water within its clay caves. Did life on Mars, if it existed, do the same?

Why is Cuatro Ciénegas endangered? Can it be saved? Humans, just like any life form, need water — especially fresh water in the desert. Rock art in the Sierras around CCB show that hunter-gatherers of the past considered water sacred and, therefore, the basin and its wetlands were also sacred, allowing all kinds of life to thrive. The town of Cuatro Ciénegas was established in the early nineteenth century, and early residents began to divert water from the springs into channels in order to dry out the wetland to allow planting of grapes, pecan trees, and wheat, among other European plants. The town grew, degrading the wetland in the process with a web of channels that exported water to the east, outside the basin. However, it was in the 1970s when technology, relocation of people (ejidatarios), water rights, and a federal mandate to transform the desert into 'a green Eden' by flooding really signed the death sentence for the wetland. Today, 95% of the remaining superficial water from CCB is exported by canal to different ranches, some of them as far as 80 km to the east of the basin. To add to this ecocide, many deep wells have been drilled to irrigate alfalfa (for cattle) within the basin and in the nearby valleys to the south and north, which share a connected deep aquifer. An important part of our work — starting in October 2002, when a dramatic increase in alfalfa cultivation was planned by the Coahuila government in the Hundido valley to the south — has been, on one side, to stop or at least slow the ecological disaster, and, from the other side, to describe as fast as possible all the biological diversity of this amazing but dying basin before it disappears due to overexploitation of the aquifer.

In 2003, with the molecular evidence of connections between valleys, we started a long battle between scientists and milk producers within Coahuila. We were fortunate that the Mexican national media sided with us and helped at this stage. In 2004, in a local scientific meeting at Cuatro Ciénegas town hall, teachers from the local high school approached us and we vowed to involve their students and teachers in our research program. It was a priceless opportunity; education is the only way to change the future of the CCB wetland. The public outcry against dairy giants in Torreón grew, and some of them decided not to use alfalfa grown with CCB water. Since 2007, Fundación LALA has paid for a long-term educational program through art, directed to K–6 children, and in 2011 along with Fundación Slim, they built a molecular lab in the Cuatro Ciénegas high school. This investment in education has paid off, as CCB has served as a place for intense scientific discovery and training for a large community. This small town now has a science museum and another lab to conduct bioprospection and training of young people in molecular biology.

We believe that the local owners of the land and water rights in the CCB should actively fight to protect the water and the future of the ecosystem. Along with national and international scientific and public support we may yet help to preserve the most diverse oasis of the world, whose destruction would represent a tragic loss for humanity and the biodiversity legacy of our planet.

Where can I find out more?

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Primer

Serotonin

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Serotonin, also known as 5-hydroxytryptamine or 5-HT, is a neuromodulator widely recognized for its role in various psychoactive drugs. These drugs can exhibit antidepressant, antipsychotic, anxiolytic, empathogenic, or psychedelic effects, depending on their specific interactions with the serotonin system as well as other neuromodulators such as noradrenaline, dopamine, and oxytocin. This has led to a widespread belief that the neurochemical processes taking place deep inside our brains affect our subjective experiences and mental health. However, a scientific understanding of how neuromodulators' functions relate to drug effects remains elusive.

Research has confirmed that naturally occurring serotonin plays crucial roles in cognition and a range of adaptive processes, from homeostasis to reproduction. But it has also underscored our struggle to fully comprehend the complexities of serotonin signaling and to integrate observations made at different levels of analysis. The diverse and multi-scale influence of serotonin on brain function made theories of serotonin function particularly difficult to construct.

Recently, the advent of transgenic animal models, viral vectors, and genetically encoded optical tools — such as calcium indicators, opsins, and biosensors — has sparked new optimism about the potential for progress in understanding what serotonin does in the brain. These tools allow researchers to record and manipulate serotonin neurons with unprecedented precision. To truly advance our understanding, however, this new wave of discoveries must consider the decades of research that have shaped our current comprehension of brain serotonin, and this is what we will attempt to do, concisely, in this primer.

Physiology and neuroanatomy

Serotonin is believed to play crucial roles in the behavior of all animal

species from worms to humans. However, its biological functions extend far beyond the nervous system. Serotonin is found in high concentrations in plants, where it contributes to development, photosynthesis, and stress responses. In mammals, 90 to 95% of serotonin is produced in the digestive system, where it regulates inflammatory and immune responses to various stimuli. In fact, Vittorio Erspamer discovered serotonin in gut enterochromaffin cells in 1935; and the term serotonin (derived from 'serum' and 'tonic') was first coined in 1948, by Maurice Rapport and colleagues, to describe the molecule's potent vasoconstrictive effects. Because of the blood–brain barrier's isolating role, central and peripheral serotonin are typically thought of as two separate systems that are controlled separately. However, a growing body of research on brain interactions with the digestive and immune systems highlights the importance of pathways connecting peripheral serotonin with cognition and behavior. Also notable is the fact that blood vessels express serotonin receptors, which further contribute to the indirect effects of peripheral serotonin on brain function by controlling blood flow.

In mammals, the neurons that produce the brain's serotonin are localized to nine tiny brain stem nuclei and similarly distributed patterns are observed among the vertebrate taxa such as fishes and birds. But serotonin neurons have incredibly wide axonal projections that enable them to communicate with almost the entire brain (Figure 1A). Three of these nuclei, B1, B2 and B3, transmit signals to the spinal cord and medulla, where they regulate bodily functions like breathing, movement, body temperature and the sleep–wake cycle. The B4 and B9 nuclei are small and mostly project within the surrounding brain stem structures; their purpose is still not well understood. Most serotonin neurons that project to the forebrain are found in the remaining nuclei. Even though they only have about 12,000–15,000 cells in mice and 150,000–250,000 in humans, the impressive axonal arborizations of the median raphe nuclei (MRN, B5 and B8) and dorsal raphe nuclei (DRN, B6 and B7) connect to most brain structures, and even reach sensory

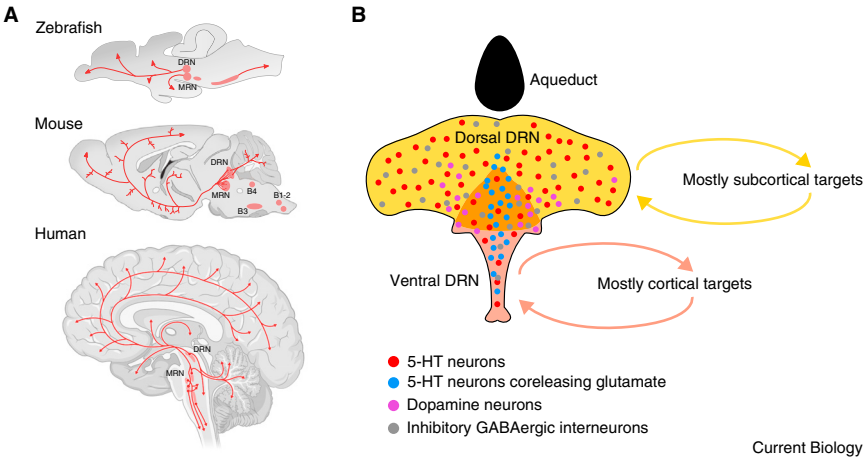

Figure 1. The neuroanatomy of the serotonin system.
(A) The serotonin system's anatomy is highly conserved across vertebrate taxa. For instance, the zebrafish and the mouse possess structures that are homologous to the human dorsal raphe (DRN) and median raphe (MRN) nuclei. (B) Numerous cortical and subcortical regions are interconnected with the DRN. Ventral DRN projects preferentially to cortical regions and displays opposite responses to rewards and punishments where the dorsal DRN projects preferentially to subcortical regions and responds positively to both types of reinforcers. Furthermore, serotonin neurons are most often interspersed with other neuronal populations such as dopamine neurons and inhibitory interneurons.

neurons in the retina and cochlea. Anatomical studies indicate that the DRN innervates more densely the basal ganglia and the cortex, whereas the MRN innervates more densely the hippocampus. Furthermore, it appears that the DRN innervates more lateral regions than the MRN, which tends to project to structures closer to the midline. The DRN may additionally be subdivided into at least two subsystems that project preferentially to cortical or subcortical regions and respond inversely to aversive stimuli (Figure 1B).

As a result of these extensive projection patterns, serotonin, like other monoamines such as dopamine and noradrenaline, can modulate neural activity within large portions of the forebrain. The neuroanatomical breadth and neurochemical diversity of the serotonin system have inspired the analogy of serotonin as an orchestra conductor, coordinating the activity of numerous instruments and fostering a coherent collective output. Any region that is 'listening', or whose cells have the appropriate receptors, receives and interprets messages sent via serotonin. Because different receptor types are localized to distinct brain regions and cell types, each neural circuit is capable of tuning into distinct components of the serotonin signal.

The two nuclei projecting to the forebrain, DRN and MRN, receive a substantial amount of ascending and descending input. Ascending projections send pain, temperature, and other interoceptive and exteroceptive signals; for example, the DRN gets a direct projection from the retina. Descending projections from cortical and subcortical regions — like the frontal cortex, amygdala, habenula and so on — send contextual information. There are also important connections between serotonin-producing nuclei and other monoamine-producing nuclei, like the noradrenergic locus coeruleus and the dopaminergic ventral tegmental area. However, little is understood about the input–output transformations that take place within each serotonin-releasing nucleus or the ways in which feedback within the raphe itself limits and controls the activity of serotonin neurons. One emerging idea, however, is that serotonin neurons frequently create functional loops by feeding back on the same input-producing target regions.

From serotonin neuron activation to serotonin release

The variables affecting the serotonin neurons' firing rates were unclear for a very long time. Early electrophysiological studies had

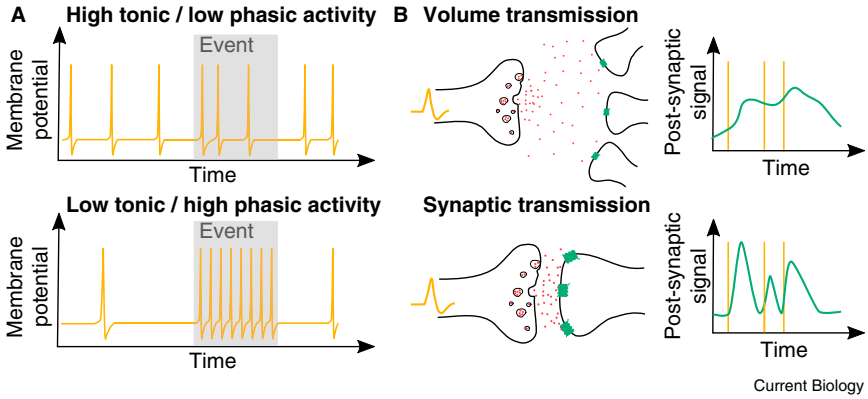

Figure 2. The electrophysiology of the brain's serotonin system.
(A) Serotonin neurons exhibit two firing modes: a tonic mode with stimulus-independent, slow clock-like firing rates, and an irregular phasic mode with burst-like responses to events. (B) Once released, serotonin can reach its postsynaptic targets via either synaptic or volume transmission. Since volume transmission acts as a low-pass filter, it can transform discrete signals such as prediction errors into slowly varying contextual variables such as uncertainty.

revealed the existence of a highly regular, clock-like firing pattern in the DRN, frequently referred to as tonic activity. This activity is characterized by slow temporal fluctuations that accompany and control arousal, stress, and sleep–wake cycles. In recent years, however, optogenetics and calcium imaging have allowed for the manipulation and measurement of endogenous serotonin activity with previously unheard-of specificity and precision. An important discovery was that salient external events also activate serotonin neurons on short timescales, resulting in bursts of activity whose functions are still unclear (Figure 2A).

Electrophysiological recordings revealed that time-locked bursts of activity convey a wide variety of signals, including not only signals of aversive, appetitive and other salient sensory stimuli but also signals related to prediction errors, task engagement, and novelty. Basal firing activity may reflect additional information such as motivational valence or uncertainty. In a comprehensive study in zebrafish and mice, Oikonomou *et al*. (2019) found that these two firing regimes have opposite effects on wakefulness. A functional separation of tonic and phasic activity could explain why pharmacological challenges (which mostly affect tonic signaling) and imaging or optogenetic approaches (which mostly look at phasic signaling) come up with different results. Specifically, it may help to explain why proserotonergic drugs, which act over long time scales, can act as mood enhancers, even while serotonin neurons respond transiently to aversive events.

Following release by axonal buttons, serotonin may reach its postsynaptic targets through point-to-point synaptic contacts or diffusely through volume transmission. Synaptic transmission is prominent on inputs to local inhibitory interneurons in the cortex, via the 5-HT3a receptor, whereas volume transmission is more common in contacts on excitatory neurons in the cortex and in subcortical structures. Because volume transmission acts as a low-pass temporal filter on the information carried by spikes, these two ways of sending information are likely to shape the time course of the signals that are passed through (Figure 2B). The enzyme monoamine oxidase A (MAO-A), which breaks down serotonin, and the serotonin transporter (SERT), which helps neurons and astrocytes take back serotonin, are two important proteins that tightly control the levels of serotonin in the brain (which are low compared to the levels of other neuromodulators like dopamine). The neurobehavioral correlates of frequent polymorphisms in the gene that codes for SERT have drawn much attention because they are linked to fear and anxiety, among other phenotypic differences.

Lastly, serotonin signaling in the brain is dependent on the bioavailability of its sole precursor, tryptophan (Figure 3A). Tryptophan is the least frequently occurring essential amino acid in mammals, and due to diet and metabolism, its blood levels can change significantly in a short period of time. Neuroscientists can use this feature to lower serotonin turnover in the brain and track the effects of this manipulation by using tryptophan-free amino acid drinks. Thus, the metabolism of tryptophan is thought to affect intra- and inter-individual variation in brain function. For instance, lower levels of tryptophan have been linked to increased impulsivity, altered social cognition, and acute depressive relapse.

Post-synaptic signaling and pharmacology

Different species have different numbers of subtypes of serotonin receptors. In humans, there are at least 16. There are three main families that have different effects on membrane potentials: the type 1 family (e.g. 5HT1a and b) are G-protein-coupled receptors (GPCRs) with slow inhibitory effects. The type 2 family (5HT2a, b, and c) are also GPCRs but have excitatory effects. These two families, through their metabotropic effects, can have long-lasting effects on gene expression, plasticity, and neural excitability. In contrast, the type 3 family (Figure 3B) is an ionotropic receptor with very rapid excitatory effects, comparable to ionotropic glutamate receptors. Within the type 1 and type 2 domains, functional opponency — for example, 5HT2a *versus* 5HT2c, 5HT2a *versus* 5HT1a — appears to be a crucial aspect of how the serotonin system performs its regulatory functions. Four additional receptor families (5HT4 to 5HT7) have been identified in humans, but their roles in brain function are less well understood.

Different receptors are expressed in distinct cell types and regions, but most receptor families are widely expressed in neurons, glia, and vascular tissue, both centrally and peripherally. In addition, it is not uncommon for a single neuronal population to express two or more subtypes of serotonin receptors. For example, serotonin neurons themselves have both somatodendritic and axonal 5HT1a and 5HT1b receptors. These two types of inhibitory autoreceptors are involved in different negative feedback loops. As

another example, excitatory neocortical neurons have both inhibitory 5HT1a receptors and excitatory 5HT2a receptors. This intricate pattern of receptors suggests that the release of serotonin interacts with local circuits to produce precise regulation of local circuit dynamics. For example, in the olfactory system activation of serotonin inputs can preferentially inhibit spontaneous neuronal activity but not sensory-driven activity.

Serotonin receptors emerged early as important therapeutic targets for a variety of psychiatric and neurological disorders (Figure 3B) and at this time, every year, hundreds of millions of patients around the world are prescribed antidepressant, anxiolytic, antipsychotic, anticonvulsant, and anti-migraine drugs that modulate various aspects of serotonin signaling. Besides receptors, important serotonergic therapeutic targets include MAO-A and serotonin's transmembrane and vesicular transporters (SERT and VMAT). An estimated one in eight Americans currently takes selective serotonin reuptake inhibitors (SSRIs). Although their neurochemical properties are relatively well understood, it remains unclear how SSRIs improve mood and why they do so only in a subset of patients. Studies show that the effects of SSRIs might be caused not by a simple rise in baseline serotonin levels, but also by changes in neural plasticity, gene expression, and serotonin release. In addition, newer generation antidepressants typically have a mixed pharmacological profile, acting as agonists or antagonists of specific receptors or inhibiting the reuptake of other neuromodulators such as noradrenaline.

Well before it became famous as the target of antidepressants, the serotonin system was identified as the target of a drug with potent psychoactive effects, lysergic acid diethylamide (LSD-25). LSD is synthetic but belongs to a class of molecules that also includes naturally occurring compounds such as psilocybin, mescaline, and N,N-dimethyltryptamine (DMT), which all share related psychoactive effects and a selectivity for the 5HT2a receptor. Early research and clinical studies indicated that the ability of this class of molecules, dubbed "psychedelics", not only occasion profound subjective

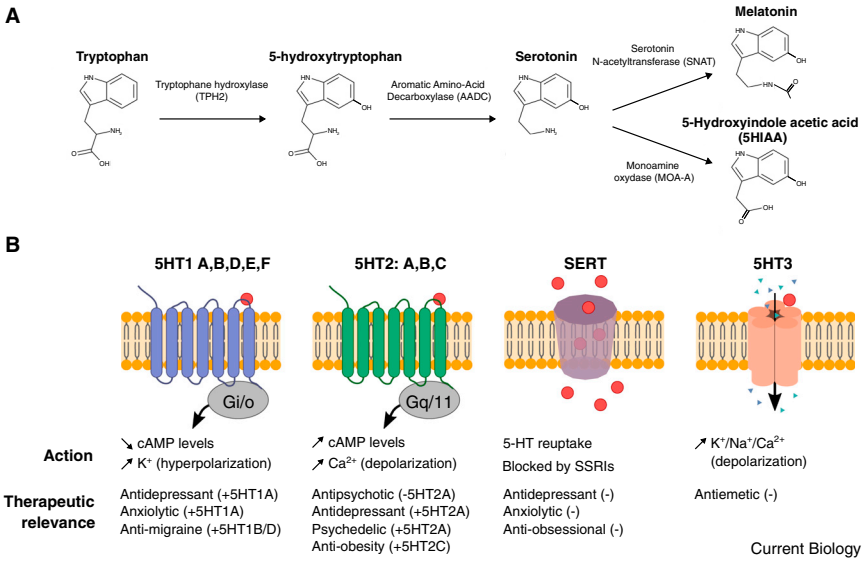

Figure 3. Molecular and metabolic characteristics of the serotonin system.
(A) Tryptophan can be turned into serotonin in only two enzymatic steps. After it is released, it is either broken down into 5-HIAA or used to make melatonin again. (B) Serotonin receptors are categorized according to their influence on membrane potential and intracellular transduction pathways (+ and – signs denote the effects of agonists and antagonists, respectively).

experiences but could be used therapeutically in conditions such as addiction and depression. One of the most salient observations about these drugs is the intriguing nature of their subjective effects that interact with the situation of their use and the state of the person taking them. This is consistent with the notion that serotonin acts as a modulator rather than a determinant of brain state and underlines the risk of incorrectly ascribing effects observed when administering a drug to the compound itself.

Serotonin is intimately associated with neural plasticity, and many serotonin receptors initiate signaling cascades that can result in genetic expression and morphological changes. For example, agonists of the 5HT2a receptor can promote dendritic arborization and the formation of new synaptic connections, 5HT4 receptors can modulate long-term depression in the basal ganglia, and serotonin release stimulates hippocampal neurogenesis and the formation of cortical circuitry. These mechanisms could underlie the proposed role of serotonin in promoting "behavioral plasticity", such as the changes that follow administration of SSRIs or psychedelics. At a behavioral level, drugs that stop serotonin neurons from firing or reduce the amount of serotonin in the brain can interfere with the normal cessation of responding to a stimulus that is no longer reinforced, causing perseveration (Figure 4A). This effect could help explain the ability of psychedelics to treat addiction or persistent maladaptive states such as depression. Much work is still needed to establish predictively valid linkages between human behavior and proposed neural mechanisms. Given the complexity of the brain, this will require both experimental advance and the development of appropriate theory and models.

Theories of serotonin function in the brain

Reinforcement learning is a theoretical framework that describes learning using algorithms in which reward values are assigned to states of the environment and used to select amongst possible actions. This framework successfully explains key properties of the firing of dopamine neurons and theorists have attempted to extend it to serotonin neurons as well. The serotonin–dopamine opponency theory, inspired by a variety of pharmacological and behavioral evidence, including the observation that release of serotonin can inhibit the release of dopamine, predicted that the phasic and topic firing of

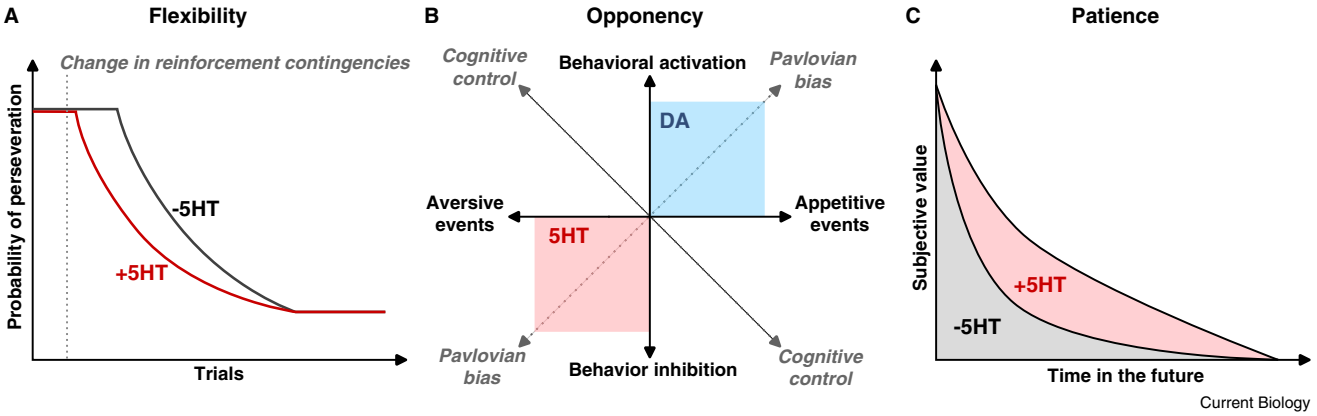

Figure 4. Principal cognitive theories of serotonin in the brain.
(A) According to the emerging flexibility theory, serotonin may reduce the behavioral weight of prior experiences to facilitate the relearning of action–outcome contingencies. (B) According to the opponency theory, DA and serotonin play opposing roles. It linked serotonin to the Pavlovian bias that couples aversion and behavioral inhibition (adapted from Boureau and Dayan, 2011). (C) According to the patience theory, serotonin reduces the discounting of future reward and punishment in models of temporal-difference learning. It was expanded to include the capacity to wait and avoid impulsive responses in general.

serotonin signaling would encode, respectively, punishment prediction errors and the average rate of rewards (Figure 4B). However, the application of controlled behavioral paradigms and genetic targeting strategies in mice revealed that serotonin neurons are rapidly activated by a variety of events including not only punishments and reward omissions but also rewards and reward-predicting cues. This theory also hypothesized that serotonin release would mediate the innate tendency to inhibit behavioral output when anticipating punishment, but recent research indicates that serotonin neurons are activated prior to active escape attempts and promote locomotion in aversive contexts.

An alternative theory proposed that serotonin regulates impulsivity by determining the time horizon over which the anticipation of future rewards and punishments influences current decisions (Figure 4C). The inspiration for this hypothesis was the observation that reducing brain serotonin increases the proportion of premature and impulsive responses in rodents, monkeys, and humans. Later experiments confirmed that selective activation of DRN serotonin neurons makes mice more likely to wait for delayed rewards and that the activity of serotonin neurons goes up while waiting. However, this theory can only explain a few of the many aspects of serotonin signaling. It does not explain, for example, why serotonin neurons respond momentarily to rewards, punishments and other salient events.

Thus, while the opponency and patience theories have received some empirical support, other evidence suggests key elements of serotonin function might not be captured by standard reinforcement learning theory. For example, studies using optogenetics to stimulate serotonin neurons have revealed striking context-dependent effects. Activating serotonin neurons during spontaneous exploration decreases locomotion; however, this effect tends to disappear during goal-directed behaviors and reverses in aversive contexts. It also appears that the effects of serotonin on patience disappear when the probability of future rewards is low. Moreover, variables such as environmental controllability and uncertainty also influence the activity of serotonin neurons.

In machine learning, the central computation performed by neural networks is prediction. To learn to make predictions, neural network models compute prediction errors: the difference between what the model predicts and what actually happens. Accordingly, algorithms that minimize prediction errors improve performance. The observation that serotonin neurons increase their activity in response to diverse kinds of unpredictable events suggests that serotonin signals may be related to prediction errors, which could in turn account for serotonin's involvement in learning and plasticity. Frameworks based on prediction errors, including predictive coding and control theory, are promising candidates to explain aspects of serotonin function that are not captured by reinforcement learning theory.

Serotonin neurons from the DRN project very broadly to the forebrain, which includes the entire neocortex. The neocortex has been theorized to perform a kind of learning known as unsupervised learning or predictive coding because it does not require a reward signal. Within a predictive coding framework, serotonin could track the relative confidence or uncertainty of the brain's predictions, helping to adjust the balance of model-driven predictions (Bayesian priors) versus new evidence in guiding behavior. This idea would be consistent with the finding that stimulating serotonin neurons can increase learning rates in a probabilistic reversal learning task, change the propensity to explore a novel environment, or enable waiting for delayed rewards. Alternatively, within a control-theoretic framework, serotonin could convey second-order prediction errors tracking to which extent an environment or a task is controllable for the organism, and helping the nervous system to adjust accordingly. Indeed, serotonin release is directly involved in the behavioral adaptations to uncontrollable stressors (learned helplessness) and serotonin neurons respond more vigorously when

changes in sensory input immediately follows motor output. This suggests that serotonin neurons may act as coincidence detectors and index the degree to which actions cause reliable outcomes.

However, the heterogeneity of serotonin neuron responses that is increasingly being recognized indicates that serotonin signals are multi-dimensional rather than unitary. Subregions of the raphe appear to carry at least partly independent signals. These may reflect prediction errors specific to different brain systems, allowing them to be independently modulated or compared. Even within individual subregions of the raphe, heterogeneous signals across individual serotonin neurons could reflect the ability of serotonin system to convey multi-dimensional error signals. Studying these possibilities calls for recording from ensembles of identified serotonin neurons using techniques such as microendoscopy, and for measuring post-synaptic serotonin levels using selective biosensors.

Challenges, prospects, and unanswered questions

The sheer number of brain functions impacted by serotonin presents a severe challenge for any unifying theory. This may be related to the functional heterogeneity of serotonin circuitry, but this has only begun to be established. For instance, the MRN appears to play a larger role than the DRN in memory consolidation and fear conditioning, whereas the DRN appears to play a more significant role in perceptual processes and goal-directed behavior. Methods based on the combination of genetic targeting, optical stimulation and recording, and electrophysiology are proving essential to resolve circuit-level complexity. Studies of this kind have revealed specificity of input–output loops: the serotonin neurons that project to a particular area also receive input from the same area. Such loops may reflect a general principle in brain circuitry. Yet circuit specificity does not entail that the serotonin system is not unified as well. Across different loops, interactions between serotonin neurons within the raphe nuclei may allow for larger-scale interactions between brain areas. Functional interactions between serotonin and other neuromodulator systems including dopamine and norepinephrine are also important to consider. To unpack these kinds of circuit-level complexity, further investigation of the anatomy and function of serotonin circuits, as well as studies of circuits within the raphe itself, are needed.

While we have been discussing the serotonin system mainly as a transmission network, the system has its own intrinsic dynamics and plasticity which are only beginning to be unraveled. One important set of observations is that serotonin activity is controlled by feedback mechanisms that include self-inhibition, changes in gene expression, and modification of axonal projections. It is also important to consider that serotonin acts over multiple time scales from sub-second to days. There is evidence that short-term and long-term effects may be functionally opposed to one another, another commonly seen theme in neuroscience. Optogenetics, calcium imaging and electrophysiology allow the manipulation and measurement of the neuronal activity underlying serotonin function, but additional layers of chemical and molecular complexity require methods to track dynamics of serotonin release and its postsynaptic consequences. Recently developed chimeric receptors whose fluorescence depends upon the binding of serotonin will be important for this.

Studying human serotonin functions is particularly difficult and contemporary views of the serotonin system are primarily constrained by animal research, especially by rodent models. The anatomy and neuronal composition of the raphe nuclei appear to be conserved across mammalian species, but in general brain anatomy and behavioral repertoires vary considerably between species, sometimes challenging extrapolation to humans. The human DRN and MRN are only slightly bigger than the typical voxel size (3 x 3 x 3 mm) used in magnetic resonance imaging (MRI) studies, and they contain a mix of neuronal types, like their rodent homologs. Furthermore, serotonin causes direct neurovascular responses which can be picked up by functional MRI methods. Thus it is challenging to interpret functional brain imaging of the serotonin system. Fast-scan cyclic voltammetry, which measures serotonin more directly, is a promising tool but can only be applied in patients undergoing brain surgery. Other possibilities include novel radioactive ligands for positron emission tomography (PET) imaging and more specific pharmacological approaches. In sum, elucidating the nature of brain serotonin computation may lead to groundbreaking advances in psychiatry, neurology, and beyond. Doing so will require conceptual and methodological innovation as well as interdisciplinary translational research.

DECLARATION OF INTERESTS

Romain Ligneul is a co-founder of RobustCircuit, which develops online behavioral tasks. The authors declare no other competing interests.

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