BRAIN
REVIEW ARTICLE

A role for the serotonin 2A receptor in the expansion and functioning of human transmodal cortex

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Integrating independent but converging lines of research on brain function and neurodevelopment across scales, this article proposes that serotonin 2A receptor (5-HT2AR) signalling is an evolutionary and developmental driver and potent modulator of the macroscale functional organization of the human cerebral cortex. A wealth of evidence indicates that the anatomical and functional organization of the cortex follows a unimodal-to-transmodal gradient. Situated at the apex of this processing hierarchy—where it plays a central role in the integrative processes underpinning complex, human-defining cognition—the transmodal cortex has disproportionately expanded across human development and evolution. Notably, the adult human transmodal cortex is especially rich in 5-HT2AR expression and recent evidence suggests that, during early brain development, 5-HT2AR signalling on neural progenitor cells stimulates their proliferation—a critical process for evolutionarily-relevant cortical expansion. Drawing on multimodal neuroimaging and cross-species investigations, we argue that, by contributing to the expansion of the human cortex and being prevalent at the apex of its hierarchy in the adult brain, 5-HT2AR signalling plays a major role in both human cortical expansion and functioning. Owing to its unique excitatory and downstream cellular effects, neuronal 5-HT2AR agonism promotes neuroplasticity, learning and cognitive and psychological flexibility in a context-(hyper)sensitive manner with therapeutic potential. Overall, we delineate a dual role of 5-HT2ARs in enabling both the expansion and modulation of the human transmodal cortex.

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Introduction

Neuroscience has long sought to understand how the size and complexity of the human cerebral cortex relates to the remarkable cognitive capacities of our species. This line of inquiry has increasingly highlighted the central role of the human transmodal association cortex: the set of limbic, paralimbic and heteromodal regions whose activity and connectivity reflect the higher-order integration of inputs from multiple modalities.[1,2] Contrasted with the rest of cortex, human transmodal association cortex has undergone a remarkable and disproportionate degree of expansion relative to non-human primates[1,3-6]—an expansion that is also mirrored by protracted ontogenetic development, with developmental trajectories extending into the second decade of life.[3] In addition, a multimodal body of research has increasingly identified a set of anatomical, genetic, molecular, physiological and functional features that set transmodal cortex apart from unimodal cortex and which are thought to enable the functional complexity necessary for the emergence of human cognitive, socio-emotional and cultural functioning.[1,5,7-11] This research has revealed that a continuous gradient of variation from unimodal to transmodal cortex may constitute the primary macroscale organizational scheme of the cortex.[1] Such findings are consistent with seminal and highly influential work which, on the basis of anatomical characteristics derived from tract-tracing and histology, identified a 'sensory-fugal' hierarchical axis spanning the cortical mantle, moving from modality-specific (primary and unimodal) sensory processing to multimodal integration, to higher-order integrative processing in transmodal cortices.[2]

Collectively, research to date suggests that the transmodal cortices represent the apex of the macroscale cortical hierarchy—from specialized, concrete unimodal processing to integrative, abstract transmodal processing—and play a central role in orchestrating human cognitive and behavioural capacities. Consistent with this, task-based functional neuroimaging investigations have implicated the transmodal cortices in a range of 'high-level' cognitive processes including attention and executive cognition, episodic and semantic memory, social cognition and narrative comprehension.[12,13] A large body of work has also implicated disruptions of transmodal cortex structure and/or function in a variety of neurological and psychiatric illnesses.[1,14,15]

Interestingly, a growing body of evidence suggests that acute pharmacological modulation of the transmodal cortices may have therapeutic potential.[16,17] This work consists of investigations with serotonergic psychedelic drugs such as psilocybin and lysergic acid diethylamide (LSD), compounds that elicit their primary effects via partial agonism at the 5-HT2A receptor (5-HT2AR)—an excitatory receptor that is most densely expressed in transmodal cortices.[18] Several preliminary clinical trials have found that 5-HT2AR agonist psychedelic drugs, when combined with supportive psychotherapy, can induce long-lasting symptom reductions following only one to three drug sessions.[19] Evidence is presently strongest for depression[20-24] but suggestive results have also been found for end-of-life distress in terminal patients,[25,26] tobacco addiction[27] and alcoholism.[28] Research with psychedelics has also specifically implicated 5-HT2AR in plasticity- and flexibility-promoting processes, at structural, functional and behavioural levels.[29-34] This suggests a unique ability for this class of compounds to modulate or transiently upregulate the properties characteristic of transmodal cortex—with therapeutic relevance.

In addition, recent findings have also begun providing support for a potential role of 5-HT2AR signalling in mammalian cortical expansion—both phylogenetically and ontogenetically—especially in relation to the disproportionate expansion of human transmodal cortex. Notably, a recent multi-species study found that 5-HT2A signalling in early developing cortical tissue significantly promoted the proliferation of basal progenitors that putatively underlie the evolutionary expansion of the human cortex.[35] This pro-proliferative role in basal progenitors appears to be unique amongst the neurotransmitters and neurotransmitter receptors[36] and is consistent with a large body of work implicating serotonin (5-HT) in a variety of critical neurodevelopmental processes.[37,38] In this regard, it is also intriguing to highlight that high resolution *in vivo* PET molecular imaging of 5-HT receptor distributions in the adult human brain has revealed that the spatial topography of 5-HT2AR densities strongly resembles the unimodal-transmodal cortical gradient, with highest densities in transmodal cortex.[18] (We note that primary visual cortex constitutes a notable exception to this pattern, given that it is situated at the opposite end of the cortical hierarchy from transmodal association cortex but is also rich in 5-HT2AR expression. We return to this point in later sections.)

Overall, there is converging evidence that: (i) 5-HT2ARs are most densely expressed in the disproportionately expanded transmodal cortex of the human brain; (ii) 5-HT2ARs are core contributors to both the ontogenetic and phylogenetic expansion of transmodal cortex; and (iii) 5-HT2AR agonism, particularly via serotonergic psychedelics, can potently modulate the functioning of transmodal cortex, thereby engaging neural and behavioural plasticity in the adult brain. In the present article, we focus on 5-HT2AR, bringing together these independent but complementary lines of research to provide an integrative account of the role of 5-HT2AR signalling in shaping the developmental expansion and adult functioning of the human transmodal cortex. We argue that thanks to the role that they play in the expansion of transmodal cortex—the apex of the human cortical hierarchy—5-HT2ARs may become especially well positioned to subsequently modulate the adult functioning of transmodal cortex. We highlight how this is supported by nascent research on 5-HT2AR agonist serotonergic psychedelic drugs, which have been found to induce complex and wide-ranging subjective effects, alongside a variety of therapeutically-relevant acute and post-acute structural, functional and behavioural changes.

Transmodal association cortex: the centrepiece of human cognitive architecture

Hierarchical organization of the human cerebral cortex

Humans' 'success' as a remarkably populous species is unquestionably linked to our ability to engage in complex cognition and cognitive neuroscience has revealed that our species' high-order cognitive faculties are fundamentally dependent on the outermost component of the human brain: the cerebral cortex. The human cerebral cortex is an exceptionally complex organ, with marked regional anatomical heterogeneity. Investigations of cortical variation in cytoarchitectonics and connectional anatomy[39-42] have delineated a continuous 'sensory-fugal' hierarchy from primary sensory and unimodal cortices to transmodal association cortices.[2,41] According to this scheme, each end of the hierarchy processes inputs of a different nature: whereas unimodal cortex only responds to stimuli pertaining to one specific modality (e.g. vision or audition), transmodal cortex is situated at the convergence of multiple sensory streams[2] and this organization outlines a progression from domain-specific sensory processing to integrative domain-general abstract processing.

Remarkably, a rapidly growing body of convergent multimodal evidence suggests that the unimodal-transmodal hierarchy represents an 'archetypal axis' that delineates principal dimensions of several axes of functional, structural, cellular and molecular variation across the cortex (Fig. 1).[1,43] This work has found that, relative to unimodal cortex, regions closer to the transmodal (and especially heteromodal) apex of the axis are characterized by lower neuron density,[44] a predominance of infragranular (feedback) efferent connections,[10] lower laminar differentiation,[45] lower intracortical myelination[7,46,47] and greater aerobic glycolysis,[48] increased excitability and greater density of large and dendritically complex pyramidal cells,[44,49-51] greater cortical thickness[3,52,53] and lower structure-function coupling.[54-56] This macroscale unimodal to transmodal hierarchy based on neuroanatomical considerations is also recapitulated by the principal axis of variation in intrinsic cortical functional connectivity from functional MRI.[8,43] In addition, functional connectivity research has found that cortical signals propagate in a sensory-fugal fashion from specialized and modular sensory processing in unimodal cortex, to distributed and integrative processing in transmodal cortices.[54,57] The convergence of these characteristics is thought to confer the unique functional properties of transmodal cortex, which afford complex human behaviour and cognition, as detailed in the following sections.

Transmodal association cortices orchestrate higher cognitive function

Transmodal association cortices represent the point of convergence for diverse modality-specific inputs.[2,58,59] This anatomical insight is reflected at the functional level. At the lower, sensorimotor end of the hierarchy, localized electrical stimulation induces modality-specific sensations—whereas the elicited experiences become richer and multimodal upon stimulation of transmodal associations cortices.[60] (The human transmodal cortex as neuroanatomically defined in early work is divided into the cytoarchitectonically and connectionally distinct heteromodal, limbic and paralimbic transmodal cortices.[2] In the present context we focus primarily on heteromodal transmodal cortex, which represents the integrative apex of transmodal cortex itself.)

Across a variety of task paradigms, functional MRI (fMRI) has revealed that primary cortices exhibit preferential involvement with modality-specific tasks and processing, such as motor control and visual/auditory/somatosensory stimulation.[8,61,62] In contrast, transmodal (and in particular, heteromodal) association cortices show relatively greater engagement during complex cognition. Even at rest, canonical 'intrinsic networks' are consistently observed across participants, which closely resemble activation patterns observed with task-based analyses.[63,64] This work has revealed that the transmodal cortex can be subdivided into at least two distinct intrinsic networks, typically referred to as the 'frontoparietal control network' and the 'default mode network' (DMN). The frontoparietal control network mainly comprises lateral prefrontal and parietal cortices, and is recruited during engagement with cognitively demanding tasks, irrespective of modality.[13,65] The DMN's key components include the posterior cingulate and precuneus, medial prefrontal cortex and (bilateral) inferior parietal cortices.[66] Although also capable of supporting externally-directed cognition in tasks that require or are facilitated by past knowledge,[67-70] the DMN is especially involved in abstract cognitive operations that rely upon perceptually decoupled mnemonic information and transcend the here-and-now.[12,71,72]

Taken together, data-driven functional investigations, as well as causal evidence from brain lesions and stimulation, converge on the conclusion that cognitive sub-specialization is present within the brain and that transmodal cortex is particularly involved in domain-general and complex forms of cognition that are most characteristic of humans.

Flexibility as key feature of transmodal association cortex

Having established the empirical relevance of transmodal association cortex for high-order human cognition, we are left with a central question: Why is transmodal cortex well suited to orchestrate high-order cognitive functions? We believe the answer lies in the exceptional 'functional flexibility' of the human transmodal cortex (and especially, heteromodal cortex)—an 'umbrella' construct or property that can be understood in multiple complementary ways (Fig. 2).

First, the flexibility of regions at the top of the cortical hierarchy is evident in terms of diversity, in terms of several characteristics: they exhibit the widest dynamic range of spontaneous temporal fluctuations[74]; and diverse (highly variable) patterns of intrinsic functional connectivity[77]; they adaptively shift their connectivity patterns in response to task demands,[76] while balancing flexibility and specialization[78]; and they exhibit the greatest diversity of neurotransmitter receptors across layers, as quantified from postmortem autoradiography.[10] Taken together, this evidence helps to explain how the transmodal association cortices can produce highly adaptive and flexible responses.

Second, the workings of the apex of the hierarchy are flexible in terms of their relative independence from the dictates of anatomy. Sensory cortices are strongly tethered to input from the sensory organs (relayed via the thalamus) but the same is not true of the transmodal cortices. Relatedly, functional and structural connectivity are increasingly decoupled along the cortical hierarchy.[55,56,73] More broadly, transmodal association cortices are developmentally constrained by the brain's myeloarchitecture and molecular and transcriptomic gradients to a lesser extent than are the unimodal

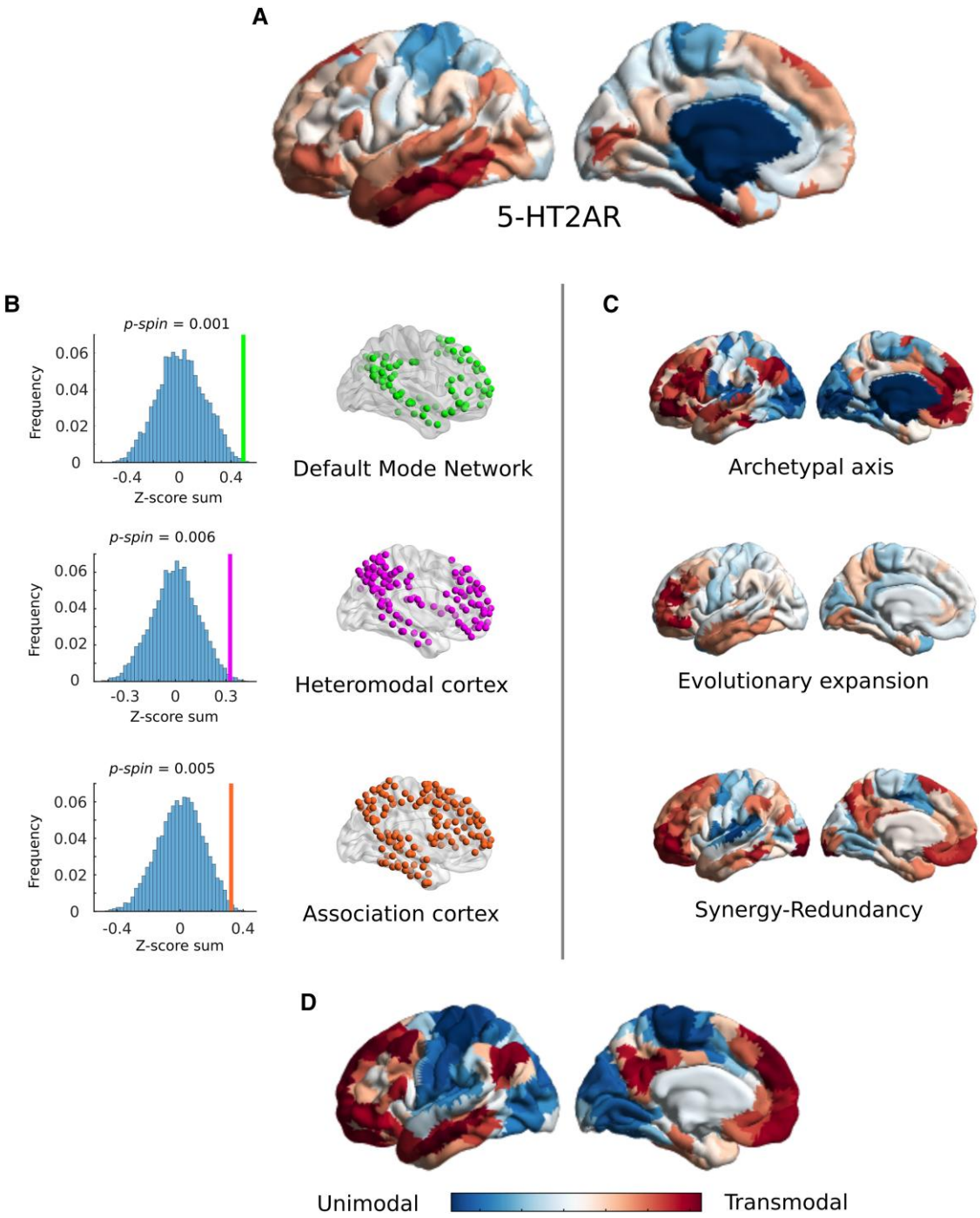

Figure 1 Hierarchical distribution of 5-HT2ARs in the human cortex. (**A**) A recent high resolution map of the regional availability of 5-HT2ARs in the human brain obtained from *in vivo* PET imaging.[18] (**B**) We show that the cortical 5-HT2AR distribution is significantly enriched at the apex of the cortical hierarchy, whether defined in functional terms (default mode network), or anatomical feed-forward projections (Mesulam's heteromodal cortex, which is part of transmodal cortex); or cytoarchitectonics (association cortex from Von Economo's classification). In each case, significance ('p-spin') is assessed against a null distribution with preserved spatial autocorrelation, with a coloured vertical bar indicating the empirically observed value.[114] (**C**) We also show that serotonin 2A receptor densities in the human cortex are spatially aligned with the regional pattern of cortical expansion with respect chimpanzees (*P. troglodytes*), the species closest to *Homo sapiens* in evolutionary terms[4]; a recently defined 'archetypal axis' of cortical organization, obtained by combining 10 distinct gradients of cortical variation defined from functional, structural, cytoarchitectonic, myeloarchitectonic, genetic and metabolic evidence[1]; and a gradient from redundancy-dominated to synergistic information processing, based on functional neuroimaging.[110] (**D**) Functional characterization of the unimodal-transmodal gradient, based on Margulies *et al.*[8]

cortices.[47] Indeed, molecular and transcriptomic gradients have, themselves, been shown to delineate hierarchies related to both anatomy and cognition.[9,11,79] Finally, it is also worth noting that, although most pronounced in humans, transmodal cortices have also been found to be less structurally constrained relative to unimodal cortices in macaques.[80]

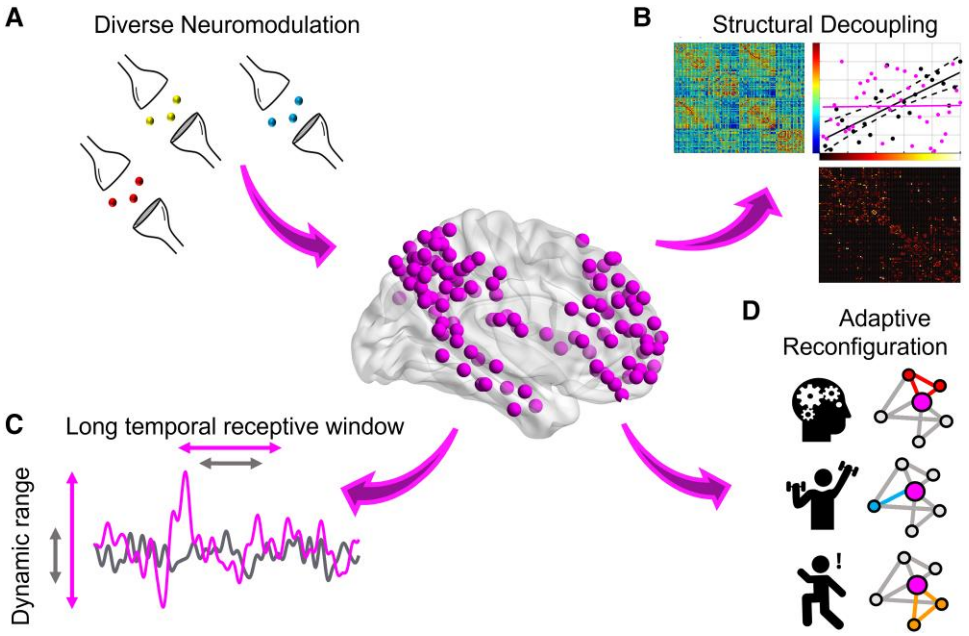

Figure 2 Flexibility of transmodal association cortex. Transmodal association cortex is flexible across multiple dimensions. (**A**) It exhibits the most diverse patterns of neurotransmitter receptors.[10] (**B**) Seed-based patterns of functional connectivity centred in transmodal cortex are relatively decoupled from the underlying patterns of macroscale structural connections[55,56,73]; purple elements of the scatter-plot indicate correlation between entries of the functional connectivity matrix (*y*-axis) and structural connectivity matrix (*x*-axis) for a region in transmodal cortex; black elements reflect the structure-function correlation for a region in unimodal cortex. (**C**) Activity in transmodal cortices exhibits relatively long windows of temporal integration and a wide dynamic range.[74,75] (**D**) Transmodal cortices exhibit varying connectivity in response to different task demands.[76]

Third, the apex of the hierarchy is flexible in terms of its independence from immediate sensorimotor contingencies. This is reflected in differences in the temporal characteristics of regional activity. The transmodal association cortices are characterized by temporally extended 'receptive windows', enabling them to reflect and bring together information from events taking place across greater periods of time.[75,81-84] For example, research with naturalistic movie-viewing has found that, while unimodal cortices track second-by-second changes in sensory information, transmodal cortices integrate scene/event-related information over multiple seconds to minutes to support abstract, multimodal interpretational processes.[85,86] This corresponds to slower intrinsic dynamics, which have been observed to arise from structural considerations in regions of the brain's densely connected 'structural core'[87] but may also be related to higher density of NMDA NR2B, which prolong excitatory synaptic activity.[1] As such, the spatial unimodal-to-transmodal hierarchy can be recapitulated by a temporal hierarchy of intrinsic timescales.[75] The independence of transmodal cortices from immediate sensorimotor contingencies is also reflected in their spatial embedding: regions within transmodal association cortex are spatially the most distant from sensory and motor regions along the cortical surface[6,8] and are functionally the most distant, as evidenced by their occupation of the opposite end of the principal hierarchical gradient of functional connectivity similarity.[8] This is consistent with the DMN's role in going beyond the here-and-now by bringing perceptually decoupled mnemonic information to bear on ongoing experience and task demands.[12,67,69,70,88] It is also consistent with the executive control network's role in inhibiting prepotent responses evoked by immediate circumstances and the selection of alternative actions.[65,89,90] Thus, evidence indicates that transmodal cortices are less constrained by the here-and-now in terms of their functioning. In analogy with today's deep-learning architectures, in virtue of its location at the apex of the cortical processing hierarchy, the transmodal cortex may be thought of as the brain's 'deepest layer', providing the opportunity for the behavioural outputs to be informed by complex, situation- and task-specific combinations of inputs, rather than a limited range of predetermined, hard-wired input-output mappings.[12,88,91]

Collectively, the above-discussed body of work suggests that the ability for the transmodal association cortex to support the adaptive, flexible and integrative processes underlying complex human cognition can be attributed to its functional and connectional diversity, relative independence from the dictates of anatomy and relative freedom from incoming sensory information. Next, we describe research which suggests that this functional flexibility is itself scaffolded upon high anatomical plasticity—what we refer to as 'meta-flexibility'.

Meta-flexibility: plasticity of transmodal association cortex

In addition to these functional definitions of flexibility, the apex of the cortical hierarchy is also flexible in another important sense: it has an exceptionally high capacity for undergoing neuroplastic change over the lifespan. In other words, the functional characteristics described above are themselves liable to change in a flexible manner. In addition, the transmodal cortex exhibits the lowest levels of intracortical myelination, as measured non-invasively by the ratio of T_1-weighted to T_2-weighted MRI.[7,47] This is relevant because evidence indicates that after closure of the 'critical period' of brain development (i.e. a temporally restricted period of heightened sensitivity to environmental factors that is relevant for neural maturation), myelin suppresses excitatory synaptic plasticity: both by constituting a physical barrier to the emergence of new neurites, and by means of myelin-associated 'nogo' receptor

(NgR1) signalling, which has inhibitory effects.[92,93] Thus, by being comparatively low in intracortical myelination, the top of the cortical hierarchy has greater potential for synaptic plasticity.

Transmodal association cortices are also characterized by metabolic differences from other cortices, which are relevant for their capacity for plasticity. Specifically, they exhibit the highest rates of aerobic glycolysis, which is a metabolic cycle whereby energy is extracted from glucose through non-oxidative metabolism rather than CO_2-producing oxidative metabolism.[48] The unique products of aerobic glycolysis include biosynthetic materials such as pyruvate and lactate, which may provide the physical substrate for ongoing synaptic turnover.[94] Moreover, Goyal and colleagues[94] observed that the regional distribution of aerobic glycolysis in the cortex corresponds to regional transcription of juvenile genes ('neoteny')—especially those pertaining to synapse formation. This may at least partially explain why transmodal association cortices exhibit the highest synaptic density, as indicated by post-mortem analyses of cortical tissue[95] as well as *in vivo* imaging.[96,97] Thus, at the top of the cortical hierarchy we find that (i) synapse formation is least inhibited by myelination; (ii) there is transcription of genes supporting synapse turnover; (iii) aerobic glycolysis makes continuously available the kind of biosynthetic materials that would support synaptic turnover; and (iv) there is the highest synaptic density.

The extended ability for transmodal association cortices to undergo neuroplastic change is also related to their slow rate of maturation. Whereas primary cortices reach adult-like spatial organization soon after birth, the apex of the cortical hierarchy continues to develop throughout childhood and adolescence[98] with heteromodal transmodal regions within the DMN being the last to reach full developmental maturation.[99] The maturation of transmodal association cortices in the human brain is also slow compared with corresponding cortical regions in non-human primates: e.g. in macaques and chimpanzees, the prefrontal cortex reaches its peak synaptic density in the first 12 months of life, but in humans this is only achieved around 5 years of age[100] and the greatest cortical surface area is found around the first decade after birth.[101] Crucially, this prolonged period of maturation makes it possible for such regions to continue to be responsive to environmental influence and support ongoing learning through experience-dependent plasticity[102]—a characteristic that is enabled by their high transcriptional and metabolic support for plasticity. In fact, evidence indicates that aerobic glycolysis increases during childhood in a manner that coincides with periods of highest synaptic growth.[94] Intriguingly, transmodal association cortices also exhibit the greatest degree of interindividual variability in functional connectivity patterns and spatial topography,[3,6,103] reflecting the special sensitivity of these regions to diverse environmental influences.

The capacity for ongoing learning of the human brain is especially relevant because it has been shown that when organisms can learn during their lifetime, evolutionary paths can become available that would be foreclosed to non-learning organisms.[104] One especially powerful way that humans can benefit from the capacity for ongoing learning, afforded by the prolonged development and plasticity of transmodal cortex, is learning from conspecifics. As a highly social species with the unique ability to exchange information through language, humans can benefit from cumulative intergenerational learning (e.g. the invention of fire-making[105]). Indeed, the 'Social Brain' account of human cognitive evolution highlights the need to adapt to the complex social dynamics arising from living in a group.[105] It is notable therefore that, in addition to being highly flexible and plastic, the transmodal association cortices include the core brain regions that support social cognition.[106] This suggests that the transmodal cortex may be well poised to support cultural aspects of learning and evolution.

Developmental and evolutionary expansion of human transmodal cortex

Robust multimodal research has therefore revealed that a cortical hierarchy from unimodal to transmodal cortex constitutes the primary organizational axis of the cortex, based on a convergence of anatomical and functional evidence at both the micro- and the macroscale. Next, we review evidence indicating that this hierarchical organization also coincides with the pattern of cortical expansion across both ontogeny and phylogeny, with transmodal cortices exhibiting disproportionate expansion.

On the developmental side, although the brain as a whole expands substantially during humans' exceptionally protracted developmental period, transmodal association cortices expand by an approximate factor of four—twice as much as the expansion of primary cortices.[3] This means that over the course of human brain development from birth to adulthood, transmodal association cortices come to constitute an increasing proportion of the total cortical volume—in correspondence with an increase in those cognitive capacities that are most distinctly human, such as executive control, abstract perceptually-decoupled thought and long-term planning. In other words, the progressive development of distinctly human cognitive capacities in human children coincides with the protracted ontogenetic expansion of the apex of the cortical hierarchy.

On the evolutionary side, similar conclusions about the role of transmodal association cortex in supporting distinctly human cognitive capacities can also be reached by comparing humans with non-human primates, such as the well studied macaque (*Macaca mulatta*, *M. fascicularis*) and the species most evolutionarily close to *Homo sapiens*: the chimpanzee (*Pan troglodytes*). Although the substantial differences between species and their unique environmental adaptations should not be underestimated when comparing cognitive abilities, it is evident that the range and complexity of cognitive aptitudes in humans far exceeds that of other mammals, including other primates. It is therefore reasonable to wonder what aspect(s) of the human brain most differentiate it from the brains of other primates. Even after accounting for differences in total brain size, humans exhibit disproportionate expansion of transmodal association cortices compared with other primates.[4,6,107] Transmodal association cortices also notably express the highest rate of human-accelerated genes pertaining to brain function and development.[4] Intriguingly, the regional prevalence of synergy (the super-additive gain in information that is present when two elements are considered together, such that the whole is greater than the sum of its parts[108,109]) over redundancy (the extent to which regions are interchangeable in terms of the information they encode) also reaches its peak in the transmodal association cortex, correlating with a region's degree of evolutionary expansion and expression of human-accelerated genes.[110] The overall reliance on synergy (but not redundancy) is also significantly higher in the brains of humans versus macaques[110] providing additional evidence for its intimate link with higher-order cognition.

Taken together, multimodal research has revealed that a cortical hierarchy from unimodal to transmodal cortex constitutes the primary organizational axis of the cortex. In the next section,

we review the neurobiological underpinnings that underlie the exceptional expansion of transmodal cortex.

5-HT2A receptors as potent modulators and key developmental drivers of human transmodal cortex

In the preceding sections we have established the unique structural and functional properties of transmodal cortex, highlighting its flexibility, plasticity and location at the apex of the cortical hierarchy. In what follows we review emerging research on 5-HT2AR supporting its potent ability to modulate the functioning of human adult transmodal cortex and its potentially critical role in driving its developmental expansion.

Neuroanatomical localization of the 5-HT2A receptor along the cortical hierarchy

The most reliable characterization of 5-HT2AR spatial distributions in the adult human brain comes from high-resolution PET imaging studies, which used the 5-HT2A/2C agonist radioligand ^{11}C-Cimbi-36.[18,111] 5-HT2AR distributions revealed by this radioligand correlate strongly with the more selective 5-HT2A (antagonist) radioligand ^{18}F-altanserin ($R^2 = 0.87$), while exhibiting greater test-retest reliability and sensitivity to high affinity receptor states.[111] *In vivo* human PET mapping with ^{11}C-Cimbi-36 has found that 5-HT2ARs are the most cortically expressed of all 5-HT receptor subtypes[18,112,113]and, critically, that 5-HT2AR densities are highest in transmodal cortex,[18,111] with the overall receptor distribution recapitulating the unimodal-transmodal cortical hierarchy.[18] We have quantitatively confirmed this visually-apparent spatial convergence (Fig. 1).

In addition to their high localization in human transmodal cortex, it is noteworthy that 5-HT2ARs, although expressed by both neurons and glial cells across layers, are especially enriched in layer 5 pyramidal neurons (L5Ps).[115-119] L5Ps are the primary excitatory neurons of the cortex and are critical for information integration at both local and whole-brain levels. At the local level, their dendrites span all cortical layers, enabling them to integrate layer-specific feedback and feed-forward signals.[120,121] At the whole-brain level, L5Ps exhibit long-range projections, which facilitate the integration of spatially distributed cortical and subcortical regions.[120,121] As such, L5Ps—particularly those that reside in transmodal cortex—are well positioned to enable hierarchical information integration at both columnar and global scales, and thereby regulate global brain connectivity and dynamics.[120,121] The localization of 5-HT2ARs on L5Ps within transmodal cortex therefore suggests that these receptors are poised to have a strong ability to modulate transmodal function and cortical hierarchical organization.

Basal progenitor cells, the 5-HT2A receptor and uniquely human cortical expansion

Intriguing additional support for linkages between the 5-HT2AR and transmodal cortex comes from recent research supporting a critical role for 5-HT and the 5-HT2AR in particular, in the developmental expansion of human transmodal cortex. A large body of previous work has highlighted 5-HT as a critical regulator of neurodevelopmental processes.[37,38] Pharmacological and transgenic studies to date have linked 5-HT to a variety of developmental processes, including neuronal differentiation, migration and myelination, axonal guidance and synaptogenesis, and dendritic pruning.[37,38,122-126] Several of these functions occur prior to the formation of synaptic circuits and therefore can be said to constitute 'non-neurotransmitter' roles for 5-HT. Indeed, evidence from the developing mouse brain indicates the presence of placental sources of 5-HT prior to the embryo's endogenous 5-HT delivered to the developing neocortex, during a time period that overlaps with multiple neurodevelopmentally critical events.[127] In addition, dysregulation of 5-HT signalling during early development (e.g. altered maternal 5-HT levels) has been strongly linked to the emergence of developmental and mood disorders, including autism, Down syndrome, generalized anxiety disorder and depression.[38] Critical to the present context, a recent multi-species study notably revealed that 5-HT, via 5-HT2AR signalling, may be critical for evolutionarily-relevant processes, which underpin human cortical expansion and, by extension, the disproportionately expanded human transmodal association cortex.[35] We will now briefly provide important background prior to fully explicating this study.

Investigations of the mechanisms underlying cortical expansion have highlighted the importance of inter-species differences in cortical neurogenesis, a core neurodevelopmental process that hinges on the relative abundance and proliferative capacity of neural progenitor cells (NPCs).[128-131] Comparative studies and studies using transgenic models have found that genetic alterations to distinct NPCs can, depending on the type of NPC targeted, result in distinct differences in cortical surface area, thickness and/or folding.[34,128] Among the NPC types, so-called basal progenitor cells—and basal radial glia (bRG) in particular—exhibit marked differences across species and are particularly proliferative in gyrencephalic species, reaching their pinnacle in humans.[128,132] bRG represent only 10% of neural progenitors in rodent species, whereas they represent ~50% in macaques and upwards of 75% in humans.[131,133,134] Exceptionally high bRG abundance and proliferation has been specifically highlighted as a primary factor in uniquely human cortical expansion[128,131] (Fig. 3).

Given the centrality of bRG in human cortical expansion, it is striking to note that 5-HT2AR signalling during early development was found to be necessary and sufficient for the evolutionarily relevant proliferation of bRG in human, ferret and mouse cortical tissue.[35] Necessity was established by the finding that disruption of 5-HT2AR in the embryonic ferret cortex specifically reduced the abundance of proliferative bRG.[35] Sufficiency was established by the finding that ectopic 5-HT2AR expression in the developing lissencephalic mouse neocortex resulted in a 2-fold increase in the abundance of bRG.[35] Rounding the findings, application of a 5-HT2AR agonist with high binding affinity (1 μM NBOH-2C-CN)[135,136] to human fetal cortical tissue *ex vivo* also resulted in a significant increase in proliferative bRG—an effect that was blocked by the administration of a 5-HT2 receptor antagonist (EMD 281014).[35] The role of 5-HT2AR is further supported by findings indicating a lack of 5-HT2AR expression in neural progenitor cells of the developing lissencephalic mouse cortex, whereas 5-HT2AR expression is evident in the developing gyrencephalic ferret and human cortex.[35,124]

A relevant question is whether our hypothesis is specific to 5-HT2AR, or whether it also applies to other serotonin receptors. With respect to 5-HT2AR specificity in cortical expansion, the study by Xing *et al.*[35] used an antagonist (EMD 281014) with affinity for 5-HT 2A, B and C receptors, thereby excluding a necessary role for receptors beyond these. Importantly, both this antagonist as well as the agonist (NBOH-2C-CN) used in this study exhibit significantly higher affinity for human 5-HT2A over 5-HT2C and 5-HT2B

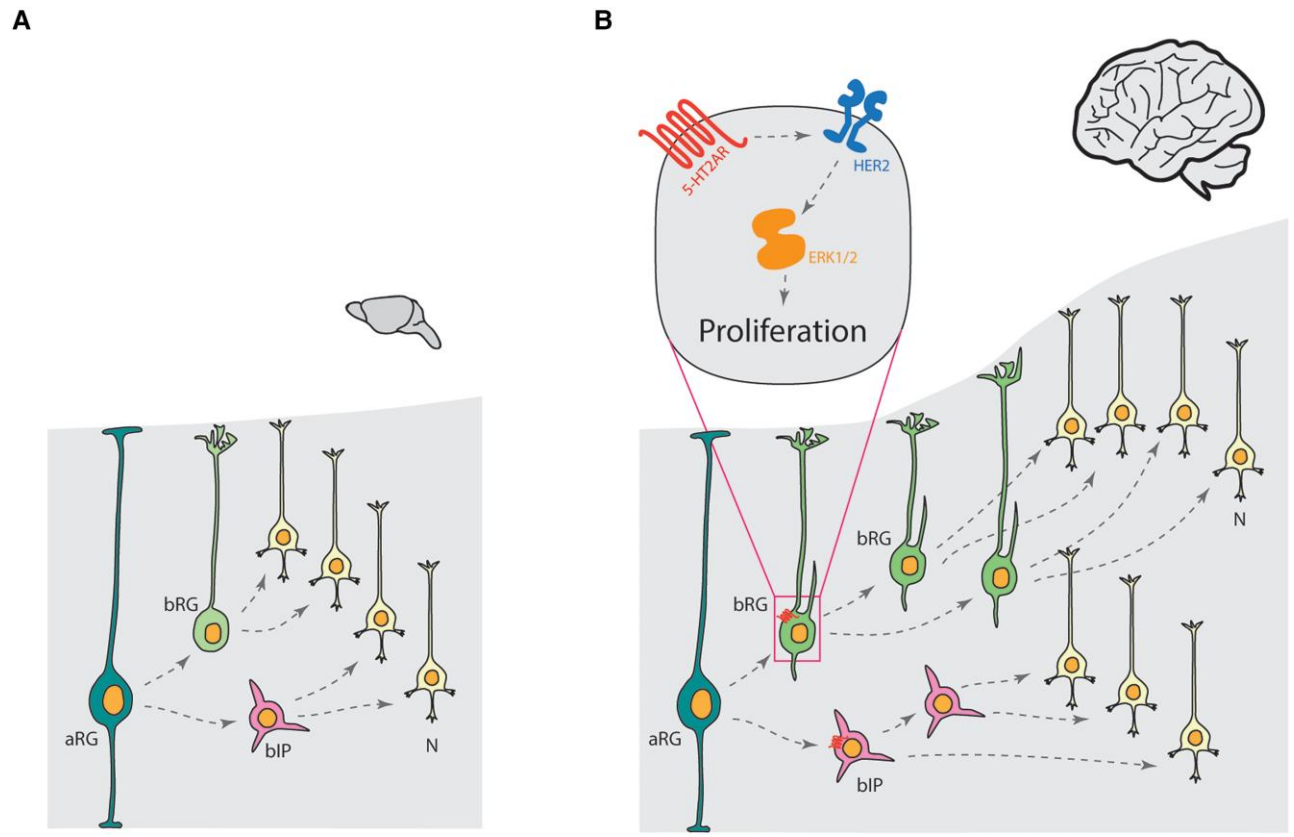

Figure 3 Model of how serotonin 2A receptor activation may contribute to the evolutionary expansion of the human neocortex. (**A**) Lineage relationships of neural progenitor cells in the developing mouse neocortex, where serotonin 2A receptor is absent. (**B**) Lineage relationships of neural progenitor cells in the developing human neocortex, where serotonin 2A receptor activation promotes the proliferation of basal progenitors such as basal radial glia (bRG) and basal intermediate progenitors (bIPs) via HER2 and ERK1/2 signalling pathways.[35] The increases in the abundance and proliferative capacity of basal progenitors lead to increased neuron (N) production and the expansion of the human neocortex.[128] aRG = apical radial glia.

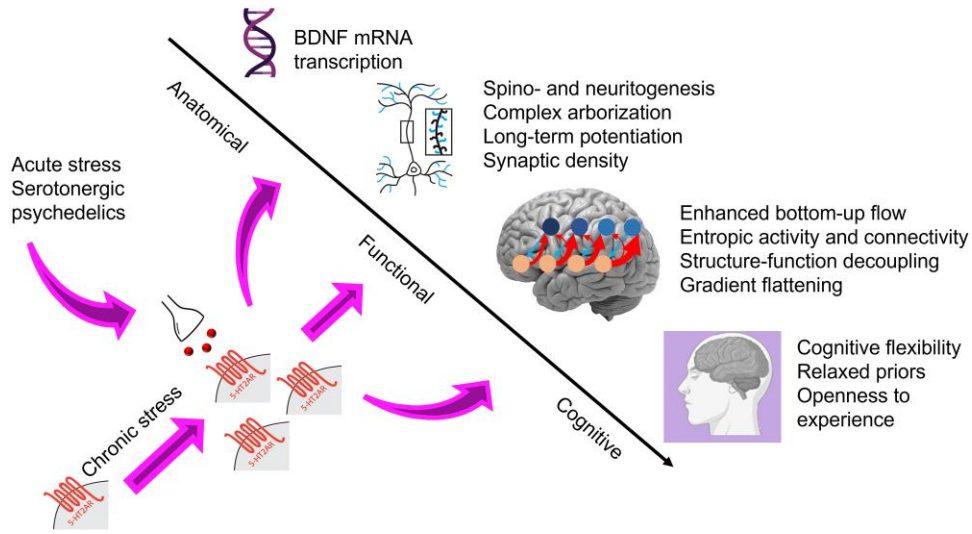

Figure 4 5-HT2AR-mediated anatomical, functional and cognitive plasticity. A schematic displaying two sources of 5-HT2AR agonism (endogenous 5-HT release via acute and chronic stress and agonism by serotonergic psychedelics), as well as the putative primary anatomical, functional and cognitive effects of such agonism. Chronic stress primes the brain by increasing expression of 5-HT2ARs and their sensitivity to signalling. The primed 5-HT2AR system can then be engaged by acute stress (which potently releases 5-HT) or by serotonergic psychedelics. Effects on plasticity can then be observed across scales, from the molecular to the cognitive level. BDNF = brain-derived neurotrophic factor. Figure parts adapted from Luppi *et al.*[328] and Vargas *et al.*[309] (both under CC-BY license).

receptors (~ 8× for EMD 281014 and ~100× for NBOH-2C-CN[137]). In addition, transcripts for 5-HT1A, 1D, 1E, 2B, 2C and 4 were not found in human basal NPCs, corroborating the specificity of these results (and our hypothesis) for 5-HT2AR.[35]

Although direct empirical evidence is needed to establish a causal role, the high density of 5-HT2ARs in adult transmodal cortex suggests that the additional neurons generated in humans as a result of 5-HT2AR-mediated increases in proliferative bRG may be those that go on to comprise the transmodal cortices. This is consistent with the timing of distinct neurogenic phases during ontogenetic cortical development.[138] In particular, studies have indicated that neurogenesis via bRG comprises late-stage neurogenesis and that, in addition to laterally expanding the cortical surface, it results in a radial expansion of cortex via an increase in upper layer neurons.[128,131] One would therefore expect that the regions of cortex that have the greatest basis in bRG-related neurogenesis would (i) be the last to develop; and (ii) have greater cortical thickness relative to other areas. Both of these properties have been observed to be the case in human transmodal cortex.[1,52,53] Collectively, these findings suggest that 5-HT signalling at 5-HT2ARs in the embryonic/fetal brain may contribute to create the expanded transmodal cortices that, in adulthood, densely express 5-HT2AR receptors.

Role of other neurotransmitter systems and receptors in cortical expansion

In addition to 5-HT, basal progenitor abundance and proliferation—and, by extension, cortical expansion—is regulated by a variety of cell-extrinsic molecular factors.[34,128] Among the most well characterized of these factors are extracellular matrix components, growth factors, thyroid hormones and neurotransmitters—each of which have been linked, via varying mechanisms, to increased NPC abundance and proliferation in developing cortex.[139-143] Amongst the neurotransmitters, glutamate and GABA have been most studied for their effects on NPC proliferation.[36,144-146] Both of these neurotransmitters regulate NPC proliferation through several distinct mechanisms, in a manner that appears to depend on the species, cortical region in question, and environmental context.[36] For example, activation of the AMPA/kainate glutamate receptor decreases NPC proliferation in germinal zones in developing rat cortical tissue,[145] whereas glutamate NMDA receptor agonism decreases NPC proliferation in the mouse cortex but increases proliferation in fetal human cortex.[147] With respect to GABA, GABA-A receptor agonism has been found to reduce the proliferation of apical progenitors in the ventricular zone in rat cortex,[145] whereas GABA-A and GABA-B agonism has been found to increase the proliferation of certain NPCs in mouse cortex.[148,149] Important for the present context, although there is heterogeneity in the manner in which glutamate and GABA affect NPC proliferation across (and within) species, their ability to regulate NPC proliferation in general is conserved across both lissencephalic and gyrencephalic species.[36] In contrast, 5-HT2AR are absent on mouse NPCs but highly expressed on the NPCs of humans[124] and, as described, selectively stimulate the proliferation of bRG that are instrumental for human cortical expansion.[35,128] As such, research to date on neurotransmitter contributions to cortical expansion suggest that, with respect to other neurotransmitters, 5-HT, via 5-HT2A agonism, may play an especially prominent role in the disproportionate expansion of transmodal cortex in humans.

5-HT2AR agonism in the adult brain: structural, functional and behavioural effects

Having reviewed neuroanatomical evidence in support of 5-HT2AR's potent ability to modulate transmodal functioning in the adult brain, as well as its potential critical role in the developmental expansion of transmodal cortex, we now discuss research on the structural, functional and behavioural effects of 5-HT2A agonism. We begin with a brief overview of the neuronal effects of 5-HTAR receptor agonism, followed by a discussion of conditions that favour endogenous 5-HT2AR agonism, and then review studies of pharmacologically-induced 5-HT2AR agonism via 5-HT2A agonist psychedelic drugs. We examine both the acute and longer term effects of 5-HT2AR agonists on brain structure, function and behaviour, highlighting a recurrent common theme: increased plasticity and flexibility, where plasticity is defined as the ability of a phenomenon (e.g. brain or behaviour) to be shaped or moulded—or, more plainly, to change (Fig. 4).

Neuronal effects of 5-HT2AR agonism in the adult human brain

The 5-HT2A receptor is an excitatory G-protein coupled receptor, with 5-HT2A agonism activating distinct intracellular cascades via G_q and arrestin signalling pathways.[150-152] Electrophysiological studies have found that 5-HT2AR agonism has the net effect of increasing neuronal excitability as a result of downstream effects on glutamatergic neurotransmission.[153,154] In particular, endogenous 5-HT2AR activation by serotonin has been found to increase both the amplitude and frequency of excitatory postsynaptic potentials in cortical layer 5 pyramidal cells.[154,155] This was found to be via an 'asynchronous' mode of glutamate release that results in a relatively sustained enhancement of excitatory currents.[154] Interestingly, electrophysiological evidence suggests that pharmacological 5-HT2AR agonism via serotonergic psychedelic drugs leads to a unique set of neuronal effects via a combination of differential G protein/arrestin recruitment and access to intracellular 5-HT2ARs.[156,157] These effects notably include the induction of recurrent loops of activation within a subset of deep layer 5 cortical pyramidal cells.[153,155,158] The resulting recurrent loops appear to result in a diffuse mode of glutamate release which, via volume transmission effects, contribute to the local dysregulation of neuronal populations.[153,159] Consistent with this, magnetoencephalography (MEG) studies with psilocybin and LSD, as well as an EEG study with *N*,*N*-dimethyltryptamine (DMT), have revealed broadband reductions in oscillatory power across most of the cortex, with peak reductions notably found in transmodal regions, such as the posterior cingulate.[160-162]

In general, the neuronal effects of 5-HT2AR agonism, combined with their high density on layer 5 pyramidal cells within transmodal cortex, suggest a particularly potent ability to modulate transmodal function and global brain dynamics. Evidence suggests that this may particularly be the case for 5-HT2AR agonist psychedelic drugs—a notion also supported by a rapidly growing body of functional MRI evidence (reviewed later) indicating that acute 5-HT2AR agonism via such drugs induces significant alterations to global brain connectivity and dynamics, centred largely on changes to transmodal cortex.[160,161,163-166]

5-HT2AR agonism via endogenous 5-HT: the central role of stress

Serotonergic innervation in the adult human brain is predominantly provided by afferents originating in the raphe nuclei of the brainstem and evidence to date suggests that these nuclei—spanning dorsal, medial and magnus subdivisions—collectively release serotonin across nearly every cortical region, with relatively low regional specificity of innervation.[167,168] (Although, it should be noted that there is spatial selectivity in the projections of distinct groups of raphe neurons.[169]) As such, complexity in serotonergic modulation of cortical function is understood as predominantly emerging from the distinct characteristics (e.g. ionotropic versus metabotropic, differential G protein activation, high versus low affinity) and spatially heterogeneous distributions of serotonin receptor subtypes, rather than regional variation in levels of serotonergic innervation *per se*.[169-172]

Of the serotonin receptor subtypes, 5-HT1A and 5-HT2A are the most abundantly expressed in the brain.[18] Notably, serotonin has significantly higher affinity for 5-HT1AR relative to 5-HT2AR[173]—suggesting that significant 5-HT2AR agonism may only occur in the context of exceptionally high 5-HT. Of the variety of behavioural and physiological factors that regulate 5-HT release,[169,170,172] perhaps the most powerful and reliable means of increasing neural 5-HT levels and engaging the 5-HT2AR system is via stress—an organism's multi-system (allostatic) response to homeostatic challenge.[174-176] Mild stress may have healthy 'hormetic' effects, e.g. stretching an organism's physiological range and associated resilience (e.g. as with intermittent moderate exercise)[177] but intense, repeated stress may be the cause of a major state transition, as in 'allostatic overload'[178] and so-called 'pivotal mental states', i.e. transient hyperplastic states conducive to psychological transformation.[175]

Evidence indicates that the effects of stress on the 5-HT2AR system are 2-fold. First, chronic stress increases cortical 5-HT2AR expression and sensitivity to signalling[179-182] (see Brouwer and Carhart-Harris[175] for a recent review). Such effects can be observed in response to physiological stressors such as deprivation of oxygen,[183] deprivation of sleep[184-186] and inadequate nutrition,[187] and also in response to social/cognitive stress, such as recurring defeat,[188] rearing in isolation[189-191] and maternal separation.[192,193] Physiological or social deprivation may be a common factor here, with a 'priming' of the 5-HT2AR system occurring as an allostatic response to these environmental deficiencies.

Second, it is well established from both human and rodent studies that acute stress reliably acts as a potent trigger for 5-HT release, e.g. in response to tail pinch, handling and swim stress,[194] fasting,[195-197] acute social defeat[198-202] and acute pain,[203] with regional PET ^{18}F-altanserin binding co-varying with pain responses in humans.[204] Acute stress has also been found to promote the plasticity marker brain-derived neurotrophic factor (BDNF) in the prefrontal cortex.[205] Other work has shown that BDNF is robustly and selectively increased in the cortex after 5-HT2AR agonism.[206]

In past work, we synthesized a large body of findings (partially reviewed later) and argued that 5-HT1AR agonism during times of low/intermediate 5-HT may facilitate a passive coping style—wherein individuals become more patient and less anxious in the face of adverse circumstances—whereas 5-HT2A agonism during times of high 5-HT facilitates an active coping style, which involves adaptively and flexibly responding to the challenges at hand.[174,175] Thus, we proposed that low-grade/chronically stressful situations that might be adequately dealt with passively are underpinned by lower serotonin levels and a relative dominance of 5-HT1A agonism, whereas intense, acutely stressful experiences (or chronic stress paired with an acute event) may demand a more active and adaptive behavioural response that is underpinned by higher serotonin and 5-HT2AR agonism.[174,175]

This notion of distinct behavioural strategies based on relative neural concentrations of serotonin is also consistent with a framework recently proposed by Shine *et al.*[171] These authors argued that states of low/intermediate cortical serotonin are dominated by non-5-HT2AR serotonergic innervation of the cortex via the cerebellum, and that this leads to behaviour that is driven by computationally cheap cerebellar automatisms.[171] In contrast, according to this proposal, during circumstances in which automatized cerebellum-based behaviours do not suffice to address environmental challenges (such as, we argue, during times of significant stress), central serotonin concentrations will be increased to a level sufficient to engage 5-HT2ARs and thereby shift the balance towards cortical computation with greater flexibility and adaptability.[171]

On the whole, a picture emerges whereby chronic stress may be seen as 'priming' the 5-HT2AR system as part of the organism's response to a situation of deprivation/stress (physiological, social or even sensory), and then this primed system can then be activated by potent 5-HT release upon acute stress.[175] The consequent high levels of 5-HT high levels of then lead to the engagement of the 5-HT2AR system, which in turn facilitates an adaptive and flexible behavioural and cognitive style aimed at actively responding to the demands of the current environment. Critically, this conception of 5-HT and 5-HT2AR largely accords with research on exogenous agonism of 5-HT2AR via psychedelic drugs, which has found evidence of increased structural, functional and behavioural flexibility. We review this research next.

Exogenous 5-HT2AR agonism via psychedelic drugs

Further insight into the effects of 5-HT2AR agonism in the adult human brain comes from work with 5-HT2AR agonist psychedelic drugs.[17,207] Such compounds include the naturally occurring substances DMT, 5-methoxy-DMT (5-MeO-DMT), psilocybin and its metabolite, psilocin, the psychoactive component of psilocybe 'magic mushrooms', as well as the peyote-derived, mescaline. Synthetic psychedelics include LSD, but also the phenethylamines 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-bromoamphetamine (DOB). 3,4-Methylenedioxy-methamphetamine (MDMA) is sometimes regarded as a psychedelic, given its profile of subjective effects and its agonist effects at 5-HT2AR. However, rather than displaying direct agonist properties at 5-HT2AR, it only indirectly stimulates these receptors via potent 5-HT release.[196] Psychedelic drugs have been found to induce a complex variety of subjective effects, spanning changes to perception, cognition, emotion and sense of self.[17,208,209] A growing body of evidence also suggests their efficacy—when combined with supportive psychotherapy—in the treatment of several mental health conditions.[210]

In both humans and other animals, the potency of a given psychedelic's effects on subjective experience, cognition and behaviour can be reliably predicted from its affinity for 5-HT2ARs at the receptor.[211] In rodent models, the subjective effects of psychedelics (as indicated by head twitching) are specific to agonism of 5-HT2ARs and can be selectively blocked by 5-HT2AR antagonists.[212] In humans, psychedelics elicit a wide range of subjective effects and significant alterations to global brain function, both of which are blocked by pretreatment with the 5-HT2AR antagonist, ketanserin.[213-215] Consistent with this, a recent PET study notably

found that the intensity of subjective effects induced by psilocin, the active metabolite of psilocybin, significantly correlated with 5-HT2AR occupancy.[216]

Taken together, there is convergent neural and behavioural evidence, from humans and animal models, as well as computational studies, that 5-HT2AR agonism is both sufficient and necessary to account for the complex effects of psychedelic agents and constitutes their main pathway of action. Psychedelic-specific 5-HT2AR signalling cascades appear to exist[157,112] and the expression of plasticity genes has been implicated.[217]

Anatomical neuroplasticity induced by 5-HT2AR agonism

The acute effects of 5-HT2AR agonism are evident at the neuroanatomical level. Evidence from mice deprived of vision from one eye indicates that 5-HT2ARs are required for cross-modal recruitment of monocular cortical territory by the whiskers, a form of plasticity that can occur even in the adult brain—and which is abolished by pharmacological antagonism of 5-HT2ARs, but not 5-HT1ARs.[218] Additionally, early work in rodents demonstrated that treatment with the partially selective 5-HT2AR agonist, DOI, produced a doubling of mRNA expression pertaining to BDNF within the cortex.[206] Although DOI is not selective between 5-HT2 receptor subtypes, this effect was shown to be specifically mediated by 5-HT2AR agonism, since it could be prevented by pretreatment with the 5-HT2AR antagonist ketanserin, but not with a 5-HT2CR antagonist (Box 1).

Even more direct evidence of psychedelic-induced increases in neuroanatomical plasticity was provided by Jones *et al.*,[226] who reported that 5-HT2AR agonism by DOI can induce a transient increase in the size of dendritic spines of rat cortical pyramidal neurons. More recently, compelling work by Ly and colleagues[29] showed that LSD, DMT and DOI significantly increase the complexity of dendritic arbours and promote neuritogenesis and spinogenesis. Corroborated by 5-HT2 receptor antagonist tests with ketanserin, overall the results of this study suggest 5-HT2AR receptor involvement in psychedelic-induced neuroanatomical plasticity, further supported by the observation that the growth of dendritic spines and synapses induced by a given compound correlated with its affinity for the serotonin 2A receptor[29] (Box 1).

Complementing these findings, longitudinal two-photon imaging of layer 5 pyramidal neurons within mouse frontal cortex (a major locus of 5-HT2AR expression) revealed that psilocybin can induce significant increases in the size and density of apical dendritic spines.[31] This effect, which could be induced within 24 h of administration of a single dose of the psychedelic, was found to persist after 1 month (although this effect was only observed in female animals, warranting further investigation), and coincided with a decrease in the rodents' behavioural manifestation of stress responses.[31] This supports a link between 5-HT2AR agonism and long-lasting and behaviourally relevant neuroplastic change. In addition, a recent study applied a novel *in vivo* measure of synaptic density from PET imaging and demonstrated that psilocybin can increase synaptic density in the brain of pigs, concomitantly with the well documented reduction in 2A receptor density that follows its acute engagement by psychedelics.[30]

Functional neuroplasticity induced by 5-HT2AR agonism

In addition to the abovementioned anatomical changes, functional changes can also be identified as a result of acute 5-HT2AR agonism. Functional MRI studies with LSD, psilocybin and DMT have found that they induce a mode of brain function that features greater integration between and reduced integration within the majority of large-scale brain networks.[161,163,165,166,215,227-229] These changes are in alignment with the regional distribution of 5-HT2ARs as revealed by *in vivo* PET imaging[166,228]; although see Preller *et al.*[215,227] Going beyond correlation, *in silico* studies using network control theory[230] or dynamic mean-field models of coupled excitatory and inhibitory populations,[79,164,220,231,232] have shown that the effects of LSD and psilocybin on both local and global brain dynamics can be modelled mechanistically by including the regional distribution of 5-HT2ARs (but not other serotonin receptors).

Leading theoretical accounts of psychedelic action that aim to reconcile neural findings with the subjective and therapeutic effects of these drugs, such as the 'Entropic Brain Hypothesis'[233,234] and its recent evolution, the 'Relaxed Beliefs Under Psychedelics' (REBUS) model,[32] postulate that the principal acute functional action of 5-HT2AR agonist psychedelics is the dysregulation of spontaneous, population-level cortical activity, manifesting as an increased complexity or entropy of spontaneous brain activity.[32,162,233-235] In virtue of 5-HT2AR localization at the apex of the cortical hierarchy in transmodal cortex, this dysregulation is thought to predominantly result in disruption of top-down predictive processing.[32,233,234,236,237]

The serotonergic psychedelics LSD, psilocybin and DMT have also been found to increase the diversity (quantified as entropy or incompressibility) of regional brain activity and functional connectivity over time whether measured with electro- or magneto-encephalography[160,235,238] or functional MRI,[221,239-247] including one study that found the entropic effect to be predictive of subsequent psychological changes.[239]

Complementing these various lines of evidence, a recent study based on the theory of optimal control recently revealed that both LSD and psilocybin induce a 'flattening' of the brain's energy landscape, corresponding to reduced energy required to transition between distinct patterns of whole-brain activity, making such transitions more fluid.[164] Across the various serotonin receptors, 5-HT2ARs are uniquely well suited to induce a reduction of the brain's optimal control energy—indicating that 5-HT2AR agonism is likely to be the key triggering mechanism accounting for the empirically observed effect.[248]

LSD and psilocybin have also been found to induce a decoupling between neural structure and function. More specifically, recent studies have observed that these two drugs induced a dissociation between the brain's macroscale network of white matter structural connections (the human connectome) and the patterns of functional activity[243,244] and connectivity[246] that unfold over it. In light of Hebb's well known dictum that 'neurons that fire together, wire together', the brain's macroscale structural connectivity may be viewed as encoding evolutionary and developmental expectations (or 'priors') about which regions should preferentially communicate with each other. In turn, the psychedelic-induced decoupling of function from structure can then be interpreted as reflecting a deviation from such predetermined patterns in favour of broader exploration, i.e. analogous to a 'journey' or 'trip' away from well-trodden paths.

A diminished influence of top-down information processing has been reported across several psychedelics and diverse investigative strategies. Specifically, an investigation of cortical traveling waves showed that DMT attenuates the top-down alpha-band EEG rhythms that usually characterize the resting brain, in favour of

Box 1 Specificity of psychedelic effects for the 5-HT2A receptor

Pertaining to both the neural and subjective effects of psychedelics, their abolition via ketanserin pretreatment has excluded a primary causal role of receptors beyond the 5-HT2 group.[207,213,215] In mice, the head-twitch response to psychedelics can be abolished via genetic knockout of 5-HT2ARs.[112,219] In humans, the preferential involvement of the 2A receptor is further (albeit indirectly) corroborated by computational studies showing that 2A expression maps provide better fit to the neural effects of LSD and psilocybin than 5-HT1A, 5-HT1B and 5-HT4 maps, as well as dopamine D1 and D2 receptor expression.[220,221] However, ketanserin is a non-selective antagonist of 5-HT2 receptors: although it has 30-fold selectivity for 5-HT2AR over 5-HT2CR,[222] these results cannot rule out 5-HT2CR involvement.

Pertaining to 5-HT2AR involvement in promoting neuroanatomical plasticity, both the study by Vaidya and colleagues[206] and the recent investigations by Jones and colleagues[226] and Ly and colleagues[29] showed that increased markers of plasticity (BDNF mRNA, dendritic spine size, and neuritogenesis and spinogenesis) could be observed after treatment with DOI, which is a highly selective agonist for 5-HT2 receptors over all other G-protein coupled receptors. Vaidya *et al.* and Ly *et al.* additionally showed that DOI-induced increases in neuroplasticity were abolished by ketanserin, and Vaidya and colleagues further excluded a role of 5-HT1AR, since its agonist 8-OH-DPAT produced no effect. On their own, these results strongly implicate 5-HT2 receptor agonism as both necessary and sufficient for inducing markers of plasticity in rodents. Adding to this, the seminal study by Vaidya and colleagues[206] was able to demonstrate 5-HT2AR specificity over 5-HT2CR: they found that DOI regulation of BDNF mRNA expression is completely abolished by pretreatment with MDL 100907, which has a 100-fold greater affinity for 5-HT2AR than 5-HT2CR.[166] In contrast, the authors still observed DOI-induced increase in *BDNF* mRNA expression after pretreatment with SB 206553, which has a 100-fold preference for 5-HT2CR over 5-HT2AR.[223,224] Thus, the results of this study converge on 5-HT2AR agonism in the regulation of plasticity.

Finally, we note that multiple serotonergic Gs-linked receptors—representing a distinct family of G protein-coupled receptors than 5-HT2AR—are present in the human brain; namely, the 5-HT4, 5-HT6 and 5-HT7 receptors.[225] Although these receptors are central to endogenous 5-HT signalling in the adult human brain, there is no evidence that these receptors are expressed in neural progenitor cells during cortical development[128] and we therefore do not focus on them in the present review.

Overall, there is evidence from a variety of investigative approaches strongly implicating 5-HT2 receptor agonism in basal progenitor cell proliferation during development, as well as adult neural plasticity in rodents, and the subjective and neural effects of psychedelics in humans—over and above other neurotransmitters, and other types of serotonin receptors. Additionally, the results suggest a preference for the 2A over 2C receptor, although the evidence is less definitive in this regard.

waves traveling from the bottom up.[229,236] Diverse methods to infer the directionality of connectivity between brain regions, including dynamic causal modelling and transfer entropy, have also consistently identified diminished top-down influences, using MEG and EEG[160,236,249,250] and functional MRI.[251]

Highly relevant to the present paper's main focus, fMRI research has also shown that LSD and psilocybin induce a 'flattening' of the cortical unimodal-transmodal functional hierarchy—as indexed via the principal sensorimotor-to-association functional[8]—by increasing cross-talk between these usually relatively segregated functional zones.[161,163,166,228,229] As we have highlighted, this gradient corresponds to the spatial distribution of 5-HT2ARs across the cortex. Therefore, this study demonstrates that acute 5-HT2AR agonism can modulate the brain's macroscale cortical functional hierarchy in the adult brain. Importantly, hierarchical functional organization is necessary for the instantiation of hierarchical predictive mechanisms, thought by many to be a key operative mechanism of the brain.[252,253] Thus, by implication, if the brain's main hierarchical gradient is 'flattened' or 'compressed' under psychedelics, top-down predictive mechanisms should be compromised—consistent with the REBUS model. One possible interpretation of this effect is that bottom-up information flow, i.e. 'prediction error', will be liberated to impress on supraordinate regions and systems—potentially driving the updating of predictive encodings (i.e. the 'posterior distribution').[32] Evidence for the revision of high-level models or beliefs post-psychedelic use can be seen here[254]—but there are multiple other ways in which this effect may express itself. Indeed, the revision of pathological predictive encodings is hypothesized to be a key component of the therapeutic action of psychedelic therapy.[255]

Cognitive and behavioural plasticity induced by 5-HT2AR agonism

Mounting evidence indicates that flexibility of cognition and behaviour in the face of environmental changes are mediated by serotonin.[256-260] Conversely, behavioural flexibility is impaired in marmoset monkeys following experimental depletion of serotonin from the orbitofrontal cortex, resulting in perseverative behavior.[261] Evidence for a role of 5-HT2AR in mediating the relationship between serotonin and cognitive flexibility comes from animal models: 5-HT2AR agonists such as LSD can improve the ability of non-human animals to learn novel associations.[262,263] In humans, evidence for increased learning capacity comes from a recent study combining acute pharmacological intervention with LSD and computational modelling of trial-and-error reinforcement learning, which found that subjects had an increased ability to update the expected value of performing a given action based on feedback.[264] Both the subjective (psychedelic) and neural effects of LSD in humans can be blocked by pretreatment with ketanserin[207,213,215]; however, given the agonism of LSD for dopamine (albeit substantially weaker) and for serotonin receptors beyond 5-HT2AR, and the involvement of dopamine in reinforcement learning,[265,266] future work will be needed to conclusively establish whether these computational effects are also uniquely attributable to 5-HT2AR agonism.

This computational evidence is in line with additional evidence that acute administration of ayahuasca induces a shift in cognition away from convergent and towards divergent modes of thinking.[267] Similar findings suggest that LSD modulates creativity towards novelty and a larger semantic spread.[268-270] Such changes in

cognitive style need not be confined to the acute experience; indeed, the evidence for an acute action of 5-HT2AR manipulation on divergent thinking and cognitive flexibility is somewhat mixed.[271-274] Post-acute increases in markers of cognitive flexibility appear to be more reliable. For example, a recent study of patients suffering from major depressive disorder found that subacute increases in cognitive flexibility were present at 1-week post-session and maintained for at least 4 weeks.[271] In addition, a study of the effects of psilocybin on common creativity tasks found evidence for post-acute improvements, with an absence of improvements acutely.[272] These studies are further consistent with additional studies indicating post-acute 'after glow' effects of increased cognitive flexibility and creativity.[275,276] Another, albeit indirect, source of evidence comes from investigations of personality change following psychedelic administration. Investigations with psilocybin have revealed significant increases in the personality domain of openness to experience at long term follow-ups in both healthy subjects[277] and patients suffering from treatment-resistant depression.[278] Increased openness was also reported 2 weeks after LSD administration in healthy subjects, an effect that could be predicted from functional MRI measures of entropy LSD administration[239]—providing preliminary evidence for a bridge between acute functional complexity and enduring cognitive plasticity. Finally, studies have also found psilocybin-induced post-acute increases in psychological flexibility, a therapeutically-relevant construct derived from acceptance and commitment therapy (ACT) that relates to one's ability to flexibly respond to the present moment.[279,280]

A recent account of serotonin's multi-faceted role in neural computation proposed that serotonin concentration may track the availability of time and resources, and whether the present state is generally beneficial.[170] According to this account, greater availability of time (signalled by high serotonin concentration) would allow for perception to be based more on incoming sensory evidence and less on priors[170]—consistent with our proposed account and a psychedelic-induced 'weakening of priors' mediated by 5-HT2AR engagement.[32] The same account also proposes that greater serotonin would promote slower learning rate, given that this would coincide with more time for learning and a consequent more exhaustive (wide and/or deep) exploration of what is being learned. At initial glance, this stands in apparent contrast with the evidence for the psychedelic and stress-induced enhancement of learning and plasticity reviewed above. However, we note that whereas our proposed account highlights an increased ability for the brain to structurally and functionally adapt to new environments and contexts, this account highlights a possible serotonin-facilitated behavioural inclination to engage in a wider search and collect a greater amount of evidence during learning. As such, these accounts are not mutually exclusive and raise interesting testable hypotheses pertaining to how serotonin/5-HT2AR agonism might differentially alter 'absolute' learning rate (via plasticity promotion), the breadth of learning that is naturally pursued (as a result of relaxed priors and a perception of more available time) and the ratio between the two.

Therapeutic applications of 5-HT2AR agonism

Abnormalities centred on transmodal association cortex have been implicated in a range of psychiatric conditions, as recently reviewed by Sydnor *et al.*[1] A large and growing literature has identified structural (e.g. reduced volume and thickness) and functional (e.g. changed large-scale network connectivity) alterations in transmodal cortices, which characterize individuals suffering from diverse psychiatric symptoms, from anxiety and depression to generalized psychopathology and psychosis.[281-283] In addition, genes pertaining to the organization of association cortex are implicated in genetic vulnerability to a host of psychiatric disorders.[284,285] Given the centrality of transmodal cortex in psychopathology and given the above-reviewed neuroanatomical and functional characteristics of 5-HT2ARs, it is reasonable to hypothesize that 5-HT2A agonist drugs may have therapeutic relevance. Notably, this is supported by recent clinical trials supporting the efficacy of psychotherapeutic interventions involving serotonergic psychedelic drugs for several mental health conditions[286] (see Supplementary Table 1 for a summary of trials to date). Evidence indicating beneficial effects of 5-HT2AR agonism on clinical symptomology and/or well-being has been steadily accumulating[19] from investigator-initiated clinical trials[20-22,24-27,287-296] (Supplementary Table 1) and controlled studies in healthy individuals.[297-300] Prospective surveys of naturalistic use have also found increased subjective well-being after the psychedelic experience[301-304] (reviewed in Johnson *et al.*[19]), even 2 years later.[305] The quality of evidence supportive of psychedelic-assisted psychotherapy was recently bolstered by the publication of high-profile clinical trials of MDMA therapy for post-traumatic stress disorder,[306] and psilocybin-therapy for major depressive disorder.[20,22] Consistently high response rates exceeding 70% were seen across all three of these studies in those treated with psychedelic-assisted psychotherapy.

A core characteristic of psychedelic treatments for mental health is their dependence on extra-pharmacological factors and their administration in the context of adjunctive psychotherapeutic support (hence, 'psychedelic-assisted psychotherapy'[307,308]). The context-dependence of the therapeutic action of psychedelics dovetails with the evidence presented in previous sections supporting a close association between increased neuroplasticity and corresponding therapeutic effects.[33,309,310] In particular, we and others have highlighted how 5-HT2AR-induced plasticity is itself agnostic with respect to outcomes: whether or not neuroplastic changes are 'therapeutic' (i.e. supportive of positive mental health) is dependent on the nature of the contextual factors present prior to, during and following drug administration.[175,311] One way this may be described is that psychedelic-assisted psychotherapy, via 5-HT2AR agonism combined with therapeutic support, may temporarily increase and harness the capacity of transmodal cortex—highly active during development—to be moulded by socio-cultural/environmental learning, in order to facilitate adaptive and health-promoting neuroplastic changes.[175,308] This idea also closely parallels recent work which found that psilocybin, MDMA and other psychedelics open critical periods for social reward learning, providing evidence that temporarily enhanced social learning (via temporarily increased plasticity) may contribute to the therapeutic effects of psychedelic-assisted therapy.[312-314]

If 5-HT2AR agonism exerts its beneficial effects by enhancing neural and psychological plasticity, then a possible synergy becomes apparent with psychotherapeutic techniques that emphasize a flexible, accepting approach to one's emotions, memories and circumstances, such as mindfulness-based therapies and ACT in particular.[32,279,280,315-317] Such psychotherapies may marry well with psychedelics due to their ability to harness the enhanced plasticity triggered by the drugs' pharmacological action, as reviewed in the previous sections. Nevertheless, we emphasize that complex psychiatric conditions such as PTSD, major depressive disorder and addiction are invariably the result of intricate interactions between a patient's neurobiology, cognition and environment, and are therefore best addressed as such; hence our focus is on the potential for psychedelics to enhance and facilitate psychotherapeutic processes, rather than being pure pharmacotherapeutic agents.

Role of other neurotransmitter systems and receptors in plasticity

It is important to emphasize that, although the 5-HT2AR system is involved in plasticity and flexibility at the anatomical, functional and cognitive levels, it is by no means the only plasticity-related system. It is well known that glutamatergic signalling involving AMPA and NMDA receptors plays a key role in long-term potentiation and long-term depression of synapses[318] both in terms of enacting short-term changes in synaptic strength and ensuring their long-term maintenance through regulation of gene expression.[319] Indeed, evidence suggests that 5-HT2A agonism induces its pro-plasticity effects via its downstream effects on glutamatergic neurotransmission.[159,320] Other neuromodulators than serotonin also shape plasticity, with both convergent and divergent roles.[321] Dopamine has been robustly associated with reward prediction errors, providing a mechanism to address the problem of 'credit assignment'[322]: which connections should be changed and how, to reduce the difference between expected and observed reward?[323] Whereas dopamine (and to some extent noradrenaline) regulates plasticity after-the-fact in response to 'unexpected uncertainty',[321] acetylcholine may facilitate plasticity proactively in the presence of 'expected uncertainty', by controlling vigilance and selective attention, which are widely known to enhance learning.[323] In addition, GABAergic inhibition has been shown to control the critical window of plasticity during development,[324] and blocking GABAergic signalling can restore the plasticity of sensory cortex in adult animals.[325] Since the duration of the critical period is greater in humans than other primates,[100] especially for prefrontal cortex and other evolutionarily expanded transmodal cortices,[98] it is likely that GABAergic signalling also played a role in the evolution of human transmodal association cortices. Intriguingly, although the majority of 5-HT2AR-expressing cells are layer 5 pyramidal neurons, this receptor is also found on GABAergic interneurons in rodents, monkeys and humans,[119] suggesting a noteworthy avenue for future research on their interactions for evolution and development. Thus, although our present account focuses on serotonin and 5-HT2AR specifically, it should be understood in the context of the brain's complex neuromodulatory landscape and the multiple influences on plasticity across spatial and temporal scales.

An integrative account of 5-HT2ARs in the development and adult function of human transmodal cortex

Taken together, there is considerable evidence indicating that human transmodal cortex exhibits a variety of unique structural and functional characteristics that collectively afford and underpin flexible, adaptive and complex aspects of behaviour and cognition. In addition, developmental and neuroanatomical evidence suggests strong linkages between 5-HT2AR and the transmodal cortex, wherein this receptor may play a critical role in the expansion of such regions over development and allow for their potent functional-anatomical modulation in adulthood. Drawing together the various separate but converging lines of research presented in the previous sections, we propose an account of 5-HT2ARs as developmental drivers and adult modulators of the macroscale cortical processing hierarchy: 5-HT2ARs may play a critical role in facilitating the developmental expansion of the transmodal regions, which sit at the top of the hierarchy and then are well poised to potently modulate its adult functioning when activated endogenously by serotonin or exogenously by 5-HT2AR agonist drugs. This account provides context for a deeper understanding of the therapeutic action of 5-HT2AR agonist psychedelics when twinned with psychotherapeutic support.

5-HT2ARs as orchestrators of the cortical hierarchy

Thus, our account articulates (i) a developmental role for 5-HT2AR in helping drive gyrencephalic cortical expansion in general and the disproportionate expansion of human transmodal cortex in particular; and (ii) a modulatory role for 5-HT2AR in driving conditions for psychological change in the adult brain, via functional and neuroanatomical changes. As reviewed in the '5-HT2A receptors as potent modulators and key developmental drivers of human transmodal cortex' section, converging multimodal evidence indicates a critical role for 5-HT2ARs in stimulating the proliferation of basal progenitor cells, which are central to human cortical expansion.[35,124,128,130] Moreover, research indicates that 5-HT2AR densities in the adult human brain as measured *in vivo* are most expressed in regions of transmodal cortex, which underwent the greatest expansion in humans relative to phylogenetically proximal non-human primates[18] (Fig. 1). These two independent sets of findings converge to suggest a process by which 5-HT2AR agonism plays a causal role in transmodal cortical expansion during development and is subsequently positioned to modulate its functioning during adulthood. The cortical expansion engendered by 5-HT2AR signalling in the early brain is mirrored by increased synaptic density in transmodal association cortices in the adult brain.[95-97] Adult neuroplasticity is likely ideal for ongoing exploratory learning—well-suited to complex, unpredictable environments.[326] A modulatory role for 5-HT2AR agonism over the activity and connectivity of transmodal cortex can be identified from functional MRI studies, with brain-wide consequences including an attenuation of the usual hierarchical differentiation of unimodal and transmodal cortex.[166,229] This is reflected in behaviour as a potential dysregulation of top-down processing and increase in behavioural and cognitive flexibility.

From a functional and evolutionary perspective, in a non-drug context, one can intuit how a background of adversity and associated chronic stress e.g. conditions consistent with considerable evolutionary pressure, could prime a 'growth' or plasticity system (i.e. the 5-HT2AR system) for engagement—in the service of environmental adaptation.[175] It is an evidence-informed speculation that this process is non-linear, i.e. upregulation of 5-HT2AR reaches a 'tipping' or bifurcation point,[175] after which, with acute stress-induced release of 5-HT onto the primed 5-HT2AR system, ideal (hyperplastic) conditions for a major state transition with potentially lasting sequelae, may ensue. When such triggering occurs (whether endogenously via stress-induced 5-HT release stress, or exogenously through 5-HT2AR agonist psychedelics), increases in neuroplasticity and cognitive and psychological flexibility can occur, freeing dynamics from structural and top-down constraints and facilitating neural and cognitive exploration. The long-term effect of this process may be lasting psychological and behavioural change, where e.g. previously 'stamped-in' circuitry and associated psychological traits, can be made more plastic, i.e. amenable to change. If plasticity and learning are elevated for a prolonged period, as seems to be true with psychedelics,[31] then the window for (re) learning (e.g. healthier traits) may endure well beyond the acute action of the drug.

As a consequence of uniquely human cortical expansion, the transmodal association cortex (where 5-HT2AR expression is

greatest) moves farther away from the more 'hard-coded' unimodal cortices, becoming relatively less 'tethered' by molecular and structural constraints.[6] Moreover, increased spatial and topographic distance of transmodal association cortex from unimodal cortices[8,12] is accompanied by a corresponding reduction of functional-to-structural coupling,[73] and an increase of regional intrinsic timescale (i.e. longer temporal windows of integration).[75] Thus, as one progresses along the cortical hierarchy, regional activity becomes increasingly less determined by genetically encoded and structurally realized patterns of anatomy and connectivity, and also less determined by immediate sensorimotor contingencies—instead reflecting the higher-order transmodal, abstract integration of information across an extended period of time [i.e. tens of seconds instead of (milli)seconds].

Overall, we argue that the serotonin 2A receptor is involved in driving the expansion of the information-processing apex of the brain, i.e. the transmodal association cortex. In this context, there is recent evidence for consumption of 5-HT2AR-agonist mushrooms of the Psilocybe family by our hominin ancestors,[327] pointing to the intriguing possibility of an active contribution to human brain evolution.[219] Moreover, after maturation to adulthood, 5-HT2ARs are uniquely poised to control this apex—and by implication—its governance of the rest of the brain (Fig. 5).

Challenges and future directions

Several questions naturally arise from the framework we have outlined in this article. For example, one may wonder about the case of prenatal exposure to selective serotonin reuptake inhibitors (SSRIs). By blocking SERT, SSRIs increase synaptic 5-HT levels and thereby increase signalling at 5-HT2ARs. Yet, there does not appear to be compelling evidence of an association between prenatal SSRI exposure and altered cortical development. Critically, however, this does not represent counterevidence to our proposal for two reasons. First, human NPCs do not express SERT during embryonic development, rendering SSRIs unable to increase 5-HT levels in the fetal brain.[128] Second, increased levels of maternal 5-HT induced by SSRIs cannot alter fetal progenitors, given that 5-HT does not pass the blood–brain barrier and therefore cannot reach the fetus from the mother's brain.[127]

Concordantly, the clinical literature on human prenatal exposure to 5-HT2A antagonists (including a variety of antipsychotic and antidepressant drugs, such as pimavanserin) has also not provided strong evidence of widespread alterations in cortical development. Indeed, based on the evidence from Xing and colleagues,[35] we predict that if neural progenitors in fetal human neocortex were directly exposed to high levels of a 5-HT2A antagonist, it would have neurodevelopmental repercussions on cortical volume. However, whether or not the antagonist can pass the placental barrier and reach the fetal brain is yet to be determined. Timing is also an important consideration: basal progenitors relevant to uniquely human cortical expansion are generated at approximately gestational week 10–16, such that out of this window, the effect of the antagonist on basal progenitors, hence on cortical development, should be rather limited. However, now that we have explicitly formulated our hypothesis, we hope that more specific investigations that take these factors (placental permeability and restricted temporal window) into consideration will be able to search for evidence of our proposed mechanism in humans. Such evidence could also be found in animals: our hypothesis predicts that reduced cortical volume should be found in 5-HT2AR knockout gyrencephalic animals where 5-HT2A is expressed in basal NPCs (e.g. ferret, pig or non-human primates), but not lissencephalic mammals, such as mice, which do not exhibit 5-HT2A expression in basal NPCs. This is already suggested by the evidence of Xing and colleagues,[35] whereby disruption of 5-HT2AR expression in the ferret led to reduced levels of basal progenitors, especially proliferative basal progenitors—an effect that should result in a decrease in neurogenesis consequently reduced cortical volume. These observations also suggest that lissencephalic rodents may present some limitations as a model for evaluating possible side effects of novel drugs, given that they do not exhibit the key proliferation-inducing 5-HT2AR signalling role during development.

Another set of questions pertains to the regional distribution of the 2A receptor. For instance, although we have focused on the high availability of 2A receptors in transmodal association cortex, 5-HT2ARs are also densely expressed in primary visual cortex (and to a lesser extent, primary auditory cortex) of the human brain.[18,112] Primary sensory cortices occupy the opposite end of the unimodal-transmodal hierarchy relative to transmodal cortex and it undergoes a more modest evolutionary expansion in humans relative to non-human primates.[3,8] Primary cortex also does not undergo protracted development or plasticity, with its circuits predominantly defined in the first year of life following a brief critical period.[222] It is reasonable to wonder why this may be the case in light of the evidence we have reviewed about the role of 5-HT2ARs in promoting cortical expansion. We speculate that this may be in part attributable to the high level of intracortical myelination observed in V1,[7] which is known to act as a physical and signalling barrier to plasticity after the end of cortical developmental maturation (which occurs much earlier in visual cortex relative to transmodal cortices).[93] This hypothesis is empirically testable and we hope that future research will take a closer look at potential non-neurotransmitter roles of 5-HT2ARs in V1. The ability of 5-HT2AR agonism to significantly increase functional connectivity between visual cortex and transmodal cortex is a consistent finding in functional MRI investigations[161,163,166,223,229] and it is tempting to speculate that the potential for bridging the visual-transmodal gap may have developed in the service of complex and flexible behaviour. In this context, it is clear that further research is needed on the anatomical, functional and developmental differences between 5-HT2ARs in V1 and transmodal cortex.

On the other hand, there is evidence that the cerebellum has greatly expanded in evolutionary terms[224]—yet it displays little 5-HT2AR expression, despite receiving substantial serotonergic innervation targeting multiple 5-HT receptors.[225] More broadly, we acknowledge that our cortico-centric account is inevitably incomplete, given that the subcortex and cerebellum play fundamental roles both in mental disorders and in healthy cognitive function[329]—with both structures displaying functional associations with cortical resting state networks, including transmodal cortex.[330] Intriguingly, cerebellar functional gradients have also been identified including a principal sensory-fugal gradient.[331] Likewise, as the source of serotonergic and other neuromodulatory innervation to the brain, we anticipate that future extensions of the framework proposed here will feature a more prominent role for brainstem nuclei, such as the serotonergic raphe nuclei. Overall, we believe that a fuller account of how the dynamics and neuromodulation of complex, distributed systems can give rise to emergent high-level psychological phenomena,[332] is an important goal for future neuroscientific research.

Finally, we emphasize that the account of brain development and evolution provided here is not intended to be exhaustive. In addition to the abovementioned role of GABAergic signalling for

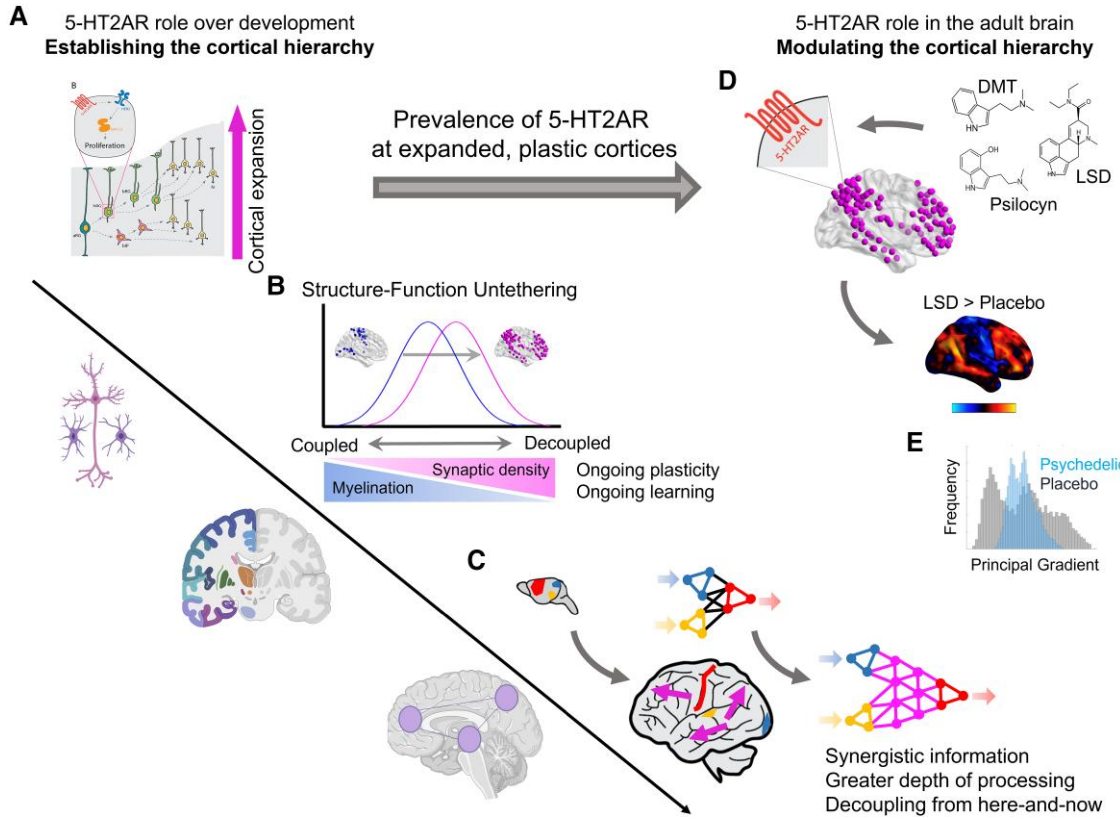

Figure 5 Schematic of the proposed dual roles of 5-HT2AR in establishing (*left*) and then modulating (*right*) the human cortical hierarchy. (**A–C**) From the molecular to the cognitive level, 5-HT2ARs shape development and evolution by driving cortical expansion (**A**), inducing untethering of function from anatomical and genetic constraints, with greater synaptic density and lower intracortical myelination (**B**), and ultimately leading to a cognitive architecture with greater depth of processing thanks to the expansion of transmodal association cortex (**C**). (**D** and **E**) In the adult brain, 5-HT2AR prevalence is elevated in transmodal association cortex and 5-HT2AR engagement by serotonergic psychedelics (**D**) differentially affects the two ends of the cortical hierarchy, inducing a collapse of the principal functional gradient (**E**). Figure elements modified from Luppi *et al.*[328] (under CC-BY license).

neural critical periods, it is clear that brain evolution can only be understood as a complex process, involving multiple mechanisms interacting across diverse temporal scales. Numerous genes have been implicated in development of the neocortex, whether due to the occurrence of microcephaly in animals and human patients upon their mutation[333] or because of their role in stimulating neurogenesis and cortical expansion in the fetus.[130,334,335] Additional biological factors include the role of differences in tissue oxygenation and metabolism[48,94] and the concomitant availability of biosynthetic materials and plasticity-related genes in transmodal association cortices.[94] In turn, the metabolic burden of an expanded brain may have been paid for, at least in part, by the invention of cooking, an example of culturally-transmitted learning that increased the digestibility of food, thereby enabling more energy to be extracted in less time.[336,337] In this context, it is intriguing to note that 95% of serotonin innervation is towards the gastrointestinal tract, where it plays a prominent role in digestion.[171] Further supporting the role of culture and social interactions in brain evolution, the ability to learn from conspecifics[338] and the need to outcompete members of one's own group[339,340] and other groups[341] may have provided converging justifications for the advantage of neocortical expansion and the ensuing cognitive flexibility. Our account of the role of 5-HT2AR adds another layer to this rich tapestry, towards understanding healthy and pathological brain function through the lens of development and evolution across scales.

Conclusion

In this multi-level synthesis, we have brought together human, non-human animal, *in vitro* and *in silico* evidence to show that serotonin 2A receptors are: (i) most densely expressed in transmodal association cortex—the apex of the human cortical hierarchy; (ii) play a key role in both the ontogenetic and phylogenetic development of the principal unimodal-transmodal hierarchical axis of the cortex; and (iii) have a unique ability to rapidly and potently modulate this hierarchy and the cognitive faculties and behaviours it encodes. By offering a unified account of the role of 5-HT2AR in both the development and adult functioning of the human brain, this work stands to enrich the neurobiological and neuropharmacological understanding of human brain evolution. In turn, these insights will provide a crucial background for understanding the action of classic psychedelic drugs and we hope that they will inform ongoing research on the potential therapeutic applications of these compounds.

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Competing interests

M.G. reports receiving scientific advisory fees in the last 2 years from EntheoTech Bioscience. R.C.H. reports receiving scientific advisory fees in the last 2 years from: Beckley Psytech. All other authors report no conflicts of interest.

Supplementary material

Supplementary material is available at *Brain* online.

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