raphe nucleus: Interactions with excitatory amino acid and GABA neurotransmission. J Neurophysiol 1989;62(2):481–486; doi: 10.1152/jn.1989.62.2.481
62. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71(4):533–554; doi: 10.1016/s0091-3057(01)00746-8
63. Huang KW, Ochandarena NE, Philson AC, et al. Molecular and anatomical organization of the dorsal raphe nucleus. Elife 2019;8:e46464; doi: 10.7554/eLife.46464
64. Ren J, Isakova A, Friedmann D, et al. Single-cell transcriptomes and whole-brain projections of serotonin neurons in the mouse dorsal and median raphe nuclei. Elife 2019;8:e49424; doi: 10.7554/eLife.49424
65. Yao Z, van Velthoven CTJ, Kunst M, et al. A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. Nature 2023;624(7991):317–332; doi: 10.1038/s41586-023-06812-z
66. Weissbourd B, Ren J, DeLoach KE, et al. Presynaptic partners of dorsal raphe serotonergic and GABAergic neurons. Neuron 2014;83(3):645–662; doi: 10.1016/j.neuron.2014.06.024
67. Krienen FM, Goldman M, Zhang Q, et al. Innovations present in the primate interneuron repertoire. Nature 2020;586(7828):262–269; doi: 10.1038/s41586-020-2781-z
68. Boothman L, Raley J, Denk F, et al. In vivo evidence that 5-HT(2C) receptors inhibit 5-HT neuronal activity via a GABAergic mechanism. Br J Pharmacol 2006;149(7):861–869; doi: 10.1038/sj.bjp.0706935
69. Queree P, Peters S, Sharp T. Further pharmacological characterization of 5-HT(2C) receptor agonist-induced inhibition of 5-HT neuronal activity in the dorsal raphe nucleus in vivo. British J Pharmacology 2009;158(6):1477–1485; doi: 10.1111/j.1476-5381.2009.00406.x
70. Bouloufa A, Delcourte S, Rovera R, et al. LSD's rapid antidepressant effects are modulated by 5-HT(2B) receptors. Biomed Pharmacother 2025;190:118348; doi: 10.1016/j.biopha.2025.118348
71. Jain MK, Gumpper RH, Slocum ST, et al. The polypharmacology of psychedelics reveals multiple targets for potential therapeutics. Neuron 2025;113(19):3129–3142.e9; doi: 10.1016/j.neuron.2025.06.012
72. Savalia NK, Shao LX, Kwan AC. A dendrite-focused framework for understanding the actions of ketamine and psychedelics. Trends Neurosci 2021;44(4):260–275; doi: 10.1016/j.tins.2020.11.008
73. Ogawa SK, Cohen JY, Hwang D, et al. Organization of monosynaptic inputs to the serotonin and dopamine neuromodulatory systems. Cell Rep 2014;8(4):1105–1118; doi: 10.1016/j.celrep.2014.06.042
74. Pollak Dorocic I, Furth D, Xuan Y, et al. A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. Neuron 2014;83(3):663–678; doi: 10.1016/j.neuron.2014.07.002
75. Ren J, Friedmann D, Xiong J, et al. Anatomically defined and functionally distinct dorsal raphe serotonin sub-systems. Cell 2018;175(2):472–487.e20; doi: 10.1016/j.cell.2018.07.043
76. Shao LX, Liao C, Gregg I, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron 2021;109(16):2535–2544.e4; doi: 10.1016/j.neuron.2021.06.008
77. Shao LX, Liao C, Davoudian PA, et al. Psilocybin's lasting action requires pyramidal cell types and 5-HT(2A) receptors. Nature 2025;642(8067):411–420; doi: 10.1038/s41586-025-08813-6
78. Kwan AC, Olson DE, Preller KH, et al. The neural basis of psychedelic action. Nat Neurosci 2022;25(11):1407–1419; doi: 10.1038/s41593-022-01177-4