BRAIN
REVIEW ARTICLE

Understanding the effects of serotonin in the brain through its role in the gastrointestinal tract

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The neuromodulatory arousal system imbues the nervous system with the flexibility and robustness required to facilitate adaptive behaviour. While there are well understood mechanisms linking dopamine, noradrenaline and acetylcholine to distinct behavioural states, similar conclusions have not been as readily available for serotonin. Fascinatingly, despite clear links between serotonergic function and cognitive capacities as diverse as reward processing, exploration, and the psychedelic experience, over 95% of the serotonin in the body is released in the gastrointestinal tract, where it controls digestive muscle contractions (peristalsis).

Here, we argue that framing neural serotonin as a rostral extension of the gastrointestinal serotonergic system dissolves much of the mystery associated with the central serotonergic system. Specifically, we outline that central serotonin activity mimics the effects of a digestion/satiety circuit mediated by hypothalamic control over descending serotonergic nuclei in the brainstem. We review commonalities and differences between these two circuits, with a focus on the heterogeneous expression of different classes of serotonin receptors in the brain. Much in the way that serotonin-induced peristalsis facilitates the work of digestion, serotonergic influences over cognition can be reframed as performing the work of cognition. Extending this analogy, we argue that the central serotonergic system allows the brain to arbitrate between different cognitive modes as a function of serotonergic tone: low activity facilitates cognitive automaticity, whereas higher activity helps to identify flexible solutions to problems, particularly if and when the initial responses fail.

This perspective sheds light on otherwise disparate capacities mediated by serotonin, and also helps to understand why there are such pervasive links between serotonergic pathology and the symptoms of psychiatric disorders.

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Keywords: serotonin; automaticity; flexibility

Received March 23, 2022. Revised June 12, 2022. Accepted June 14, 2022. Advance access publication July 23, 2022

Introduction

The ascending neuromodulatory system consists of a diverse collection of nuclei in the brainstem and forebrain that send axonal projections throughout the CNS. By releasing ligands that either open ion channels or modulate internal neuronal state via second-messenger systems, the neuromodulatory system works in concert with the excitatory and inhibitory signals communicated between neurons to imbue the brain with the dynamic flexibility required to facilitate adaptive behaviour.[1]

Although there are numerous different neuromodulatory chemicals in the nervous system, the most well studied are the dopaminergic system (projections from the ventral tegmental area and substantia nigra), the noradrenergic system (locus coeruleus), the serotonergic system (raphe nuclei), and the cholinergic system (pedunculopontine, laterodorsal tegmentum and basal forebrain). Despite similar mechanisms of action,[1] idiosyncratic anatomical details of different pathways betray the unique functional signatures of each system. For instance, dopaminergic projections from the substantia nigra modulate the excitability of direct-pathway spiny projection neurons in the striatum, activating firing patterns in the frontal cortex that have been linked to both planning and action.[2] In contrast, unmyelinated projections from the noradrenergic locus coeruleus diffusely innervate the entire cerebral cortex, promoting network-level integration and fast, effective cognitive performance.[3] Cholinergic cells tend to project in a more segregated fashion, mediating a range of inhibitory mechanisms that promote normalization and focused attention.[4,5]

By comparison, the serotonergic projections of the dorsal raphe nuclei remain much more poorly understood.[6,7] Much like the fibres of the locus coeruleus, the axons of the dorsal raphe project relatively diffusely to the whole cerebral cortex.[8] Their varied influence over firing rates in the cortex are mediated by a diverse range of receptors that can be characterized as either fast-acting, ionotropic or slow-acting, metabotropic receptors, the latter of which alter neural gain through second messenger mechanisms.[1] The fact that these receptors are expressed on both excitatory and inhibitory cell types adds further complexity. Despite these uncertainties, central serotonergic activity levels have been convincingly linked with a rich repertoire of cognitive functions, including explore/exploit dynamics,[9,10] cognitive flexibility,[11] adaptive responses to adversity,[12] temporal discounting,[13,14] aversive processing,[15] and behavioural inhibition[16]; as well as being implicated in an array of abnormal psychological states (anxiety, depression, hallucinations, etc.[17,18]). The question remains: how can the central serotonergic system mediate these diverse functions?

A potential clue comes from an often overlooked anatomical detail: around 95% of serotonin is actually expressed outside the nervous system in the gastro-intestinal tract (GIT). In the GIT, activation of serotonin receptors control motility and peristalsis, primarily via 5-$HT_{3/4}$ receptors (5-$HT_{3/4}$Rs), which are of the fast-acting, ionotropic and slow-acting, metabotropic (Gs) type, respectively.[19,20] Peristaltic waves controlled by 5-HT (serotonin) in the GIT facilitate crucial digestive functions—they coordinate functional subunits of the GIT to create motility and hence act to break down boluses of food so that the body can extract nutrients required for energy synthesis and homeostasis. Serotonin levels in the GIT are under the control of a well defined circuit, in which chemicals that increase in concentration following food intake and satiation (e.g. leptin, insulin, glucose and ghrelin) travel through the bloodstream to the circumventricular subfornical organ,[21] which then contacts the arcuate nucleus of the hypothalamus. Here, the satiation-related chemicals promote the transcription of genes (e.g. POMC). The products of this process are transcribed into intermediary proteins, such as ACTH and α-MSH, ultimately acting to decrease the excitability of the serotonergic cells in the dorsal motor nucleus of the vagus (DMX) that control gut motility.[22] These circuits create a dynamic, non-linear feedback loop in which intermediate levels of neuronal serotonergic activity are required for effective digestion[23,24]; and the activity of this system is closely regulated by the presence of downstream products of digestion (i.e. it knows when to 'shut off').

In this Review article, we argue that framing the central serotonergic system as a rostral extension of the gastrointestinal serotonergic system helps to explain the role that 5-HT plays in shaping cognitive function. By analogy, we contend that 5-HT controls a process akin to 'cognitive digestion'—when there is cognitive work to be done (i.e. decisions to be made, or actions to be executed), higher concentrations of cerebellar than cortical 5-HT recruits a distributed set of corticocerebellar circuits in a non-linear fashion that first attempts to solve cognitive problems using previously learned processes, whereas elevated concentrations of central 5-HT promote heightened top-down influences in the cerebral cortex that allows for novel, flexible and creative solutions to persistent problems. In this way, 5-HT is proposed to play a crucial role in shaping the systems-level response to cognitive challenges. In the final section, we will demonstrate how this model helps to explain diverse features of the neuronal 5-HT system, both during healthy cognitive function and across a range of abnormal brain states. We hope that this analogy can provide a novel framework for understanding the function of the central serotonergic system, and further that it might motivate new approaches for understanding and treating neuropsychiatric symptoms.

The anatomy and physiology of gastrointestinal serotonergic system

The GIT is a set of specialized organs that form the basis of a patent tube running from the mouth and oesophagus, through the stomach, small intestine, large intestine to the rectum (Fig. 1). Innervating these organs is a dense network of neurons that course through the vagus nerve to form the enteric nervous system. The presence of food in the GIT—signalled either through mechanical stretch receptors[25] or the presence of chemicals, such as cholecystokinin[23]—is transmitted via the vagus nerve to central brain structures, such as the nucleus solitarius and raphe magnus. In these nuclei, the neuromodulatory ligand serotonin (synthesized by removing a hydroxyl group from the essential amino acid, tryptophan[26]) is shuttled by axons from the raphe nuclei[19] and the DMX[27] to the GIT, where it modulates the local release of 5-HT from enterochromaffin cells.[23,25,28] Through complex actions on GIT smooth muscle cells, 5-HT promotes increased gastric motility via peristalsis,[23,24] which accelerates the digestive process, and the extraction of nutrients required to mediate ongoing homeostatic processes in the body.

Like many biological feedback circuits, the 5-HT system uses multiple feedback loops (both positive and negative) to control its own concentration in the GIT, and hence, to sustain effective digestion. As described above, the efferent projections from the GIT via the vagus nerve appear to control a positive feedback circuit that triggers the 5-HT release that facilitates digestion. Importantly, if this positive feedback circuit runs unchecked, heightened concentrations of 5-HT in the GIT can promote problematic and

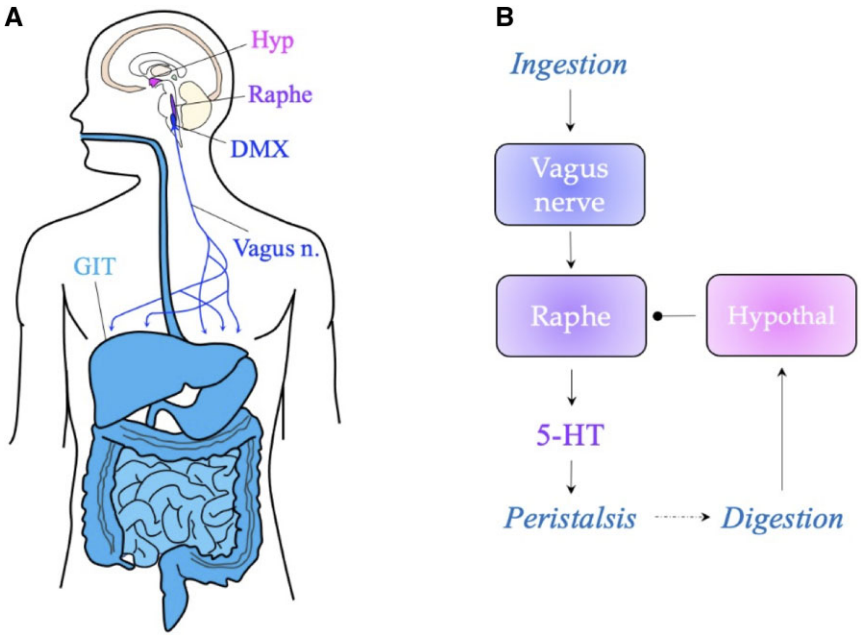

Figure 1 Anatomy of the serotonergic systems of the body. (**A**) The anatomy of the gastrointestinal tract (GIT; light blue) and its connections with the dorsal motor nucleus of the vagus (DMX; dark blue), which is controlled by inputs from the raphe magnus (purple) and ventromedial hypothalamus (Hyp; pink). (**B**) Following ingestion, chemo-mechanical signals travel via the vagus nerve to the medulla, wherein descending serotonergic signals (via the raphe and DMX) stimulate peristalsis and further ingestion (digestive work). If this peristalsis leads to digestion, then chemical byproducts of digestion (leptin, ghrelin, insulin, etc.) travel via the vascular system to the hypothalamus and stimulate the transcription of the POMC gene, which decreases raphe firing via alpha-MSH stimulation of MC_4R, ultimately leading to satiation. If appropriate negative feedback signals do not occur, then the positive feedback loop between the vagus nerve and the GIT can cause an increase in peristaltic frequency (or flux).

sustained increases in motility (which we refer to here as 'Flux')—that is, heightened 5-HT concentrations can promote diarrhoea. For this reason, the system requires negative control loops that help to shut down 5-HT release after a meal has been effectively digested. These slower negative feedback loops tend to be humoral rather than neuronal—for the GIT, circulating levels of leptin (from adipocytes), insulin (from the pancreas), glucose (from the blood) and ghrelin (from the GIT) travel slowly via the blood to reach the arcuate nucleus of the hypothalamus,[29] wherein they catalyse transcription of the POMC gene. Following further modifications of the gene products of POMC, alpha-MSH acts as an inhibitory (Gi) neuromodulator on the raphe nuclei and nucleus solitarius,[30] terminating the descending signals that mediate peristalsis. In this way, the GIT can reduce the activity of peristalsis (e.g. by controlling the frequency of pacemaker cells in the GIT[31]) once the work of digestion has been completed. How do these well described circuits controlling the GIT relate to the serotonergic circuits of the brain?

The anatomy and physiology of the neural serotonergic system

The basic organization of the serotonergic system in the brain shares many similarities with the 5-HT system of the GIT. For instance, the majority of central 5-HT release is controlled by the raphe nuclei of the brainstem, which themselves are under the feedback control of numerous regions in the brain, including the hypothalamus, cerebral cortex and habenula. In keeping with the GIT, the three major raphe nuclei in the brain—the magnus, median and dorsal raphe—together diffusely blanket almost every area of the brain in unmyelinated axons that release serotonin at target structures in the cerebral cortex, thalamus, and colliculi[6,8,32] (Fig. 2A), whereas the cerebellum receives the majority of 5-HT from the medullary and pontine reticular formation.[33] The firing rate of centrally-projecting raphe nuclei varies as a function of distinct behavioural states.[34] Perhaps unsurprisingly given the links to the GIT, 5-HT concentrations in the brain are elevated during feeding,[35] but also at other times—for instance, serotonergic activity is typically lowest during sleep (particularly REM[36]), and then increases substantially upon awakening.[37] There is a well known link between serotonin activity and motor behaviour, particularly for the nuclei that project to the cerebellum and spinal cord.[38] In addition, 5-HT activity has been linked to a number of different cognitive processes, including working memory,[37] cognitive flexibility,[11] response inhibition[39] and the balance between exploration and exploitation.[9] Serotonin levels also prevent the hippocampus from entering into modes that promote sharp-wave ripples,[40,41] which may help animals maintain focus over their current goal state by inhibiting the likelihood of memory retrieval events during moments that require goal-directed focus.[42]

Once serotonin is released in the brain its impact on local neuronal firing is quite complex (at least in comparison to the GIT), in part due to the vastly increased diversity of serotonergic receptors.[6,20] In the brain, serotonin receptors loosely fall into four distinct classes: (i) slow-acting, metabotropic $5\text{-}HT_2Rs$, that liberate Ca^{2+} from intracellular stores using a Gq mechanism; (ii) $5\text{-}HT_{4/6/7}Rs$, which increase cAMP (and subsequent second-messenger cascades) using a Gs mechanism; (iii) $5\text{-}HT_{1/5}Rs$, which decrease cAMP (via a Gi mechanism); and (iv) fast-acting, ionotropic $5\text{-}HT_3$ receptors, that promote the flow of either Na^+ or K^{++}.[1,19] The more slowly acting metabotropic receptors, which are the main focus of this manuscript, exert their influence over neural spiking activity somewhat indirectly. Through second-messenger cascades that alter the gain (or excitability) of targeted regions, these receptors essentially

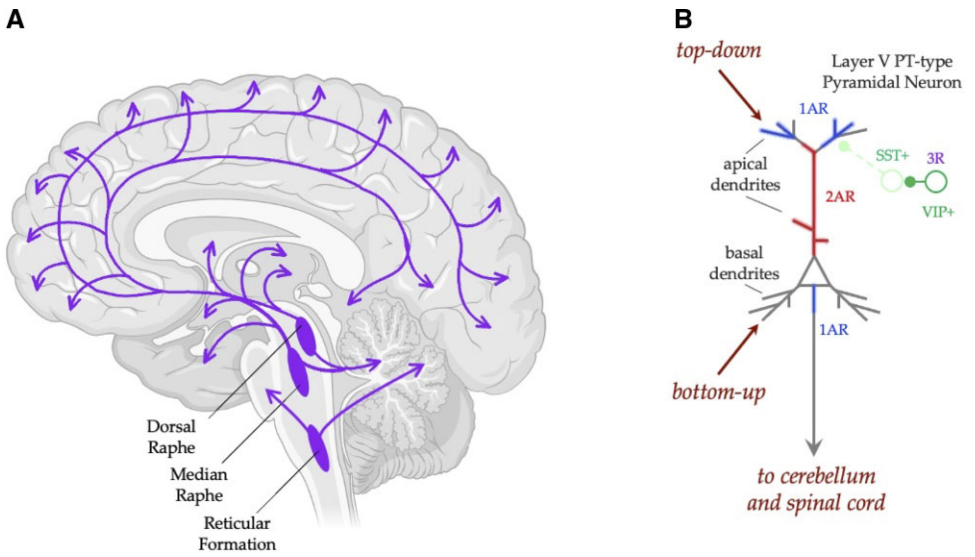

Figure 2 Controlling the systems that define adaptive decision making. (**A**) The raphe nuclei send diffuse projections out to widespread regions in the brain, whereas serotonergic neurons in the reticular formation predominantly innervate the cerebellum and its input structures. (**B**) Although 5HT$_{1A}$Rs (blue) and 5-HT$_{2A}$Rs (red) are thought to be expressed ubiquitously across pyramidal neurons in the frontal cortex,[45] we demonstrate here how different classes of 5-HTRs are expressed in different compartments of a layer V PT-type pyramidal neuron, whose apical dendrites (which receive top-down projections) are electrically isolated from its basal dendrites (which receive bottom-up projections)—high-affinity, inhibitory (Gi/o) 5-HT$_{1A}$Rs (blue) are expressed on the axon initial segment, and distal apical dendrites, whereas low-affinity, excitatory (Gq) 5-HT$_{2A}$Rs (red) are expressed on proximal apical dendrites, and ionotropic 5-HT$_3$Rs (purple) are expressed on interneurons (VIP+; dark green) that gate inhibitory control over apical dendrites (by disinhibiting inhibitory SST+ interneurons; light green).

make targeted regions more (or less) likely to fire action potentials when they receive a glutamatergic input from another neuron.[1] In contrast, ionotropic receptors (such as 5-HT$_3$R) directly open ion channels, which can then excite (or inhibit) their target cells. Interestingly, while 5-HT3Rs are the most prevalent within the GIT, metabotropic receptors are highly expressed across the nervous system (see Okaty *et al.*[6] and Sharp and Barnes[20] for a thorough review).

The different metabotropic receptors, which are expressed in unique locations within the brain, also respond differently to the concentration of serotonin, which in turn can change the information processing dynamics that emerge from coordinated neural activity.[43] For instance, while the majority of pyramidal neurons in the frontal cortex express both 5HT$_{1A}$ and 5-HT$_{2A}$Rs,[37] the receptors are expressed on different compartments: inhibitory 5-HT$_{1A}$Rs are localized to the axon initial segment,[37,44] whereas excitatory 5-HT$_{2A}$Rs are heavily expressed on proximal apical dendrites[45–47] (Fig. 2B). These two classes of receptors also have different affinities for serotonin: 5-HT$_{1A}$Rs have higher-affinity for 5-HT than 5-HT$_{2A}$Rs, and hence require lower concentrations of serotonin in order to recruit their associated second-messenger cascades.[48] This implies that, at low-to-intermediate concentrations, 5-HT attenuates outputs from pyramidal neurons (i.e. it has an inhibitory effect), whereas at higher concentrations, 5-HT increases the effects of diverse top-down signals on pyramidal neuron firing. The specificity of the circuits recruited during heightened concentrations of 5-HT could also be shaped and constrained by the recruitment of fast-acting, ionotropic 5-HT$_3$Rs, which are highly expressed on superficial-layer VIP+/CR+ GABAergic interneurons in the cerebral cortex[49,50] and have been shown to disinhibit specific top-down patterns in the cerebral cortex by gating SST+/CB+ interneurons (Fig. 2B).[51] We will return later to the potential importance of these distinct receptor expression profiles.

Much like the central serotonergic regions associated with the GIT, each of the centrally projecting raphe nuclei receives both excitatory and inhibitory inputs that embed the firing of serotonergic neurons within complex feedback loops that control their firing rate. For instance, the raphe nuclei receive substantial glutamatergic innervation from the ventromedial prefrontal cortex (vmPFC),[8] a limbic area of the cerebral cortex involved in a variety of different functions, such as behavioural control, valuation and decision-making.[52] By integrating conceptual and affective information, the vmPFC calculates subjective value of available affordances[53]—that is, what matters to an animal from moment-to-moment. In addition, there are also substantial disinhibitory projections from the ventral tegmental area (another area that reflects motivational and valuation signals) to the raphe nuclei,[54] as well as reciprocal excitatory connections in the opposite direction.[55] While these inputs might be considered as analogous to the feed-forward vagal afferents that innervate the nucleus solitarius,[27] it is important to note that many of the cortical projections actually contact GABAergic cells in the raphe,[56] suggesting that they may act as feedback inhibitors, or at the very least gate 5-HT release to occur at specific times. In a compelling demonstration of such descending inhibitory control, the vmPFC was shown to regulate dorsal raphe firing based on how much control an animal had over an environmental stressor.[57] Taken more broadly, the vmPFC may 'instruct' raphe cell firing based on environmental and motivational contingencies.[58]

Firing rates in the dorsal raphe are also under the control of the habenula, which is a critical neuroanatomical hub that connects and regulates brain regions important for motivational and cognitive states.[59,60] There are two anatomical subdivisions of the habenula: the lateral habenula,[61] which is predominantly glutamatergic and uniquely positioned as a hub connecting a range of subcortical and cortical structures with the dopaminergic, serotonergic and noradrenergic systems; and the medial habenula,[62] which is

predominantly cholinergic, and receives inputs from the cholinergic septum and projects to the interpeduncular nucleus and periaqueductal grey matter, where it mediates freezing and avoidance behaviour.[63] There is ample evidence to suggest that the lateral habenula inhibits the release of 5-HT from the dorsal raphe, likely via the recruitment of GABAergic interneurons.[64,65] In turn, the dorsal raphe also inhibits the lateral habenula [via both 5-$HT_{1B/5}$Rs (G_i) and 5-HT_{2C} (G_q)[66]], creating a complex, multi-stage feedback loop. The lateral habenula also receives inputs from the anterior cingulate cortex, a region that integrates the outcome values of actions over a longer timescale, in contrast to lateral habenula neurons that detect ongoing negative outcomes associated with shorter latencies.[67] In this way, the habenula can act as an intermediate control structure that is related both to what an animal needs (i.e. via the hypothalamus), but also what is actually available (i.e. via the anterior cingulate cortex), across varying timescales.

Serotonin controls systems-level information processing in the brain

What factors bind together these seemingly diverse features of the central serotonergic system? By way of analogy with the GIT, we suggest that central 5-HT activity is recruited when there is cognitive work to be done—i.e. when there is 'food for thought' to be digested. While awake, animals are bombarded with sensory information that reflects a constantly changing set of features in the world around them. These patterns of activity suggest affordances (i.e. opportunities for action) that can shift and change as a function of fluctuating behavioural needs.[68] Studies in zebrafish have confirmed that serotonergic structures in the brain act as a controller in the balance between behavioural exploration and exploitation.[9] Similar results have been observed in locusts, where 5-HTR agonism in the thoracic ganglia controls the expression of gregarious behaviour.[69] A role for 5-HT in modulating the expression of aggressive social behaviours is remarkably conserved across phylogeny.[70,71] This cross-species evidence of 5-HT arbitrating between modes of behaviour aligns well with our perspective.

So how might the concentration of 5-HT mediate complex, adaptive dynamics in the human brain? The expression of 5-HTRs offers a potential clue as to how these mechanisms are mediated at the systems level. As described above (Fig. 2B), low concentrations of 5-HT inhibit spiking output in cortical pyramidal neurons via 5-HT_{1A}Rs, whereas higher concentrations of 5-HT augment feedback into pyramidal neurons via 5-HT_{2A}Rs,[45–47] suggesting that different dynamic cortical states (Box 1) can be recruited as a function of increasing 5-HT concentrations.[12] Importantly, the other key circuits in the brain are similarly responsive to 5-HT, albeit with distinct effects at different concentrations of 5-HT. For instance, the cerebellum receives substantial innervation by serotonergic fibres[33,77] (Fig. 3A) and 5-HT is known to mediate a general increase in cerebellar activity through a wide range of different 5-HTRs.[77] The cerebellum is reciprocally connected with layer V PT-type pyramidal neurons, which are the major output neuron of the cerebral cortex that fire in bursts whenever an animal undertakes an action[78] (Fig. 3A). The axons of these neurons make strong contact with the pontine nuclei that act as one of two major input structures to the cerebellum, and 5-HT has been shown to increase the susceptibility of the pontine nuclei to high-frequency (i.e. bursting) inputs.[79] Based on their differential responsivity to 5-HT and the fact that cortical and cerebellar 5-HT likely arise from distinct inputs that are themselves reciprocally (and negatively) interconnected,[80] we propose that intermediate concentrations of serotonin will lead to a boost in feedforward activity in the cerebral cortex driven by cerebellar activity,[81] and a relative silencing of inter-regional connectivity within the cerebral cortex.[37] That is, intermediate concentrations of serotonin will lead to a cerebellar driven cortical computation regime.

In previous work, we have argued that the modular, algorithmic circuitry of the cerebellum[73,82] and its capacity to store sparse, high-dimensional signals[82] would have the effect of mediating fast, anticipatory responses to cognitive challenges.[73,83] Although typically associated with the motor system, in humans (as well as in a number of other species[84]) the cerebellum is intricately connected with the lateral frontal cortices via the thalamus, such that it is ideally placed to coordinate the fast, intuitive modes of cognition—what some might call a 'gut feeling', but here we refer to as 'cognitive automaticity' (Fig. 3B). In this state, serotonin excites the nervous system sufficiently to mediate complex, adaptive behaviour, in such a way that the system relies on stored information (e.g. in the weights of connections within the cerebellar cortex) and hence, acts in a relatively automatic fashion.[73,83] Assuming that intermediate dorsal raphe firing patterns co-occur with heightened activity of the reticular formation inputs to the cerebellum, the relative inhibition in the cerebral cortex mediated by 5-HT would ensure that, in the presence of a particular cognitive challenge, the brain would initially recruit previously learned processes in an attempt to solve a particular problem. If the challenge is well-matched by a previously learned response pattern, the cognitive process is free to unfurl without impediment, and hence would not require any additional cognitive work[73,83]—that is, the problem can be solved relatively automatically.

If the food to be digested requires more work than baseline motility is capable of (e.g. due to composition and/or volume), concentrations of 5-HT will increase in the GIT, leading to an increase in peristalsis (i.e. digestive *Flux*) in an effort to complete the digestive process.[28] We argue that similar mechanisms can be recruited by the central 5-HT system in situations when cognitive challenges remain unsolved by the initial, automatic responses suggested by the cerebellar architecture. These 'cognitive flux' (Fig. 3B) states are characterized by heightened excitability in the cerebral cortex (mediated by excitation of 5-HT_{2A}Rs[37]), particularly in the apical dendrites of layer V PT-type pyramidal neurons that receive top-down signals from more agranular regions of the cerebral cortex.[78,85,86] By boosting these top-down signals, increased concentrations of 5-HT can facilitate a mode of processing that is less reactive (i.e. you don't simply respond to primary features of the external environment the way that you typically would), and more flexible (i.e. you can act to novel contexts using in ways that you might have previously overlooked[86]).

In this way, enhancement of the top-down effects can help to discover novel opportunities for action that are distinct from those that would be typically relied upon by the animal. This permits novel neuronal ensembles to activate—as opposed to well-established patterns—allowing new associations to form, facilitating problem solving and imagination.[42] Consistent with our proposed framework, research into problem-solving has found that insights are often preceded by a feeling of impasse or 'getting stuck'. Here, the impasse reflects a state in which more automatic, conventional approaches to solve the problem have failed, and creates a scenario in which flexible, novel solutions are required. Our framework hypothesizes that these impasses bring about heightened 5-HT, which activate 5-HT_{2A}Rs that enhance inputs to apical dendrites and thereby facilitate top-down effects in the cerebral

Box 1 Serotonin and cognitive digestion—a dynamical systems perspective

Through the lens of our analogy, what exactly does it mean to 'digest' information? Given the complexity of neural circuitry and the diversity of 5-HTRs around the brain, cognitive digestion is likely to be a far more complex process than peristalsis or the absorption of nutrients. To improve our understanding of this process, we suggest that a dynamical systems perspective—which treats neurons as entities that change in time in precise ways governed by their glutamatergic, GABAergic and neuromodulatory inputs—is likely to catalyse rapid developments in our appreciation of how 5-HT levels can modulate specific neuronal processes related to working memory, evidence-accumulation, urgency, attention, and top-down modulation of perception and action. Although we have argued that 5-HT levels differentially effect distinct neural circuits in the brain, here we isolate a cortical microcircuit in order to demonstrate the utility of dynamical systems modelling. As reviewed above, 5-HTRs display an intriguing division of labor in the cerebral cortex: on pyramidal neurons, inhibitory 5-HT_{1A}Rs are preferentially located near the axon initial segment, whereas excitatory 5-HT_{2A}Rs tend to be located on apical dendrites. Based on their location and modes of action, increased occupancy of high-affinity 5-HT_{1A}Rs should reduce the ability of pyramidal neurons to excite other neurons (due to a relative dampening of spiking output)—in turn, this will reduce local recurrent (positive) feedback, rendering a microcircuit more sensitive to other sources of excitation, including long-range inputs arriving at the dendrites. By contrast, occupancy of low-affinity 5-HT_{2A}Rs will enhance sensitivity to inputs arriving at the dendrites, potentially increasing the effect of local recurrent feedback.

At the level of an individual neuron, moderate 5-HT levels will trigger 5-HT_{1A}Rs and quell spiking, whereas higher 5-HT levels or phasic bursts of 5-HT will activated 5-HT_{2A}Rs and promote the inclusion of contextual signals via the cells' apical dendrites. At the circuit level, assuming that cortical microcircuits form competitive networks via 'on-center off-surround' connectivity (short-range excitation and medium-range inhibition; REF), regulation of the amount of recurrent excitation will tend to control key aspects of competition between neurons. Weakened recurrent feedback (predominant 5-HT_{1A}R agonism), will tend to slow down feedback-driven stabilization—in the context of working memory, this can lead to weaker persistent activity and enhanced distractability (REF). Strong recurrent feedback (5-HT_{2A}R agonism) will cause the opposite effect: stronger persistent activity and lower distractability. Computational modeling work has demonstrated roughly analogous non-monotonic effects of different 5-HT levels on working memory in prefrontal cortex.[72] From a dynamical systems perspective, we can say that 5-HT_{1A}Rs, acting via inhibition of the axon initial segment, can reduce the depth of an attractor at the microcircuit level, whereas 5-HT_{2A}Rs, acting via excitation of dendrites, can increase the depth of an attractor.

The attractor framework can also be extended to other functions mediated by cortical microcircuits, and more broadly, by corticothalamic loops.[73] Integration of evidence for possible actions,[74] as well as integration of urgency to select among possible actions,[75] involve cortical circuitry that may be modulated by 5-HT in a manner analogous to that seen in working memory. A landscape of shallow attractors can integrate evidence for a variety of possible decisions, whereas a shift to deeper attractors can push the system to pick one of the available options by generating winner-take-all dynamics. Thus, weakened recurrent feedback via 5-HT_{1A}Rs will prevent or delay winner-take-all dynamics from precipitating a particular course of action. Moderate 5-HT would then contribute to weakened urgency, whereas both abnormally low or abnormally high 5-HT would contribute to elevated urgency and even impulsive, premature decision-making (albeit via different mechanisms). Studies showing that depleting 5-HT can lead to impulsivity may provide part of an inverted-U curve of 5-HT effects on decision speed.[76]

Thus, in a variety of processes ranging from working memory to decision-making, shallow attractors may correspond to satiety and automaticity, whereas deep attractor may correspond to cognitive flux—a combination of cognitive diarrhea (impulsive, premature decisions) and cognitive constipation (excessively stable decisions). In summary, a simple conceptual analysis of the effects of 5-HT_{1A}Rs and 5-HT_{2A}Rs on cortical attractor dynamics, which can be suggest experimental tests as well as computational models, allows us to flesh out the possible mechanistic implications of the cognitive digestion hypothesis.

cortex that promote novel opportunities for solving cognitive problems. This is similar to the heightened 5-HT concentrations seen in response to acute stress,[12] which is thought to be of major adaptive value as it promotes an organism to develop novel ways to remove itself from the stressful situation.[87] Sometimes, as a culmination of this flux state, a novel solution can arise through a momentary insight—an 'Aha' moment. Interestingly, insights often arise after active cognitive work, when the system has returned to a more relaxed, automatic state.[88,89] Hence, similar to the manner in which passive and active peristalsis are required for effective digestion, both neural states (automaticity and flux) and their alteration are required for successful cognitive function.

In addition to promoting flexibility and goal-directed behaviour, there is also evidence that 5-HT_{2A}Rs act to prolong the intrinsic timescale of thalamocortical circuits,[90] likely through the augmentation of cortico-thalamic interactions.[91] For instance, abundant experimental data support the notion that increased 5-HT activity promotes patience when waiting for delayed rewards.[92–95] Such is the intimate relationship between serotonin and time, that signalling the available amount of time an animal has to realize its goals has been offered as a unifying account of serotonergic function.[7] To coax this into the realm of our GIT analogy, we might appropriate a quote from Stravinsky, who said this of music: 'it is the best means we have of digesting time'. From our perspective, 5-HT may be the best means we have of digesting time. Indeed, there is now evidence that a class of 5-HT neurons responding to taste signals go on to trigger anticipatory digestive responses, thus identifying a key role for 5-HT in co-ordinating energy homeostasis across timescales.[96]

Importantly, extending activity patterns in the brain over longer periods of time does afford important cognitive benefits. For one, protracted patterns have more opportunity to influence ongoing process,[97] which is a feature that has been linked to conscious awareness.[98–100] Prolonging activity patterns also provides the chance to explore a range of available options in a particular scenario, as opposed to running with the first opportunity for action that

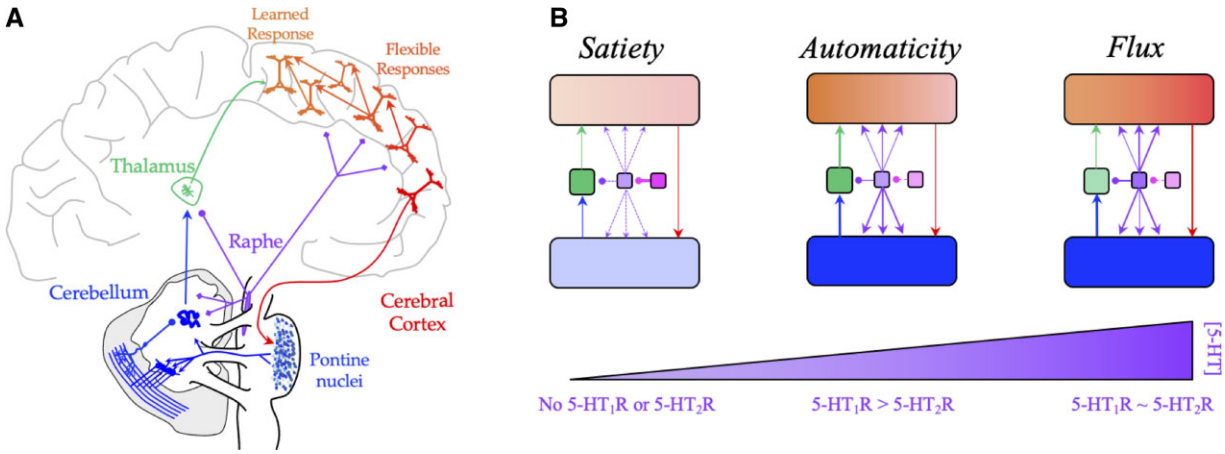

Figure 3 Cognitive satiety, automaticity and the flux state. (**A**) The major neural structures implicated in our framework—the dorsal raphe (purple) modulates activity in the cerebellum (blue), thalamus (green) and cerebral cortex (orange-red), with elevated firing of the dorsal raphe effectively shifting the balance from a cerebellar-dominated mode (controlled by the serotonergic projections of the reticular formation) that recruits relatively well-learned responses, to a cortically-dominated mode that recruits novel, flexible solutions to problems. (**B**) A schematic detailing the three different cognitive modes that are recruited with increasing cortical 5-HT concentration—during Satiety, hypothalamic structures (pink) inhibit the raphe (purple), and diminish its influence over the rest of the brain; during Automaticity, low levels of 5-HT recruit 5-HT_{1A}Rs and shift the brain into a cerebellar-dominant mode; and during Flux, heightened 5-HT levels recruit 5-HT_{2A}Rs and shift the brain into a cortex-dominant mode. Arrows = excitatory; circles = inhibitory; diamonds = variable effects.

suggests itself. It also buys time for an animal to make quasi-optimal decisions that balance many different factors,[13] allowing them to form and test hypotheses about the causal structure of their environment and the likely outcomes of their actions.[101] In this way, 5HT_2R stimulation may be one mechanism that supports deliberation—a process that features prominently during novel scenarios and early learning, and tends to diminish as behaviour becomes more automatic.[73,102,103] This capacity is clearly important for situations that require creative solutions to complex problems, and hence suggest that 5HT_2Rs are a key component of higher cognitive functions.[37,104] This extra flexibility likely comes with costs as well, particularly with respect to the ability to maintain sustained attentional focus, which is a capacity typically linked to the cholinergic system[105] that also becomes diminished with heightened 5-HT.[106] These ideas are enriched by studies of temporal discounting, where optogenetic activation of the serotonergic system has been shown to facilitate long-term optimal behaviours and suppress premature (impulsive) behaviours.[13,14] This type of effect is seen over multiple timescales, whereby serotonergic neurons respond to immediate feedback (i.e. within a trial) and also track environmental variables over the course of minutes (i.e. across task blocks).[107] Fascinatingly, there is also now evidence that 5-HT can act as a direct epigenetic modifier,[108] suggesting that pharmacological state can be used to shape adaptive behaviour over even longer timescales than had been previously appreciated.

A key question that arises from this perspective is: what in cognition is an analogous state to the satiation that accompanies a full meal? If we consider the CNS as a distributed, decentralized system for making decisions, what signals that enough work has been completed—i.e. that the process has reached a 'satisficing' state[109,110]? When a decision is being made (at whatever threshold the animal settles upon), the amount of uncertainty in the system (i.e. the proportion of hung decisions) will quell the drive towards further exploratory cognitive operations. The diminution in serotonergic drive could arise due to the lack of external need (e.g. if the cognitive rumination or flux fulfils the goal), cortical projections onto GABAergic cells in the dorsal raphe signalling a reduction in volatility or uncertainty in the environment,[111] or slower, humoral inhibitory feedback mediated by the hypothalamus, such as the expression of endogenous enkephalin[112] or cannabinoids,[113] each of which are known to signal relatively satiated, apathetic states.[114,115] There are undoubtedly numerous other humoral mechanisms for mediating motivational states and the willingness to employ cognitive effort, both of which are clearly linked to the central serotonergic system.[116,117]

A plausible neural mechanism for these satiating effects are the substantial negative feedback circuits that control the firing of the raphe nuclei (Fig. 2C). Perhaps the most pervasive form of inhibition occurs via 5-HT_{1A}R autoregulation. Through inhibitory Gi-coupled second-messenger systems, 5-HT can sequester intracellular calcium,[1] and hence cause a reduction in the propensity of targeted neurons to fire. With this mechanism in mind, the location of 5-HT_{1A}Rs becomes a key consideration. For instance, on dorsal raphe neurons, 5-HT_{1A}Rs are located on the cell body, and hence act as negative feedback circuits that keep raphe firing rates within physiological limits.[37,44] 5-HT_{1A}Rs can also be expressed on post-synaptic terminals,[118] where they can control the release of other neurotransmitters, such as dopamine.[119] Another prominent source of this inhibition arises from the hypothalamus.[22,30] For instance, the recruitment of $mTORC_1$ (a protein complex that functions as a nutrient/energy/redox sensor that controls protein synthesis) in the arcuate nucleus of the hypothalamus and their projections to the paraventricular hypothalamus changes the balance between alpha-MSH and endogenous cannabinoids.[120] Another byproduct of the POMC pathway—enkephalin—has also been shown to reduce excitability in the raphe.[112] Irrespective of the specific mechanism, there is clear evidence that the hypothalamus acts to inhibit spiking activity in the raphe.

Anatomical characteristics of the serotonergic system make it especially well-suited to drive the balance between distributed and localized information processing. Specifically, the raphe nuclei are one of the most diffusely-projecting ascending neuromodulatory systems (Fig. 2A), innervating most regions throughout the

brain.[8] Whilst this enables widespread modulation, precise targeting is also possible through the expression of specific classes of 5-HTRs on different local subsystems. Considering the serotonergic system in this light has specific implications for a system level understanding of decision-making. An emerging consensus describes decision-making in the brain as the accumulation of information distributed across multiple sites in parallel.[68,121,122] Within this framework, decisions are proposed to emerge from competitive processes that involve the same brain regions that are ultimately involved in the execution of a particular function. A decision as to whether a particular visual input is present or absent may be confined to the ventral visual stream, superior colliculus, and pulvinar,[123] whereas the decision as to whether to saccade will play out amongst parts of the frontoparietal cortex and basal ganglia.[124] Amidst this evolving process, decisions reflect the presence of neuronal quorums, each signalling for a particular option, such as an outcome, an action plan, or the presence (or absence) of a particular feature in the external (or internal) environment. We presume that this decision-making process is distributed across the brain, with the idiosyncratic features of different subcircuits providing distinct constraints over the evolving competitive process.

The algorithms that best describe how these competitive processes play out over time still remain to be delineated.[121,125] Interestingly, there are numerous examples of distributed decision-making processes in biology that can provide intuition for how the same processes may play out in the human brain.[126] For instance, bacteria use chemical signals to track population decisions,[127] and both ants and bees[128] appear to rely on positive feedback patterns to determine the appropriate time to move to a new site, and in which direction to travel. In each of these cases, a key variable that tracks the ability to form quorums is the balance between the amount of information stored in individuals and the amount shared amongst the population. Importantly, this balance is precisely the variable mediated by 5-HT, which can alter the gain of layer V pyramidal neurons—the major output neuron of the cerebral cortex that fires in bursts whenever an animal undertakes an action[78]—via second-messenger mechanisms,[1] such that the neurons are either less (via 5-HT_{1A}R, Gi-mediated inhibition of axonal firing; Fig. 2B) or more (via 5-HT_{2A}R, G*q*-mediated excitation of apical feedback; Fig. 2B) likely to be involved in the evolving coalitions that define the decision-making process. Evidence from computational modelling suggest that the gain-altering mechanism of neuromodulatory systems can facilitate precisely this informational transfer,[43] wherein changes in neural gain can alter the topological configuration of macroscale brain networks, as measured by techniques such as functional MRI.[3,129] These computational links lead us to predict that, during cognitive processing, low levels of 5-HT will promote a cerebellar-dominated mode that is associated with relatively high local information storage[43] and a segregated network architecture,[3,129] whereas at higher levels of 5-HT, heightened feedback in the cerebral cortex will lead to increased information transfer[43] and a more integrated network topology.[3,129]

In summary, the impact of serotonin in the brain is a complex function of chemical precursors (i.e. tryptophan from the diet[26]), baseline firing rates (which are controlled by inputs from the hypothalamus and habenula, among others), and the receptor profiles of target structures (which can be ionotropic or metabotropic, and either facilitatory or inhibitory, depending on the specific location and characteristic of the receptors). We have described serotonin's role in shaping the balance between modes of behaviour: a cerebellar-dominant mode corresponding to exploitation and cognitive automaticity, and a cortical-dominant mode corresponding to exploration and cognitive flux. These are analogous to other dual-systems frameworks, typically couched as either goal-directed versus habitual, or model-based versus model-free. Such dichotomies do a good job of capturing key low dimensional signatures of behaviour and decision-making, however something is inevitably lost when viewing the complexities of behaviour and decision-making through a dichotomous lens.[130–132] This has contributed to the misconception that behaviour is ultimately shaped by a competitive, zero-sum game.[133] In contrast, we argue that the local versus diffuse effects of 5-HT, accompanied by regionally specific patterns of receptor densities, lay the groundwork for a system that might simultaneously support aspects of automatized behaviour, whilst engaging in explorative processes at the same time.[73] In this way, considering the role of serotonin may inform emerging theories that aim to capture more complex, high-dimensional signatures of behaviour and decision-making where dual-systems interact.[130]

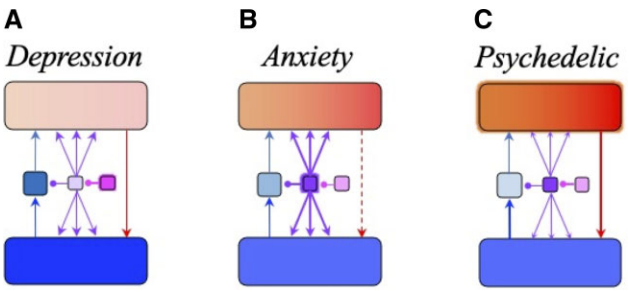

Figure 4 Psychiatric symptoms associated with abnormal serotonergic states. (**A**) Depression/compulsion is analogous with cognitive constipation—i.e. relatively low levels of 5-HT lead to a relatively cerebellar-dominant mode of processing. (**B**) Anxiety is analogous with cognitive diarrhoea, in that there is a relatively high level of 5-HT despite the fact that there are no problems to solve. (**C**) The psychedelic state is related to low levels of raphe firing but high levels of externally-induced 5-HT_{2A}R agonism—in this way, psychedelics are analogous to cognitive laxatives.

The impact of serotonergic pathology

There are an impressive number of studies linking dysfunction of the serotonergic system to specific features of psychopathology. Rather than attempt to highlight each of these links (for a review, see Lin *et al.*[17]), we will instead sketch out a few interesting implications for disease states that emerge from the analogy we have made between the brain and the GIT. Rather than focusing on specific disorders, we will highlight several illustrative symptoms with an eye towards our alimentary analogy.

If we conceptualize central 5-HT as regulating the balance between automatic versus novel, explorative behaviour, then insufficient 5-HT activity relative to the demands of the behavioural landscape may lead to an individual becoming overly reliant on recurrent, well-established behaviour patterns. This scenario would result in thoughts and behaviours that are increasingly stereotyped and inflexible—which can be thought of akin to 'cognitive constipation' (Fig. 4A). Two examples where this scenario occurs in clinical populations are depressive rumination and compulsive behaviour. Early improvements in depressive disorders treated by serotonergic medications can be attributed to altering recurrent, maladaptive thought processes, which may resolve the cognitive experience of 'being stuck in a rut' or rumination that is characteristic of a major

depressive episode.[134] The lack of 5-HT-mediated inhibition of hippocampal sharp-wave ripples[40,41] would potentially shift the balance of cognition towards endogenous over exogenous sources, which may in turn further exacerbate abnormal patterns of self-referential thinking.[135,136] Importantly, there is now early support suggesting that drugs acting on 5-HT_{2A}Rs might be useful in the treatment of depression.[137–140] The augmentation of 5-HT_{2A}Rs would contribute to a flux state—consistent with the idea that serotonergic therapy has a permissive function: shifting the system towards a set of possible options,[141] allowing individuals to reappraise situations that they had otherwise responded to relatively automatically.[142]

Compulsive behaviour occurs in many neuropsychiatric disorders. It refers to the tendency to respond in a perseverative, stereotyped way that is inappropriate to the current context.[143] In this way, compulsivity represents a context-insensitive reliance on automatized behavioural patterns, mirroring the rigidity and inflexibility we associated with cognitive constipation above. A wealth of cross-species work links low 5-HT with perseverative responding.[144–147] This perseverative responding is commonly measured in the context of reversal learning tasks,[148] whereby perseverative errors interfere with an animal's ability to switch to a new response contingency. Together, this supports low 5-HT biasing the system towards previously learnt (but no longer appropriate) responses, instead of exploring other available options. Relevant to our framework, compulsive responding has been even more specifically linked with 5-HT_2R activity, although 5-HT_2R subclasses may make distinct contributions: 5-HT_{2A}R antagonism increases perseverative responding (as we might predict), whereas 5-HT_{2C}R antagonism has the opposite effect and improves performance (although this effect may be driven by downstream increases in dopamine transmission caused by 5-HT_{2C}R antagonism[149–151]). Neuroanatomically, serotonergic actions at the orbitofrontal cortex have been a key focus in understanding the systems-level alterations that cause compulsive behaviour.[152] While it has received comparatively far less attention, a role for cerebellar dysfunction in compulsive behaviour is recognized.[153,154] Our framework would predict that relatively low levels of 5-HT would contribute to a cerebellar-dominant mode, where automatic behaviours are expressed at the expense of flexible, exploratory behaviours.

In contrast to depression, symptoms such as anxiety may instead relate to heightened levels of serotonin (Fig. 4B). Another parallel can be drawn here, considering such cases as analogous with 'cognitive diarrhoea'—despite the fact that all food has been digested, there is still a high amount of functionally unnecessary peristalsis. At first glance, the fact that depression and anxiety disorders are frequently comorbid might suggest a difficulty in reconciling the presence of simultaneous cognitive constipation and diarrhoea. Yet, considering that anxiety and depression, while two distinct symptoms, may partly be driven by disruption to a common system (i.e. 5-HT), it is perhaps unsurprising that we see their co-occurrence in individuals. Indeed, as we have highlighted in this Perspective, how 5-HT shapes behaviour is exquisitely sensitive to an organism's environmental and motivational context. In a compromised 5-HT system, it is conceivable that a given context may drive 5-HT levels outside of their optimal range in either direction, contributing to certain facets of anxiety or depression manifesting in the same individual. This is consistent with observations across neuropsychiatric disorders where seemingly opposite symptoms (e.g. apathy and impulsivity) tend to co-occur, and are attributed to context-sensitive disruptions in common neural systems—rather than representing opposing ends of a static, unidimensional spectrum.[155–157] Achieving a parallel with the GIT, such co-occurrence of diarrhoea and constipation is known as 'overflow diarrhoea' and occurs when a compromised system is pushed outside of its optimal range in both directions.

There is evidence from both invertebrate[158] and vertebrate[159] model organisms to support the links between heightened levels of 5-HT and anxiety-like behaviours. The patterns make sense from an adaptive perspective—if an animal learns to distrust the opportunities and affordances present within its local environment, exploitative behaviours will diminish as the animal searches for new options to fulfil its needs. Importantly, the cause of elevated 5-HT will likely be multi-factorial. For instance, 5-HT could be high due to genetic polymorphisms (e.g. in serotonin re-uptake transporters[160]), a poor world-model (i.e. a failure to effectively anticipate opportunities to exploit[161]), stress[162–164] or (as we expect) a complex combination of all of these factors. In this light, the literature on learned helplessness[165]—the prominence of anxiety-like behaviours following exposure to an uncontrollable stressor—becomes of major interest. Animals that are stressed to extreme levels show a substantial increase in 5-HT release from the dorsal raphe nucleus.[166] In normal circumstances, this elevation in 5-HT would recruit 5-HT_2Rs and hopefully afford new options for removing the source of the stress. However, given that the animal can't control the stressor, there are no new behavioural options for the 5-HT_2Rs to facilitate. The passivity and instrumental learning deficits that persist with this heightened dorsal raphe activation,[165] imply an animal that cannot adaptively explore affordances in its environment. In this way, we can conceptualise anxiety as a heightened 5-HT state with no options for reducing the issues that are recruiting the increase in 5-HT. This could also be why higher doses of the same serotonergic medications used in depression are sometimes required to treat anxiety disorders, but also why lower starting doses are recommended to limit further agitation or worsening initial anxiety, and why longer periods are generally recommended to consider a trial of medication adequate (i.e. allowing the time required for remodelling of the serotonergic synapses).[167,168] Again, treatments that use re-appraisal techniques can be extremely helpful in these scenarios,[169] as they suggest novel means for the 5-HT_2R system to reduce the problem.

There is also evidence that heightened agonism of 5-HT_{2A}Rs can mediate abnormal perceptual experiences, such as hallucinations, and disorders of thought, such as delusions.[170–172] Many atypical anti-psychotic medications antagonize 5-HT_{2A}Rs[173,174] (among other receptor targets[173]), which both suggests a crucial role for heightened 5-HT levels in a range of different psychiatric disorders. Importantly, these same receptors are heavily agonized by classical psychedelic agents, and as such, the agonism of these receptors has been hypothesized to underpin the majority of subjective experiences associated with the 'psychedelic state'[175–178] (Fig. 4C). Fascinatingly, it was recently shown that there is a physical explanation for why psychedelic agents act as such strong agonists at 5-HT_2Rs—the diethylamide portion of LSD acts like a physical lid that keeps the chemical bound to the receptor for extended periods of time.[179] Interestingly, a range of common psychedelic agents can strongly augment 5-HT_{2A}R across longer timescales than 5-HT_{2A}R are typically agonized by endogenous 5-HT, and hence promote a hyper-flux state, where cortical processing relies more on diverse top-down effects, which help to over-ride previously learned stimulus-response patterns of thoughts and behaviour.[12,89,180] This argument stems from the cellular mechanism described above: the activation of 5-HT_{2A}Rs enhances the effect of top-down

processing on neurons. This capacity helps to explain why psychedelics offer therapeutic benefits across a wide range of psychological disorders which, despite different underlying pathologies, share a tendency towards repetitive thoughts and behaviours that can only be alleviated by establishing new, adaptive associations.[12,181] There is now substantial neuroimaging[182,183] and computational modelling[184] evidence to support this integrative feature as the systems-level signature of the effect of psychedelic drugs on the human brain.[185]

With respect to future clinical advances, our model could provide a framework for understanding the novel serotonergic agents to treat as-yet unaddressed aspects of psychopathology. For example, the novel antipsychotic pimavanserin—a selective $5HT_{2A}$ antagonist/inverse agonist (with weaker $5HT_{2C}R$ antagonism) without dopamine receptor antagonism—has demonstrated benefits as an add-on treatment to atypical antipsychotics for individuals experiencing predominant negative symptoms of schizophrenia.[186] While the aetiology of negative symptoms in schizophrenia is not completely understood, it is noteworthy that patients with predominantly negative symptoms exhibit cortical hypometabolism and cerebellar hypermetabolism,[187] and diminished connectivity between the prefrontal cortex and cerebellum corresponds to negative symptom severity, with negative symptoms improving following transcranial magnetic stimulation (TMS)-induced increases in connectivity between these sites.[188] The above suggests a potentially cerebellar-dominant mode of functioning contributing to negative symptoms. While it may initially appear counter-intuitive that $5HT_{2A}$ antagonism could rescue a cerebellar dominance of brain function underlying negative symptoms, it could be hypothesized that once $5HT_{2A}$Rs have been saturated by atypical antipsychotics and pimavanserin, the less robust action of pimavanserin as an antagonist at $5HT_{2C}$Rs is responsible for the clinical improvement (potentially through its impact on selective dopaminergic circuits, a discussion that is beyond the scope of the current proposal). This hypothesis is supported by work in mouse models with D_2R receptor overexpression, where motivational negative symptoms are improved by systemic injection of a 5-HT_{2C}R antagonist.[189] A 5-HT_{2C}-mediated recruitment of the frontal cortex has been identified, as $5HT_{2C}R$ antagonism increases frontal dopamine and noradrenaline (without altering levels of serotonin[190])—suggesting this may be a mechanism for upregulating frontal activity to overcome cerebellar-driven negative symptoms. However, given the preferential binding of pimavanserin to $5HT_{2A}$Rs this likely only occurs once $5HT_{2A}$Rs are already saturated by both atypical antipsychotic and pimavanserin binding. Thus, our model linking serotonergic function to cerebellar-cortical interaction can serve as a framework to guide this critical area for further investigation, as negative symptoms remain unaddressed by the D_2R antagonism common to antipsychotic action, and they profoundly impact quality of life and limit social and occupational functioning in schizophrenia.

Another phenomenon that clearly overlaps the gastrointestinal and neurological function of the serotoninergic system is nausea. Although nausea is typically a prelude to the act of overt vomiting (or emesis), the former has not been translated to animal models near as frequently as the latter.[191] In humans, visually induced nausea positive correlates with cortical activity, but negatively with cerebellar activity.[192] While there remains limitations to the physiological understanding of nausea, the serotonergic system likely makes an important contribution as it does in emesis.[193] Serotonergic medications used to treat nausea and emesis (e.g. ondansetron) are antagonists of the 5-HT_3R acting centrally at the chemoreceptor trigger zone and peripherally at intestinal vagal and spinal afferents. Interestingly, ondansetron is currently being investigated as an adjunctive therapy in schizophrenia,[194] a novel treatment for hallucinations in Parkinson's disease[195] as well as anxiety disorders.[196] We propose that our model for understanding the overlap of neurological and gastrointestinal serotonergic systems could serve as a framework for further clinical investigation of nausea and its treatments—as nausea can be common to both psychopathology and its medication side effects, and represents both a distressing experience and an important phenomenological signal for the organism that something is awry in the brain and body.

Concluding remarks

Here, we have outlined a novel perspective on the role of serotonin in the CNS that respects the predominantly gastrointestinal organization of the serotonergic system. Serotonin is of course not the only neurotransmitter associated with cognition and behaviour that also regulates gastrointestinal processes—dopamine, noradrenaline and acetylcholine likewise play important roles in the GIT.[197] Yet would we expect to derive such insights into brain and behaviour, via studying these neurotransmitters at the level of the GIT? Perhaps, but it seems rather unlikely. The phylogenetically ancient serotonergic feeding networks that arbitrate approach/avoidance decisions in invertebrates are thought to be precursors of the evermore complex foraging, explore-exploit behaviours of vertebrates.[198–200] In this way, the serotonergic GIT may afford us privileged insight into the more elusive aspects of serotonergic brain function.

We have argued that intermediate levels of serotonin promote a state of cognitive automaticity, in which agents rely on existing cognitive models to exploit known resources. With heightened levels of serotonin, animals instead begin to explore the cognitive landscape in an effort to identify new resources that can later be exploited. In this way, levels of 5-HT are proposed to arbitrate between automatic and flexible modes of cognitive processing, shaping the manner in which distributed patterns of neural activity across the brain coordinate in order to mediate decision making processes. Further, we propose that numerous dysfunctional psychological states can be reappraised as impairments in the balance between satiety and frequency. We hope that this manuscript will help to stimulate future research, and more broadly, to integrate models of nervous system function with well described mechanisms in the other organ systems of the body.

Funding

J.M.S. was supported by an NHMRC fellowship (1193857) and the University of Sydney. C.O. was supported by a Talented Researcher Fellowship from the University of Sydney. J.A. was supported by the European Social Fund through the IT Academy Programme and the Estonian Research Council grant PSG728.

Competing interests

The authors report no competing interests.

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