BRAIN
REVIEW ARTICLE

Models of psychedelic drug action: modulation of cortical-subcortical circuits

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Classic psychedelic drugs such as psilocybin and lysergic acid diethylamide (LSD) have recaptured the imagination of both science and popular culture, and may have efficacy in treating a wide range of psychiatric disorders. Human and animal studies of psychedelic drug action in the brain have demonstrated the involvement of the serotonin 2A (5-HT_{2A}) receptor and the cerebral cortex in acute psychedelic drug action, but different models have evolved to try to explain the impact of 5-HT_{2A} activation on neural systems.

Two prominent models of psychedelic drug action (the cortico-striatal thalamo-cortical, or CSTC, model and relaxed beliefs under psychedelics, or REBUS, model) have emphasized the role of different subcortical structures as crucial in mediating psychedelic drug effects. We describe these models and discuss gaps in knowledge, inconsistencies in the literature and extensions of both models. We then introduce a third circuit-level model involving the claustrum, a thin strip of grey matter between the insula and the external capsule that densely expresses 5-HT_{2A} receptors (the cortico-claustro-cortical, or CCC, model).

In this model, we propose that the claustrum entrains canonical cortical network states, and that psychedelic drugs disrupt 5-HT_{2A}-mediated network coupling between the claustrum and the cortex, leading to attenuation of canonical cortical networks during psychedelic drug effects.

Together, these three models may explain many phenomena of the psychedelic experience, and using this framework, future research may help to delineate the functional specificity of each circuit to the action of both serotonergic and non-serotonergic hallucinogens.

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Abbreviations: 5-HT$_{2A}$ = serotonin 2A receptor; CCC = cortico-claustro-cortical model; CSTC = cortico-striatal thalamo-cortical; DMN = default mode network; FPN = frontoparietal network; IOR = inhibition of return; LSD = lysergic acid diethylamide; MD = mediodorsal nucleus; PPI = pre-pulse inhibition; REBUS = relaxed beliefs under psychedelics model; SN = salience network

Introduction

Psychedelic drugs, which we define as agonists or partial agonists of the serotonin 2A receptor (5-HT$_{2A}$)[1] such as psilocybin (the main psychoactive constituent of *Psilocybe* mushrooms) and lysergic acid diethylamide (LSD), have recaptured the imagination of both science and popular culture. Recent studies have provided empirical evidence that psychedelic drugs evoke a unique array of alterations in perception and cognition,[2–5] with subjective experiences in humans ranging from blissful and profound to anguished and paranoid.[6–8] Psychedelics may also have efficacy in treating a wide range of medical indications, including mood,[9–13] substance use[14,15] and headache-related disorders.[16,17] Understanding the neural circuit basis of psychedelic drug action has the potential to inform strategies for maximizing the therapeutic efficacy of these drugs, as well as minimizing their harm, while potentially elucidating novel functions of these circuits in both health and disease.

The cerebral cortex is thought to be central to the neural mechanisms underlying the psychedelic experience due to its high expression of these receptors. 5-HT$_{2A}$ receptor activation via the psychedelic 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) induces a substantial increase in the frequency and amplitude of excitatory postsynaptic current events in rodent prefrontal layer V pyramidal neurons, which are the major projectors and integrators in the cortex.[18] DOI also increases c-fos expression in prefrontal and somatosensory GABA-releasing interneurons, which are important neuromodulators.[19] Additional findings in rodents show that LSD induces gene expression changes in the cortex,[20] and DOI increases extracellular GABA[21] and glutamate in the cortex.[22] Complementary work in humans has shown that psychedelic drugs acutely increase glutamate concentrations in the medial prefrontal cortex.[23] Recent evidence from rodent studies suggests that a subset of 5-HT$_{2A}$ receptor-containing 'trigger neurons' in the medial prefrontal cortex and somatosensory cortex are responsible for the initial neural response to psychedelics.[19] These neurons appear to recruit other neuronal populations, leading to cascading disruption of cortical and subcortical pathways in the development of psychedelic drug effects. In line with these observations, psychedelics generally attenuate the functional segregation of human cortical networks.[24,25] Finally, 5-HT$_{2A}$-mediated signalling pathways in the cortex are required for stereotyped animal behaviours produced by psychedelics such as the head-twitch response,[26–28] and 5-HT$_{2A}$ receptor antagonism in humans blocks the subjective, cognitive and neural system effects of psilocybin,[29–34] LSD[35–37] and N, N-dimethyltryptamine (DMT).[38]

Although the role of cortical 5-HT$_{2A}$ receptors in psychedelic drug action is evident (primarily in prefrontal regions), the downstream effects of cortical psychedelic drug activation on subcortical targets and the activation of subcortical 5-HT$_{2A}$ receptors[1] may also be crucial to psychedelic effects. Two leading models of the neural basis of psychedelic drug action differ on their views regarding the importance of different subcortical structures and extracortical 5-HT$_{2A}$ receptors. One model, the cortico-striatal thalamo-cortical loop model (CSTC; Fig. 1), proposes that psychedelic drugs modulate both the cortex and subcortical structures including the striatum and thalamus, resulting in aberrant thalamocortical coupling.[39–41] This is thought to increase the flow of sensory information to the cortex, leading to perceptual alterations and effects on cognition, including diminished attention and sensorimotor gating. Another model, referred to as relaxed beliefs under psychedelics (REBUS; Fig. 2), asserts that cortical modulation by psychedelic drugs reduces the ability of higher-level cortical networks (i.e. the default mode network) to control lower-levels in the brain (e.g. 'lower' relative to the default mode network), specifically the hippocampus and parahippocampal gyrus (but also sensory cortices).[42] This hypothesized reduction in top-down control is proposed to disrupt typical predictive coding processes and is expressed as increased entropy in measures of cortical function and network topology.

Here, we briefly review evidence for the CSTC and REBUS models, while describing potential gaps and extensions of each. Then, we introduce a third circuit-level model centering on the claustrum, a subcortical telencephalic nucleus that contains a subpopulation of 5-HT$_{2A}$-containing neurons. These neurons appear to be responsible for the initial neural response to psychedelics[19] and have widespread, largely bidirectional cortical connections.[43–49] This model, termed the cortico-claustro-cortical model (CCC; Fig. 3), emphasizes the function of the claustrum in the control of cortical network states, which arise from the synchronization of stereotyped sets of cortical regions across time. In the context of this new model, we highlight the potential role of psychedelic disruption of cortico-claustro-cortical circuits that may contribute to our understanding of the neural and subjective effects of psychedelic drugs.

Cortico-striatial thalamo-cortical model and the disruption of thalamocortical gating

The thalamus is, in part, a collection of subcortical nuclei that 'relay' sensory information from sensory organs to the cortex. In this role of relaying sensory information, the thalamus acts as a 'gate', restricting the flow of information to permit only a subset of sensory information at any given time. All thalamic relay nuclei receive cortical inputs that control this gating function to support cognition and action, and the thalamic reticular nucleus may especially be important to gating via local inhibition of other thalamic nuclei.[50] Apart from the reticular nucleus, all thalamic nuclei provide direct glutamatergic input to the cortex.[51] CSTC loops have a rich history in the study of both neural development and the pathophysiology of a number of disorders,[52] including psychotic disorders. In the context of psychedelic drugs as psychotomimetic substances, disruption of the gating of sensory information through thalamocortical circuits was hypothesized to underlie the acute alterations in perception and cognition that accompany

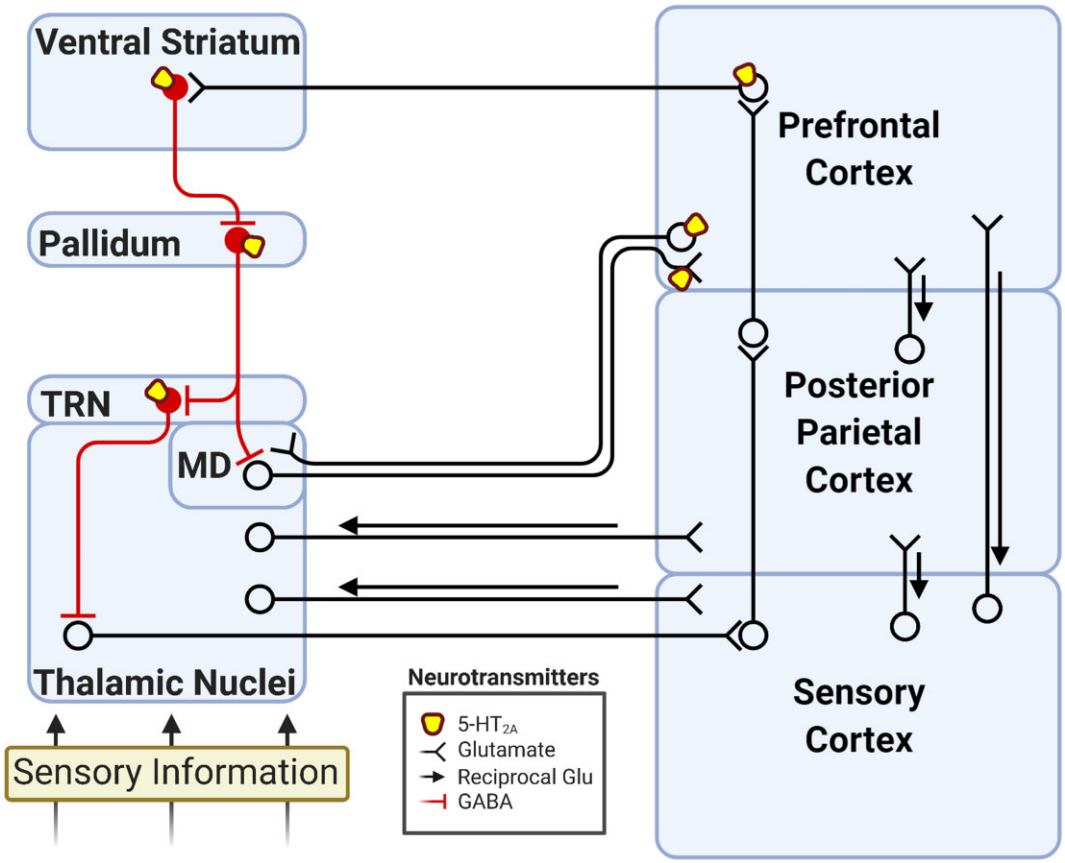

Figure 1 Summary of the cortico-thalamo-cortical and CSTC loops. Disruption of this circuit by 5-HT_{2A} activation is hypothesized to inundate the cortex with sensory information, contributing to the alterations of cognition and perception during psychedelic experiences.[39–41] Glu = glutamate; TRN = thalamic reticular nucleus.

psychedelic experiences.[39–41] Here, we will review the basic conceptualization of the CSTC model as it pertains to psychedelics, discuss thalamic nuclei that are most likely to be involved, summarize the behavioural and neuroimaging evidence that supports this model and consider potential limitations and extensions of the model.

Cortico-striatal-thalamo-cortical loops

In the original conception of psychedelic disruption of CSTC loops,[39] psychedelics are understood to activate medial prefrontal layer V 5-HT_{2A}-containing pyramidal neurons projecting to GABAergic neurons of the ventral striatum, which in turn inhibit GABAergic pallido-thalamic neurons within these CSTC circuits (Fig. 1). Disruption of these GABAergic pallido-thalamic neurons results in disinhibition of the thalamus and inundation of the cortex with sensory information. Accordingly, independent groups have found that LSD administration in humans increases functional connectivity (i.e. the temporal coupling between the activity of two regions) between the thalamus and much of the cortex under task-free conditions.[53–55] Moreover, directional modelling of human neuroimaging data has found evidence that LSD increases thalamic influence on posterior cingulate activity in a 5-HT_{2A}-dependent fashion, but an accompanying decrease in striatal input to the thalamus was found to be independent of 5-HT_{2A} activation.[56] Although the CSTC model describes 5-HT_{2A} receptors in regions within CSTC loops other than the thalamus and emphasizes specific thalamic nuclei such as the mediodorsal (MD) and reticular nuclei of the thalamus,[39,40] it remains unclear how the model may account for the contribution of other subnuclei and extracortical 5-HT_{2A} receptors to the effects of psychedelics.

Thalamic nuclei of interest

It is worth noting that human studies with acute psychedelic manipulations that report on changes in thalamic connectivity have not parcellated the thalamus into its constituent nuclei, despite differential 5-HT_{2A} expression, functional specificity and anatomical connectivity of thalamic nuclei. One would expect those thalamic nuclei expressing 5-HT_{2A} mRNA or receptor protein to be more important to consider when determining the basis of psychedelic drug action within the brain. However, only a subset of thalamic nuclei exhibits such receptor expression. For instance, the reticular nucleus expresses 5-HT_{2A}[57] receptors and was one of the thalamic nuclei originally proposed to be of importance to psychedelic effects in CSTC loops.[39,40] Indeed, LSD increases burst firing in some reticular nucleus neurons, while suppressing burst firing in others.[58] The reticular nucleus is thought to function as a 'neuronal oscillator',[59] regulating the frequency of cortical rhythms, especially gamma waves.[60–64] Oscillations of this kind are thought to support synchronization between brain regions and enable communication and information transfer.[65,66] Some evidence indicates that presynaptic 5-HT_{2A} receptors in the reticular nucleus are involved in GABA release,[67] providing a potential mechanism by which psychedelics desynchronize low frequency bands in a 5-HT_{2A}-dependent manner.[34,38,68–74] The reticular nucleus also

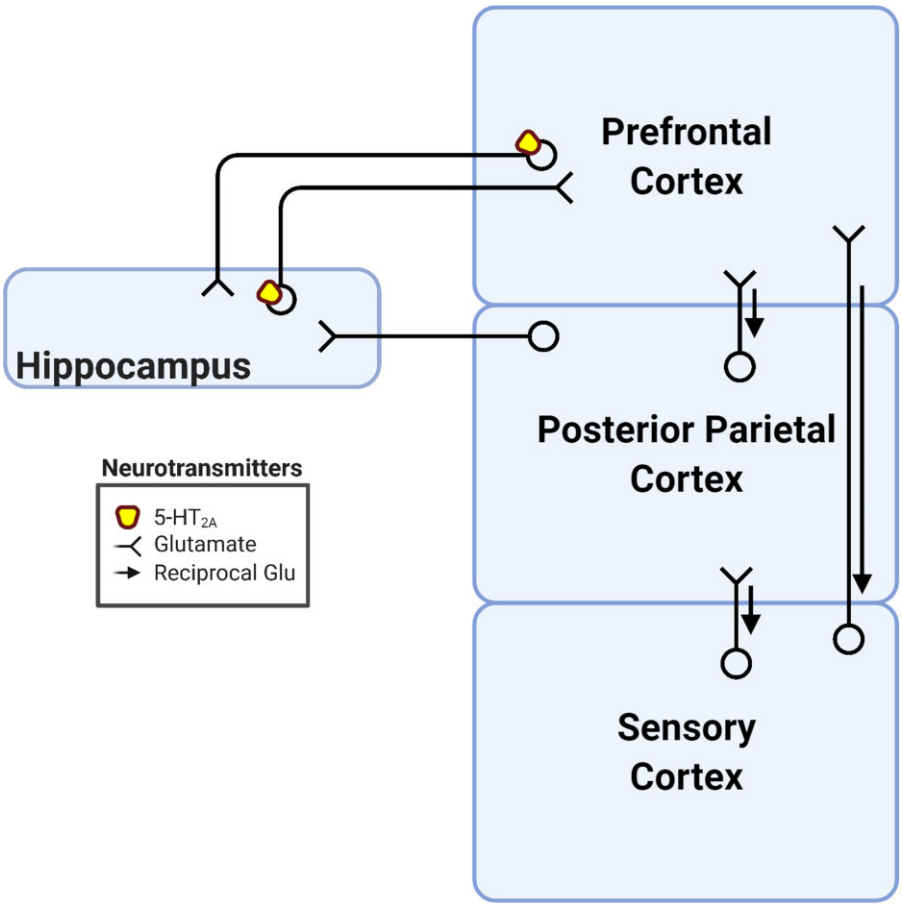

Figure 2 Summary of the hippocampal-cortical processing loop implicated in the REBUS model. Psychedelic action is hypothesized to preferentially enhance bottom-up prediction error signalling to higher-level structures compared with top-down reciprocal signalling. This manifests as decreases in cortical synchrony in addition to relaxed priors. The REBUS model specifies hippocampus and the parahippocampal gyrus as originators of this bottom-up signalling, in concert with other unspecified structures.[42] Glu = glutamate.

supports selective visual attention by controlling the gain of the lateral geniculate nucleus,[75] the main target of the retina. Finally, neurons of the reticular nucleus are dependent on prefrontal interactions via the basal ganglia,[76] suggesting a potential role for striatal nodes of CSTC circuitry in psychedelic-induced impairments of attention.[30,77,78]

The MD is a higher-order nucleus (i.e. not directly receiving sensory information), receiving inputs from the cortex, medial temporal lobe, pallidum and other thalamic nuclei[79] that was originally proposed to be important to psychedelic action in CSTC loops[39,40] (Fig. 1). Of relevance to psychedelics, the MD projects to the medial prefrontal cortex, thus completing a CSTC loop with a cortical region containing neurons that may be particularly sensitive to 5-HT_{2A}-mediated activation by psychedelic drugs.[19] Moreover, the MD expresses 5-HT_{2A} receptors both within the thalamus, at the somatic level and on presynaptic projections in medial prefrontal cortex,[80,81] suggesting multiple points within an MD to medial prefrontal cortex loop that could be targeted by 5-HT_{2A} receptor activation. One study found DOI activation of the presynaptic 5-HT_{2A} receptors of this circuit to increase excitatory postsynaptic currents in medial prefrontal cortex, and deletion of these receptors impaired episodic-like memory in mice.[82] In another study, LSD increased action potential firing frequency, including burst firing, of neurons in a subregion of MD known to receive GABAergic input from the reticular nucleus and to project out to medial prefrontal cortex.[58] This LSD-induced increase in MD firing, which was also met with increases in spontaneous firing activity in medial prefrontal cortex pyramidal neurons,[58] lends further support to the notion that psychedelics increase thalamic activation of cortex. Interestingly, although psychedelics impair most aspects of cognition in humans, episodic memory encoding is relatively less impaired, even at high doses of psilocybin.[5]

Somatic and perceptual distortions often accompany the subjective effects of psychedelics.[3] Thus, 5-HT_{2A} receptor-containing sensory nuclei of the thalamus, such as the ventrobasal thalamus and pulvinar, may also play a role in psychedelic drug action. The ventrobasal thalamus is a first-order relay (i.e. a nucleus receiving direct sensory projections) that carries ascending tactile information to somatosensory cortex. Glutamatergic projections from the ventrobasal thalamus are activated by DOI and induce immediate early gene c-fos expression in layer V somatosensory neurons.[22] Consistent with these findings, LSD increases functional connectivity between the thalamus and somatosensory cortex in humans,[53–55] although it is unclear whether these effects play a role in specific psychedelic effects such as loss of perceptual boundaries between one's body and the world.

Compared with somatosensation, psychedelics appear to have more reliable and complex effects on vision, perhaps in part due to modulation of the pulvinar, a nucleus that receives higher-order visual inputs from visual cortex. The pulvinar contains 5-HT_{2A} protein without expressing 5-HT_{2A} mRNA.[83] This indicates that the pulvinar receives inputs that express the 5-HT_{2A} receptor on axon terminals, and thus, psychedelics may alter pulvinar output to the

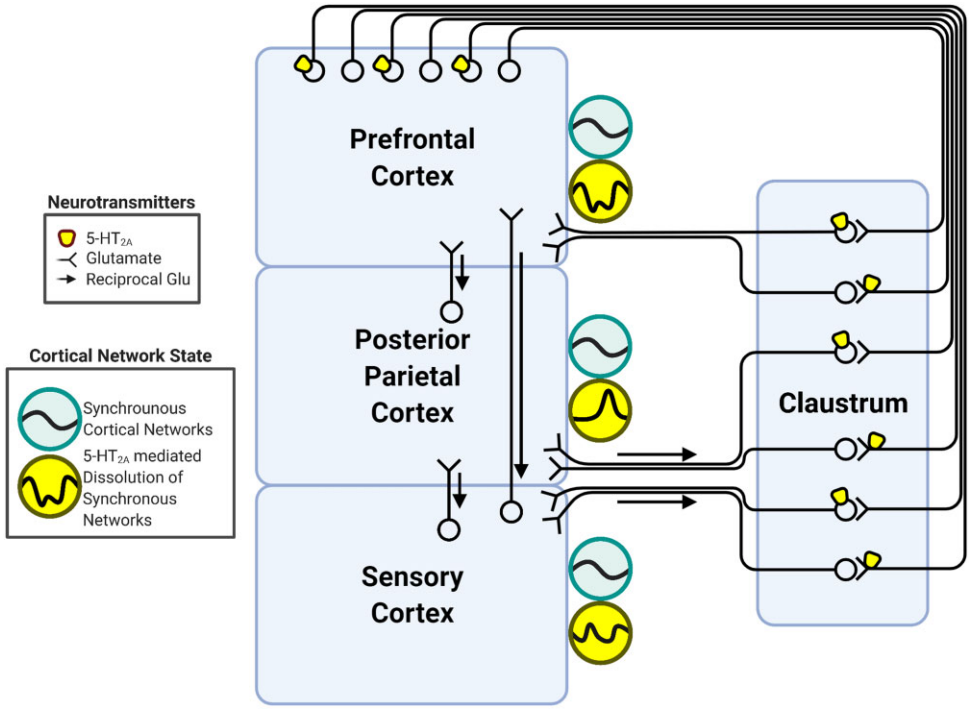

Figure 3 Summary of the CCC model circuitry. In this model, disruption of prefronto-claustro-cortical circuitry by 5-HT_{2A} activation dysregulates cortical network initiation, which contributes to the disruption of cortical network states (yellow circles). Turquoise and yellow circles depict two network states that arise from the dynamic synchronization of cortical regions across time. The first (turquoise circles) is a network state in which frontal, associative and sensory cortices are synchronized (represented by a similar wave form in each of the turquoise circles), and the second (yellow circles) is a state in which the network is disrupted across various cortical regions (represented by different waveforms in each of the yellow circles). Glu = glutamate.

cortex in a polysynaptic manner. Consistent with the pulvinar's role in visual attention and object motion,[84,85] psychedelics impair visual attention[77,78] and motion perception,[86] increase thalamic connectivity with visual cortex[53–55] and increase activity in primary visual cortex during an attention task.[78] However, pretreatment with ketanserin (a 5-HT_{2A}/5-HT_{2C} antagonist) did not block psilocybin effects on visual attention[30] or binocular rivalry,[31] suggesting other potential receptor targets of psilocybin [e.g. the serotonin 1B receptor (5-HT_{1B})] in mediating these effects.

Behavioural evidence, limitations and extensions

Behavioural models relevant to thalamocortical gating include pre-pulse inhibition (PPI) and inhibition of return (IOR), and some evidence from animal and human models suggests that psychedelics impact these behaviours. PPI is a phenomenon that occurs when a startle response is reduced by a preceding weaker, non-startling stimulus, and IOR refers to suppressed processing of a stimulus to which one has recently attended. PPI and IOR are thought to reflect pre-attentive sensory gating processes. Thalamic nuclei within thalamocortical circuits, including MD and sensory nuclei, facilitate these processes, and prefrontal cortical nodes are thought to control these processes.[77,87,88] Animal models demonstrate that LSD and DOI reduce PPI of the acoustic startle response,[89] but evidence for the presence or direction of an effect of psychedelics on PPI in humans is mixed. Some have reported that psilocybin dose-dependently reduces PPI when there are short intervals between pulses (30 ms) but has either no effect or increases PPI at intermediate and longer intervals ($\geqslant$120 ms).[90,91] Another study that used intermediate and longer intervals (100 and 240 ms) failed to show any effect of DMT on PPI.[92] Although DMT has been found to attenuate IOR,[93] DMT was also found to blunt neural responses in primary sensory cortices during sustained attention tasks in auditory and visual modalities.[78] This is seemingly inconsistent with an attenuation of suppressed sensory processing and a general prediction of the CSTC model that cortical regions are inundated with sensory information under psychedelics. Alternatively, decreased activation of primary sensory cortices during the acute effects of psychedelics could represent increased noise and decreased sensitivity to experimentally controlled stimuli.

Other mixed evidence for the CSTC model comes from its prediction that psychedelics should produce increased activity within the prefrontal cortex. Activity within the prefrontal cortex might reasonably follow from disinhibition of the MD in CSTC loops[58] and subsequent attempts by the prefrontal cortex to exert control over ungated sensory thalamic information.[39–41] Diminished thalamic gating might also presume an accompanying increase in thalamic activity. However, both decreases[24,94,95] and increases[54–56,96,97] have been reported in overall prefrontal and thalamic activity in humans. This inconsistency could be a product of the unconstrained nature of task-free scans in which small samples of participants might not necessarily perform the same range of mental functions during relatively short scans. Such work could be improved through the use of task-based sensory paradigms and parcellation of the thalamus into its subnuclei.

Although the CSTC model focuses on psychedelics disrupting thalamo-cortical striatal-thalamic circuits, a recently revised view of thalamic anatomy suggests a potential role for other bi-directional thalamocortical projections in psychedelic drug action (Fig. 1; for reviews, see Sherman[98,99]). Layer V pyramidal neurons receiving first-order thalamic relays (e.g. lateral

geniculate nucleus to primary visual cortex) project to higher-order thalamic nuclei (e.g. primary visual cortex to the inferior pulvinar). Interestingly, these projections back to the thalamus also branch to synapses on subcortical motor centres.[100–103] Because of these branches, such corticothalamic projections have been proposed to carry 'efference copies', or motor messages sent to sensory areas that allow for prediction of the sensory consequences of self-generated movements.[104] This bidirectional connectivity is not limited to early sensory processing. Thalamic nuclei receiving these putative efference copies also project back to higher levels of cortex (e.g. parietal association cortex), which in turn continue this pattern of branched projections to subcortical motor centres and subsequently higher-order thalamic nuclei (e.g. medial pulvinar). This neural scaffolding suggests that as information is processed through a sensory hierarchy, efference copies allow higher levels to predict the sensation of possible lower-level motor commands. Because 5-HT_{2A} receptors are widely expressed both in thalamic nuclei and on layer V pyramidal neurons within these circuits, psychedelics may drive aberrant predictions via such efference copies, potentially explaining sensory distortions and a sense of surprise that is often encountered during psychedelic experiences. Interestingly, efference copies are also thought to be sent to the striatum from the cortex in CSTC circuits, suggesting that aberrant predictions from the cortex could also be involved in disinhibition of the thalamus.[105] In the next section, we discuss a model that describes how psychedelics might break down functional hierarchies in the brain, resulting in predictions from lower levels exerting greater influence on processing at higher levels.

Relaxed beliefs under psychedelics and the disruption of cortico-medial temporal constraints

The REBUS model proposes that psychedelics disrupt the hierarchical nature of the brain by reducing the typical constraints that higher levels place on lower levels. This reduction in top-down control results in the increased influence of low-level prediction errors on higher levels of processing that encode or maintain prior beliefs. By allowing greater influence of incoming stimuli in prediction circuits, a greater number of cortical brain states may be expressed, thereby increasing cortical 'entropy' and putatively allowing updates or changes to prior beliefs. Although the hierarchies described in this model are stated to encompass sensory-centric circuit relationships (e.g. association to sensory cortices or secondary visual to primary visual cortex), the 'lower levels' are stated to include evolutionarily older subcortical structures, including the hippocampus, amygdala and thalamus. The REBUS model specifies the hippocampus (but also evolutionarily more recent cortical regions of the parahippocampal gyrus) as a structure involved in this psychedelic-mediated prediction error signalling.[42]

Whereas the CSTC model is less specific in terms of which cortical regions are of primary importance to psychedelic drug action (e.g. medial prefrontal cortex and sensory cortices,[39] posterior cingulate and the superior temporal gyrus[56]), the major cortical focus of the REBUS model has been on higher-level cortical networks composed primarily of prefrontal and parietal association cortices such as the default mode, frontoparietal and salience networks (DMN, FPN and SN, respectively). Specifically, the DMN is the crux of this model and posited to be at the top of the brain's hierarchy. In contrast to the CSTC model, and as described below, the REBUS model is rather vague regarding the subcortical structures of greatest importance to psychedelic drug effects or what constitutes a 'lower' level. Here we will review the basic conceptualization of REBUS, neuroimaging and behavioural evidence that supports this model and potential limitations and extensions of the model.

Default mode network centricity, egocentricity and medial temporal entropy release

The DMN is one of the most studied networks in the brain and its major hubs, the medial prefrontal and posterior cingulate cortices, densely express 5-HT_{2A} receptors.[106] The DMN is implicated in a number of high-level cognitive functions, including episodic memory, theory of mind, semantic processing and self-referential processing.[107,108] The DMN's role in self-referential processing has situated it at the top of the brain's hierarchy in the REBUS model, with the DMN proposed to be the neurobiological substrate of the 'ego' (in the Freudian sense)[109] and attenuations of DMN function have been interpreted as reflecting the 'ego dissolution' sometimes reported to be produced by psychedelics (but see Millière *et al.*[110] for inconsistencies regarding *post hoc* neural correlates of psychedelic-mediated ego dissolution). Psychedelics have been shown to impact the activity or functional connectivity of regions belonging to the DMN, but whether such effects are increases or decreases, or even selective to the DMN, has varied by study. Some studies in humans found relatively selective decreases in activity in regions of the DMN under psychedelics compared with drug-free conditions,[24,111] but most other studies have found both increases and decreases in regions within and outside the DMN.[74,94–97,112] Although psychedelics consistently decrease functional connectivity within the DMN,[23,24,74,111,113] equal or stronger decreases within other brain networks, including the FPN, SN and sensory networks,[23,74,113] have also been reported during acute psychedelic effects. Rodent studies have failed to find selective decreases in activity or functional connectivity of the DMN during acute psychedelic drug effects, however this may be confounded by the isoflurane anaesthesia that was concurrent with drug administration and imaging procedures.[114,115]

One explicit hypothesis of the REBUS model is that psychedelics increase bottom-up, over reciprocal top-down, information flow from the hippocampus and parahippocampal gyrus to higher-level cortical areas, especially the DMN[42] (Fig. 2). The hippocampus and parahippocampal gyrus both express 5-HT_{2A} receptors,[106,116] and the entorhinal cortex of the parahippocampal gyrus is a particularly important site for serotonergic transmission.[117] The entorhinal cortex is the principal input to the hippocampus and has been referred to as a 'wall of inhibition', due to its intrinsically inhibitory circuitry that appears to gate selective inputs to the hippocampus.[118] In addition to episodic memory, the hippocampus has been shown to be involved in prediction that can determine the fate of episodic memories.[119–121] Although speculative, psychedelics could attenuate entorhinal gating of information to the hippocampus and drive erroneous predictions that could subsequently flood higher-level cortical areas with aberrant mnemonic representations (analogous to disrupting thalamic gating). Empirical evidence, however, is contrary to this view. Psilocybin and LSD decrease functional connectivity of the hippocampus and parahippocampal gyrus with DMN regions.[74,122] Moreover, perirhinal and parahippocampal cortices of the parahippocampal gyrus are considered higher levels of the ventral and dorsal visual processing streams, respectively, yet contrary to the REBUS model, directional modelling has found evidence for psychedelics to increase top-down information flow from the

parahippocampal gyrus to visual cortex.[123] These analyses suffer from a similar problem as analyses of thalamic connectivity, namely, treating the hippocampus and the parahippocampal gyrus as unitary structures when they are understood to have a more segregated functional anatomy. Future work may benefit from parsing the parahippocampal gyrus (i.e. entorhinal, perirhinal and parahippocampal cortices) and hippocampus (e.g. anterior and posterior or hippocampal subfields) into their subregions to hone in on potential increases in bottom-up modulation of higher-level cortices under psychedelics.

According to the REBUS model, psychedelic release of low-level information manifests as an increase in cortical entropy or complexity (in the information theoretic sense).[42,122,124] Several studies have shown that psychedelics desynchronize scalp electrophysiological oscillations, especially in lower frequencies,[34,38,68–74] while simultaneously increasing the complexity (i.e. decreasing the information compressibility) of these signals.[125,126] Moreover, psychedelics increase various measures of entropy and variability within the DMN or between the hippocampus and cortex.[122,127,128] However, these increases appear to be more widespread[129] and greater in magnitude in the SN, FPN and even sensory and motor networks than in the DMN.[122,127] Together, these findings have been interpreted as an expansion of 'brain states'; although as described below, behavioural evidence for this assertion is lacking.

Behavioural evidence, limitations and extensions

A broad behavioural prediction put forth by the REBUS model is that 'higher-level' cognitive functions (i.e. processes later than initial sensory information processing such as attention and memory) should be more impaired than lower-level functions (e.g. perception).[42] Consistent with this prediction, one study found psilocybin to impair motion perception but not contrast sensitivity.[86] Moreover, due to a relaxation of top-down priors in favor of bottom-up signalling, some lower-level cognitive functions may even be enhanced. For example, noticing a unique stimulus with a salient feature in a visual array of otherwise similar objects (i.e. the 'pop-out' effect)[130] appeared to be enhanced under the effects of the *R*-enantiomer of 3,4-methylenedioxyethylamphetamine (MDEA),[131] a hallucinogenic 5-HT_{2A} agonist like the *R*-enantiomer of its more commonly known analog 3,4-methylenedioxymethylamphetamine (MDMA; in contrast, the *S*-enantiomers of these drugs have entactogenic, stimulant and monoaminergic effects). Extinction learning in mice, a form of memory evolutionarily older relative to other types of memory such as episodic, has also been found to be enhanced by psilocybin and the psychedelic TCB-2.[132,133] However, as previously described, psychedelics impair PPI and IOR, pre-attentive processes that are arguably even lower levels of sensory memory than extinction.[89,90,93] Moreover, inconsistent with the neuroanatomy highlighted by the REBUS model, various forms of hippocampally-dependent learning are unaffected or even impaired by psychedelics. Specifically, in rodents, psilocybin does not enhance trace fear conditioning,[132] DOI impairs the learning of a novel spatial location[134] and TCB-2 impairs the encoding of hippocampal place fields.[135] Similarly in humans, encoding of recollection memory, which is a form of episodic memory dependent on the hippocampus, is impaired by psilocybin[5] and the entactogen-stimulant-psychedelic hybrid MDMA[136] (the amnestic effects of the latter stemming from 5-HT_{2A} activation).[137]

Although it has been claimed by proponents of the REBUS model that cognitive impairments under psychedelics are simply due to 'generalized disengagement',[42] psilocybin has been found to more selectively impair working memory compared with episodic memory, while the opposite pattern was found with the hallucinogenic NMDA antagonist dextromethorphan[5] (see also Lofwall *et al.*[138] and Braun *et al.*[139]). Such double dissociations obfuscate claims of generalized disengagement (see also Doss *et al.*[136] for disproportionate effects of MDMA on emotional compared to neutral memory). One interesting finding from these studies of episodic memory is that the encoding of familiarity, a mnemonic process dependent on the perirhinal cortex of the parahippocampal gyrus,[140] was unaffected or even enhanced under psychedelics.[5,136] Similarly in mice, post-encoding (i.e. during consolidation) administration of TCB-2 enhanced novel object recognition,[132] a perirhinal-dependent analogue to familiarity.[141] Together, these findings suggest that psychedelics could have a unique profile of effects on cognition via episodic memory hubs that the REBUS model proposes to drive cortical entropy. These findings also highlight the nuances of specific episodic memory processes and medial temporal subregions (for review see Ranganath and Ritchey[142]) compared with more generalized effects within the brain that may be elucidated by careful comparative pharmacology.

The functional outcomes of increased entropy and diversity of brain states under psychedelics remain unclear. Successful memory retrieval, arguably greater information content than the failure to retrieve a memory, is associated with less entropy in scalp electrophysiological signals,[143] and GABAergic sedatives increase entropy during episodic memory retrieval[143] but reduce resting state measures of complexity.[144,145] Greater neural diversity has been suggested to be of relevance to cognitive flexibility,[42,146,147] and 5-HT_{2A} antagonism can attenuate models of cognitive flexibility[148,149] in rats. However, in mice, psychedelics impair or have no effect on cognitive flexibility,[150,151] and in humans, LSD was found to acutely impair cognitive flexibility.[37] Furthermore, studies supporting psychedelic-induced increases in the number of brain states are based on task-free conditions and thus are under ambiguous control of cognitive operations. Increased cycling between brain states under task-free psychedelic conditions may simply be produced by participants inadvertently 'performing cognitive tasks' (e.g. related to visualization, memory retrieval, shifts in attention and theory of mind operations) instead of 'resting.' That is, under drug-free conditions, participants possess the capacity to cycle through multiple cognitive states despite not typically doing so, but under psychedelics, cognitive control is impaired, resulting in more cycling between cognitive states and less rest-like neural activity. In the next section, we discuss a model that describes how psychedelics might disrupt cognitive control and an associated neural interface that permits switching between cortical networks for complex cognition.

Cortico-claustro-cortical model and disruption of canonical cortical networks

The claustrum is a thin, ribbon-like telencephalic nucleus located lateral to the putamen, medial to the insula and in between the external and extreme capsules. The claustrum densely expresses 5-HT_{2A} receptors and possesses bidirectional glutamatergic connections with the majority of the cortex,[47,152] suggesting a role for the claustrum in psychedelic drug effects.[1,153] This structure was famously proposed to mediate sensory binding and, therefore, generation of conscious percepts.[152] However, functional assessments of the claustrum have pointed to a role for the claustrum in cognitive control functions rather than in sensory binding or the generation of consciousness (see also Bickel and Parvizi[154]). A synthesis of recent evidence points to a specific role of the claustrum as a

brain structure of central importance in supporting cortical network states. Additional evidence supports a role of psychedelic drugs in disrupting higher-level cortical networks through claustro-cortical circuits, which may subsequently contribute to the neural and subjective effects observed during psychedelic experiences (Fig. 3). The claustrum also densely expresses κ-opioid receptors,[153,155] the primary target of the atypical dissociative hallucinogen salvinorin A. Interestingly, some of the effects of salvinorin A on task-free brain function (e.g. reductions of DMN functional connectivity) resemble those of psychedelics (i.e. 5-HT2A activating hallucinogens),[156] suggesting that the CCC model may also explain some effects of κ-opioid activating hallucinogens.

The cortico-claustro-cortical model

In rodents, the claustrum receives dense projections from primarily contralateral areas of association cortices[157–164] such as prefrontal (including regions of the DMN and FPN) and cingulate cortex (including the anterior cingulate cortex, a hub of the SN), while receiving comparatively sparser input from sensory and motor regions.[163–166] Similarly, the human claustrum is functionally connected to much of the DMN, FPN and anterior cingulate cortex.[48,49] Accordingly, claustrum neuron firing is primarily driven by input from prefrontal cortex.[163,167] In contrast, the claustrum provides expansive ipsilateral projections back to prefrontal cortex, as well as to sensory and parietal association cortices.[157–164] Claustrum input to the cortex powerfully and transiently suppresses cortical activity, followed by rebound excitation.[168,169] Optogenetic activation of the claustrum results in widespread cortical synchronization.[169] In the process of frontal regions initiating synchronous network activity,[170–173] the CCC model proposes that a prefrontal cortico-claustro-cortical circuit configuration allows for prefrontal cortex-mediated instantiation of higher-level cortical networks that include prefrontal and posterior association cortices (Fig. 3). Thus, the CCC model proposes that the prefrontal cortex entrains canonical cortical network states through the activation of the claustrum, which in turn coordinates the recruitment of cortical networks in response to changing task demands. Claustrocortical neurons thereby provide a cortical network synchronization broadcast signal necessary for appropriate goal-directed or internally directed mental activity. We refer to these context-appropriate instantiations of cortical region synchrony as network states.

Supporting this role of the claustrum in instantiating network states, during performance of an attention task that elicits FPN responses in humans, the claustrum is activated along with the deactivation of the DMN.[48] Moreover, in mice, the claustrum receives a preparatory signal from the anterior cingulate cortex, and this input, along with activation of the claustrum itself, are both required for accurate performance on the cognitively demanding five-choice serial reaction time task.[167] Consistent with these findings, the mouse claustrum is also required for resilience to distraction.[164]

Psychedelic disruption of the cortico-claustro-cortical system

Interestingly, the claustrum expresses both 5-HT_{2A} receptor mRNA and the 5-HT_{2A} receptor protein, suggesting that it both contains 5-HT_{2A} projection neurons and receives 5-HT_{2A}-expressing projections.[43,46,83,174] A large proportion of 5-HT_{2A} receptor-containing psychedelic 'trigger neurons' were also found to be claustrum neurons, in addition to prefrontal cortical neurons.[19] This finding led to the proposal that disruption of claustrum function by psychedelic drugs could amplify neuronal avalanches that eventually result in the destabilization of network states.[175] We propose that, during psychedelic drug action, 5-HT_{2A} activation causes a misalignment between the claustrum and cortex by driving prefrontal inputs to the claustrum and also by independently activating the claustrum. Thus, according to the CCC model, broad disruption of canonical network states may be effected by 5-HT_{2A}-mediated decoupling of prefrontal activity from claustral activity, leading to aberrant cognitive control.[176] This decoupling may ultimately lead to attenuation of cortical network (e.g. FPN and DMN) states (Fig. 3). While such states typically fluctuate depending on the goals, cues, cognitive load, prior cognitive state and upcoming states required for ongoing goal-directed behaviour, this natural fluctuation is altered during psychedelic drug action.

Supporting the CCC model account of psychedelic drug action, in humans, psilocybin decreases resting state claustrum activity, which was found to correlate with a sense of ineffability,[49] a facet of 'mystical experiences' that closely aligns with a decrease in cognitive control. Moreover, psilocybin was found to decrease functional connectivity between the claustrum and cortical networks.[49] Specifically, psilocybin decreased right claustrum connectivity with the DMN and auditory network and left claustrum connectivity with the FPN. Unexpectedly, psilocybin increased connectivity between the right claustrum and FPN. Although the CCC model might predict widespread decreases in connectivity of the claustrum with cortical networks, the laterality effects observed during acute effects of psilocybin may be a function of the claustrum's laterality bias in structural connectivity.[163,165,166] Considering the potential lateralization inherent in cognitive control processes,[177] a task-based study may help to contextualize such idiosyncratic network states. Finally, some evidence supports the hypothesis that 5-HT_{2A}-mediated disruption of prefrontal-claustrum coupling attenuates cortical network instantiation. During the acute effects of psilocybin, within-network connectivity of the DMN and FPN (which can be interpreted as 'network integrity') is correlated with their functional connectivity with the right and left claustrum, respectively.[49]

Together, these data provide support for the hypothesis that coordination between the claustrum and cortex is critical to establishing cortical network states necessary for cognitive control. In the context of prior evidence of psilocybin effects on prefrontal cortex,[95,96,178] psilocybin may induce a 'two-hit' dysregulation of this system by disrupting both the prefrontal cortex and claustrum. In humans, claustrum activity was found to be prominently coupled with activity in the thalamus, striatum and the parahippocampal gyrus.[48] Thus, while speculative, the claustrum may be positioned as a hub connecting key components inherent in all three circuit models of psychedelic drug action. While the human evidence of direct impingement of psychedelics on claustrum function is currently limited, new methods are allowing for this structure to be studied in humans.[48,49] Given the integral involvement of the claustrum and prefrontal cortex with dynamic changes in goal-directed behaviour, psychedelic-induced disruption of this prefrontal cortico-claustro-cortical system may contribute to cognitive control dysfunction induced by psychedelic drugs.

Potential shared neural circuit mechanisms of 5-HT_{2A} and κ-opioid hallucinogen effects

In addition to the claustrum densely expressing 5-HT_{2A} receptors, it also densely expresses κ-opioid receptors,[153,155] the primary

target of atypical dissociative hallucinogens such as salvinorin A and enadoline. Compared with psychedelics, atypical dissociative hallucinogens seem to be more dysphoric,[179] perhaps owing to their reduction in striatal dopamine transmission[180–182] (but see Carlezon *et al.*[180] and Braida *et al.*[183] for no changes or even increased dopaminergic transmission at lower doses). Despite the sale of salvinorin A being unregulated in many states, it appears to be less commonly used than psychedelics, further suggesting fewer 'good' subjective effects and more frequent or stronger 'bad' subjective effects of salvinorin A compared with classic psychedelics. Nevertheless, atypical dissociative hallucinogens produce some subjective effects similar to classic psychedelics (i.e. 5-HT_{2A} agonists) such as laughing, visual imagery and mystical-like experiences.[184–187] Moreover, like psychedelics, there is increasing evidence that atypical dissociative hallucinogens may be useful in the treatment of addiction.[188]

Interestingly, some of the effects of salvinorin A on task-free brain function in humans resemble those of psychedelics. Similar to psilocybin, LSD and ayahuasca,[70–72,74] salvinorin A was found to decrease power across frequency bands as measured using EEG.[189] Also, in a recent functional MRI study,[156] the largest effect of salvinorin A on human brain functional connectivity was a decrease of connectivity within the DMN, accompanied by trends for increased between-network connectivity of the DMN. Some of these effects were recently associated with changes in claustrum function during the acute effects of psilocybin.[49] Finally, entropy was found to be increased across much of the brain during the acute effects of salvinorin A.[156] However, despite a high, breakthrough dose of salvinorin A administered in the recent functional MRI study,[156] changes in connectivity of task-positive networks during the acute effects of salvinorin A were not nearly as substantial as those observed during the acute effects of classic psychedelics.[54,55,74,113,178,190]

These data interpreted together suggest that claustrum disruption by both serotonergic psychedelics and κ-opioid receptor agonists may represent a polypharmacological mechanism underlying some 'psychedelic-like' effects. This interpretation must be tempered, though, as salvinorin A functional MRI data are limited to only one small-sample study, and claustrum functional MRI data during acute psychedelic effects are limited to only one separate small-sample study. Also, as noted earlier in this review, reductions in DMN connectivity and increases in entropy may be less specific than previously claimed and may be a direct result of participants cycling through various task-positive-like states, which has been understood to reduce DMN activation and connectivity for decades.[108,191]

κ-opioid receptors are also densely expressed in prefrontal cortex. It is possible that κ-opioid receptor-mediated disruption of the medial prefrontal cortex, or activation of striatal-projecting neurons in the medial prefrontal cortex, could result in disinhibition of the thalamus and a flooding of the cortex in line with the CSTC model, though of course this is speculative. Of note, decreases in DMN connectivity and increases in entropy are explicit features of psychedelic action in the brain that are proposed by REBUS. In fact, REBUS may be more applicable to salvinorin A, considering the largest effects of salvinorin A on human brain function were found in the DMN. Nevertheless, as described earlier, one has to be cautious when interpreting task-free connectivity. Increases in between-network connectivity and entropy may simply be an artefact of comparing a drug-free rest condition to a condition in which cognitive operations (that are able to be carried out while sober) are unconstrained (leading to inconsistent increases in specific between-network increases observed during psychedelic drug action).[113]

Conclusion

Here, we discussed three circuit models that may explain various effects of classic psychedelic drugs and highlight potential revisions to each. With bidirectional glutamatergic projections between the cortex and thalamus, the CSTC model's role for the thalamus in psychedelic drug action is likely incomplete. Not only might psychedelics cause the thalamus to inundate the cortex with activity, psychedelics may also drive layer V cortical inputs to the thalamus (i.e. motor predictions or 'efference copies'). However, similar to the REBUS model, there may be differences along the sensory processing hierarchies (e.g. under psychedelics, the thalamus may have more influence on association cortices than vice versa). Moreover, aberrant lower-level motor predictions that typically inform higher levels of cortex aligns with the REBUS model's proposal that psychedelics can release lower-level predictions (due to less cortical constraints, however). The REBUS model also must be revised particularly regarding what constitutes a higher or lower level of the brain or cognition. Nevertheless, the brain regions specified and effects of psychedelics on behaviour suggest the possibility for unique effects of psychedelics on processes dependent on the medial temporal lobes such as episodic memory. Both the CSTC and REBUS models could benefit from more precise definitions in neuroanatomy (e.g. subnuclei of the thalamus and medial temporal lobe). Finally, the CCC model is in its infancy, and with newer technologies for probing the claustrum, future work will be needed to test its validity.

Although we discuss how disruption of claustrum function could contribute to the disruption of network states,[49] cortical layer V pyramidal neurons[18,19,192] and the thalamus[22,53–55,94–96] could also be directly involved in such disruption. Network state disruption could take three possible forms: inhibition of sensory gating resulting in increased sensory information flow to higher cortical regions,[39–41] a relaxation of predictive codes acquired from past experience,[42] and disengagement of executive faculties and control of network states.[49] Each of these cases could be used to explain why psychedelic drugs can allow new interpretations of familiar sensory cues, which may, in turn, promote novel behavioural responses. Modulation of maladaptive network states observed in clinical populations could provide clues to how psychedelics exhibit efficacy for brain disorders in which inelastic responses to cues foster repetitive behaviour or thoughts (e.g. addiction, depression, obsessive-compulsive disorder). Finally, differential modulation of one or all of these circuits might explain similarities among and differences between classic and atypical hallucinogenic compounds, specifically NMDA receptor antagonists (e.g. ketamine or dextromethorphan) and κ-opioid receptor agonists (e.g. salvinorin A) that have been shown to exhibit psychedelic-like effects.[5,156,184,185,193,194] Pharmacological modulation of these other receptors is also being explored for therapeutic effects, and the claustrum, specifically, has a high density of both of these receptors. Mechanistic, hypothesis-driven work based on circuit models of cortical function coupled with the careful control of behaviour and cognition is needed to further establish evidence for and differentiate between the role of each model in explaining psychedelic drug effects.

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Competing interests

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