# Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders

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Abstract | Renewed interest in the use of psychedelics in the treatment of psychiatric disorders warrants a better understanding of the neurobiological mechanisms underlying the effects of these substances. After a hiatus of about 50 years, state-of-the art studies have recently begun to close important knowledge gaps by elucidating the mechanisms of action of psychedelics with regard to their effects on receptor subsystems, systems-level brain activity and connectivity, and cognitive and emotional processing. In addition, functional studies have shown that changes in self-experience, emotional processing and social cognition may contribute to the potential therapeutic effects of psychedelics. These discoveries provide a scientific road map for the investigation and application of psychedelic substances in psychiatry.

Substance-assisted psychotherapy
A therapy model that refers to the adjuvant use of one or a few doses of a classic psychedelic in combination with psychotherapeutic support. The process will commonly include a few drug-free preparation sessions, followed by a drug session and a few follow-up integration sessions of the psychedelic experience.

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During the 1950s and 1960s, classic psychedelics (also known as serotonergic hallucinogens) such as lysergic acid diethylamide (LSD) and phosphoryloxy-*N*,*N*-dimethyltryptamine (psilocybin) were extensively investigated in psycholytic (low dose) and psychedelic (low to high dose) substance-assisted psychotherapy, resulting in more than 1,000 scientific papers and reports that included findings from about 40,000 subjects[1]. Although these early, largely explorative studies used various psychotherapeutic techniques and had serious methodological flaws by contemporary standards, four systematic reviews of these early clinical studies reported impressive improvement rates in patients with various forms of depression and neuroses[2–4], anxiety disorders[2,4], personality disorders[2,4], sexual dysfunctions[2,4] and alcohol dependence[2,4,5].

During the counterculture movement in the United States in the mid-1960s, the use of psychotropic drugs became popularized. This led LSD and related drugs to be placed in Schedule I (Controlled Substances Act, 1970) in the United States and in an equivalent category in most other countries. Thus, human research with psychedelics became severely restricted, leaving many questions unexplored[6]. However, with the development of modern neuroimaging techniques in the 1990s, renewed interest in the investigation of psychedelic substances has emerged[7]. Current behavioural and neuroimaging data show that psychedelics induce their psychological effects (BOX 1) primarily via 5-hydroxytryptamine (serotonin) type 2A (5-$HT_{2A}$) receptor activation and modulate neural circuits involved in mood and affective disorders. Additional findings show that psychedelics enhance glutamate-driven neuroplasticity in animals and may provide a novel mechanism for the lasting symptom improvements observed in recent clinical trials in patients with psychiatric disorders.

In the present article, we review the advances that have taken place in recent years. We focus on new discoveries about the neurobiology and neuropharmacology of psychedelic substances and discuss potential mechanisms through which they may exert therapeutic effects in the light of modern neuroscience concepts. Discrepancies between research results and knowledge gaps are highlighted, and potential new directions are discussed. We conclude the Review by summarizing the implications of these findings for understanding cognitive processes in health and disease, the discovery of potential trans-diagnostic treatment mechanisms and the development of novel therapeutics.

## The neurobiology of psychedelics

***Receptor activation and signalling.*** The classic psychedelics comprise three main classes of chemicals. The first class are plant-derived indoleamines, including *N*,*N*-dimethyltryptamine (DMT), 5-methoxy-DMT (5-MeO-DMT), psilocybin and 4-hydroxy-DMT (psilocin, the active metabolite of psilocybin). The second class are phenylalkylamines, including mescaline (derived from the peyote cactus) and synthetic 'amphetamines' such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-bromoamphetamine (DOB). The third group of compounds are semi-synthetic ergolines, such as LSD[8]. The phenylalkylamines are selective agonists of 5-$HT_2$ receptors, including 5-$HT_{2A}$, 5-$HT_{2B}$ and

**Box 1 | Psychometrical assessment of altered states of consciousness**

Quantifying altered states of consciousness was problematic in the early years of psychedelic research. However, over recent years, several psychometric instruments have been developed for assessing various aspects of consciousness. The 5-Dimensional Altered States of Consciousness Questionnaire is one of the most widely used and validated rating scales to measure the subjective response to psychedelics[170–172]. This questionnaire assesses five core dimensions of altered states of consciousness that can be further described by 11 order scores[171]. The five core dimensions are as follows:

- Oceanic Boundlessness: referring to positively experienced loosening or loss of self/ego boundaries that is associated with changes in the sense of time and emotions ranging from heightened mood to sublime happiness and feelings of oneness with the environment. This dimension resembles the so-called mystical-type experience also reported in religious exaltation.
- Visionary Restructuralization: referring to perceptual alterations such as illusions and hallucinations, synaesthesia, changed meaning of percepts, increased imagination and facilitated memory recollection.
- Dread of Ego Dissolution: referring to negatively experienced loss of self/ego boundaries associated with anxiety over the loss of control over thinking and body, and thought disturbances that may result in delusional thinking and/or panic. This response type occurs rarely at moderate to medium doses of a psychedelic in a controlled clinical setting[111], but can occur at higher doses (psilocybin >25 mg, lysergic acid diethylamide (LSD) >200 μg)[144,173].
- Acoustic Alterations: hypersensitivity to sound or noise and auditory hallucinations.
- Altered Vigilance: changes in the level of alertness.

$5\text{-HT}_{2C}$ receptors[9]. The indoleamines and ergolines act as partial agonists upon $5\text{-HT}_1$, $5\text{-HT}_2$, $5\text{-HT}_6$ and $5\text{-HT}_7$ receptors[8]. LSD and other ergolines also act upon D1 and D2 dopamine receptors and adrenergic receptors[8].

Compelling evidence indicates that the activation of $5\text{-HT}_{2A}$ receptors located in cortical and subcortical structures is a unifying mechanism through which psychedelics mediate their various behavioural and psychological effects in animals[10], including humans[11–15] (FIG. 1). Specifically, pharmacological studies have shown that the 'head twitch response' in rodents, a behavioural proxy for the effects of hallucinogens on humans[9,10], depends on $5\text{-HT}_{2A}$ but not on $5\text{-HT}_{2C}$ or $5\text{-HT}_{2B}$ receptor stimulation[9,16–19]. Consistent with these animal studies, the administration of the $5\text{-HT}_{2A}$ receptor antagonist ketanserin abolishes virtually all of the subjective effects of psilocybin, LSD and DMT in humans[11–15,20,21]. Moreover, the psychedelic effects of psilocybin in humans have been shown to correlate with $5\text{-HT}_{2A}$ receptor occupancy measured via positron emission tomography in the prefrontal cortex (PFC) and other cortical regions[22,23]. However, it is important to note that some studies also suggest that $5\text{-HT}_{1A}$ receptor activation contributes to the visual[24] and attention-disrupting[25] effects of psilocybin in humans.

It has been demonstrated that hallucinogenic and non-hallucinogenic $5\text{-HT}_{2A}$ receptor agonists, such as LSD and lisuride, respectively, activate different intracellular signalling pathways in cortical pyramidal neurons[26]. Although both LSD and lisuride activate signalling via $G_{q/11}$ subunits, only LSD additionally increased the expression of early growth response protein 1 (EGR1) and EGR2 by activating $G_{i/o}$ subunits and the protein tyrosine kinase SRC[27]. Further investigation of this functional selectivity may inform the development of novel, possibly more specific, compounds with therapeutic properties and could help to resolve long-standing questions about whether non-hallucinogenic $5\text{-HT}_{2A}$ agonists can also exert antidepressant or neuroplastic effects in humans[7].

In addition to its effects on serotonin signalling, psilocybin has been found to increase striatal dopamine concentrations in humans, with these increases correlating with euphoria and the emergence of depersonalization[28]. Although psilocybin does not act directly on dopamine receptors and may increase striatal dopamine concentration via $5\text{-HT}_{1A}$ receptor activation[29], LSD does show high intrinsic activity at dopamine D2 receptors[8]. In animal studies, LSD's activation of dopamine receptors has been linked to its behavioural effects[30], but the relevance of dopaminergic stimulation for psychedelic effects in humans is less clear[31]. Studies specifically blocking dopaminergic receptors after LSD administration, which would help to resolve this issue, are currently lacking.

***Regulation of neuronal activity.*** In humans, $5\text{-HT}_{2A}$ receptors are highly expressed in the apical dendrites of layer 5 pyramidal (L5p) neurons in the cortex and are particularly enriched in the PFC[32–34]. A smaller proportion are located presynaptically on thalamocortical afferents projecting to the neocortex[34]. In addition, inhibitory GABAergic interneurons in the cortex and subcortical structures also express $5\text{-HT}_{2A}$ receptors[34]. In vitro electrophysiological recordings have shown that DOI or LSD increases the frequency and amplitude of spontaneous excitatory postsynaptic potentials and excitatory postsynaptic currents in L5p neurons in the rat medial PFC and other cortical regions by activating $5\text{-HT}_{2A}$ receptors[35,36]. In vivo, DOI produced a striking net-excitatory effect (a 481% increase in the mean firing rate (spikes/s)) on most pyramidal neurons (38%) examined in the rat PFC, although a lower proportion of L5p neurons (27%) were also inhibited via activation of GABAergic interneurons[37]. In another study, a lower dose of DOI evoked a marked activation of neuronal populations in the rat orbitofrontal cortex and anterior cingulate cortex, whereas higher doses tended to inhibit these regions[38,39]. Thus, it appears that psychedelics may exert different modulatory effects across cortical regions, depending on the dose, the specific drug used and — presumably — the density of $5\text{-HT}_{2A}$ receptors in different neuronal populations.

The increase of L5p neuron activity in the PFC upon treatment with LSD or DOI was shown to be mediated by an increase of glutamate release and a subsequent activation of postsynaptic AMPA receptors[35,39–41]. It is widely believed that the increase in extracellular glutamate is due to recurrent network activity triggered by an activation of postsynaptic $5\text{-HT}_{2A}$ receptors located in the deep L5p and L6p neurons that project to L5p neurons[27,39,40] (FIG. 1). However, prefrontal L5p neurons receive excitatory glutamatergic input not only from higher and lower cortical areas but also from specific and non-specific thalamic projections, and send output back to both the cortex and thalamus[35,42] (FIG. 1). One recent study indicates that activation of presynaptic $5\text{-HT}_{2A}$ receptors located on these thalamocortical afferents also contributes to the psychedelic-induced modulation of glutamatergic transmission in the PFC[35]. In support of this idea, it has been

Positron emission tomography
A nuclear medicine functional imaging technique that uses radioligands to assess metabolic processes and receptor density and occupancy in the brain.

Excitatory postsynaptic potentials
Temporary depolarizations of the postsynaptic neuronal membrane potential that make it more likely that the neuron will exert an action potential.

Recurrent network activity
A self-generated network activity that arises from the recurrent synaptic architecture of the cortex. One form of such activity is the up state, in which neurons transiently receive bombardments of excitatory and inhibitory synaptic inputs that depolarize many neurons to the spike threshold before returning to a relatively quiescent down state.

shown that activation of presynaptic 5-$HT_{2A}$ receptors located in thalamocortical synapses by DOI increases NMDA receptor-mediated transmission[43]. Interestingly, the concomitant activation of the apical compartment of L5p neurons (which receives input from higher cortical areas and non-specific thalamic nuclei) and of the basal compartment (which receives input from lower cortical areas, such as the visual cortex) markedly increased the burst firing of L5p neurons[44,45] and correlated positively with the animal's stimulus detection behaviour[42]. Thus, it has been proposed that L5p neurons have the unique ability to couple bottom-up cortico-thalamic and top-down cortico-cortical loops of informational streams with each other[42,45].

Within the network outlined above, the PFC is known to be involved in the control of high-level cognitive and emotional processes, and in enabling a sense of self[12,46–49]. Disruption of the functional integrity between or hyperactivity within components of this network has been associated with the dissolution of self-boundaries and alterations of cognitive and emotional processing in psychedelic states[50,51] (BOX 1) and has also been linked to the pathophysiology of psychotic disorders.

***Neuroplastic effects.*** In addition to its acute effects, 5-$HT_{2A}$ receptor activation has been shown to drive neuroplastic adaptions that have been proposed to underlie the persisting symptom improvements observed in psychiatric disorders[52–54]. The finding that LSD and DOI increase levels of glutamate[8,55,56] and brain-derived neurotrophic factor (BDNF)[57] in the rat cortex has led to the hypothesis that psychedelics promote neuroplasticity via glutamate-driven increased AMPA receptor activation[7]. AMPA receptor activation has been shown to increase the release of BDNF[58], which in turn is essential for neuronal remodelling associated with learning and memory in both animals[59] and humans[60].

In fact, several recent studies showed that psychedelics induce both structural and functional changes in cortical neurons in mice in vitro and in vivo[52–54]. These changes include increased synaptogenesis, which appears to be mediated through activation of 5-$HT_{2A}$ receptor, tyrosine receptor kinase B (TRKB) and mammalian target of rapamycin (mTOR) signalling pathways[54]. Two recent studies in mice also showed that stimulation of postsynaptic 5-$HT_{2A}$ receptors by DOI gates synaptic plasticity via AMPA receptor-dependent long-term depression of L5p neuron transmission[61] whereas stimulation of presynaptic 5-$HT_{2A}$ receptors located in thalamocortical synapses gates neuroplasticity and associative learning via NMDA receptor-dependent mechanisms[43]. In animals, neuroplastic adaptions have also been associated with the ability of psychedelics to facilitate the extinction of fear memory[52,53].

The capacity of psychedelics to induce functional and structural neuroplasticity could lead to a shift in the approach to treatment of various psychiatric disorders. However, whether the neuroplastic effects of psychedelics observed in animal studies are replicable in humans and are responsible for the long-lasting symptom improvements seen in recent clinical studies requires further investigation.

## Altered activity and connectivity

As discussed above, 5-$HT_{2A}$ receptor activation can have profound neuromodulatory effects. These effects can manifest as changes in measures of connectivity assessed with neuroimaging techniques such as functional MRI (fMRI). There are numerous different neuroimaging approaches for the measurement of connectivity. Functional connectivity approaches assess the correlation between the signals observed in different brain areas, whereas effective connectivity approaches such as dynamic causal modelling provide models of neuronal coupling (that is, the effect of one neural system on another). Alternatively, the neuromodulatory effects of psychedelics can be expressed in terms of changes in fast neuronal dynamics and assessed with electrophysiological measures.

Recent neuroimaging and electrophysiological studies of the human brain in its resting state have revealed psychedelic-induced systems-level changes that have given rise to various hypotheses regarding the neural underpinnings of psychedelic states. The empirical evidence from these studies described below suggests that changes in thalamic gating, between-network and within-network integration and temporal dynamics are induced by psychedelic compounds. Further studies investigating the neurobiological correlates of specific psychedelic-induced emotional and cognitive alterations are discussed in later sections.

***Evidence for altered thalamic gating.*** Within cortico-striato-thalamo-cortical (CSTC) feedback loops, the thalamus is crucial in the gating of the flow of internal and external sensory and cognitive information to the cortex[51,62]. Thalamic gating is under the control of glutamatergic cortico-striatal and cortico-thalamic pathways that project to specific and non-specific nuclei of the thalamus and is also under the modulatory influence of serotonergic and dopaminergic neurons in the raphe and ventral tegmentum, which project to several components of the CSTC loops[63]. Hence, the CSTC model proposes that psychedelics disrupt thalamic gating by stimulating 5-$HT_{2A}$ receptors located in several parts of the CSTC loop, resulting in a feedforward information overload of the cortex and subsequent disruption of cortico-cortical integration of distributed neuronal activity[51,62] (FIG. 1). It is suggested that this may eventually cause the increased sensory perception, cognitive disturbances and ego dissolution that occur in psychedelic states[51,62]. This hypothesis is also compatible with the suggested increase of sensory bottom-up information flow and relaxed priors formulated in the REBUS[64] model described below.

The CSTC model is supported by evidence that infusion of DOI into the ventral pallidum in rodents[65] and systemic administration of psilocybin, LSD and DMT in humans disrupts sensorimotor gating and is associated with alterations in cognitive functioning in a 5-$HT_{2A}$-dependent manner[66–69]. Two neuroimaging studies have provided further support for this model by demonstrating increased thalamic functional connectivity after the administration of LSD, particularly between the thalamus and the sensory and sensory

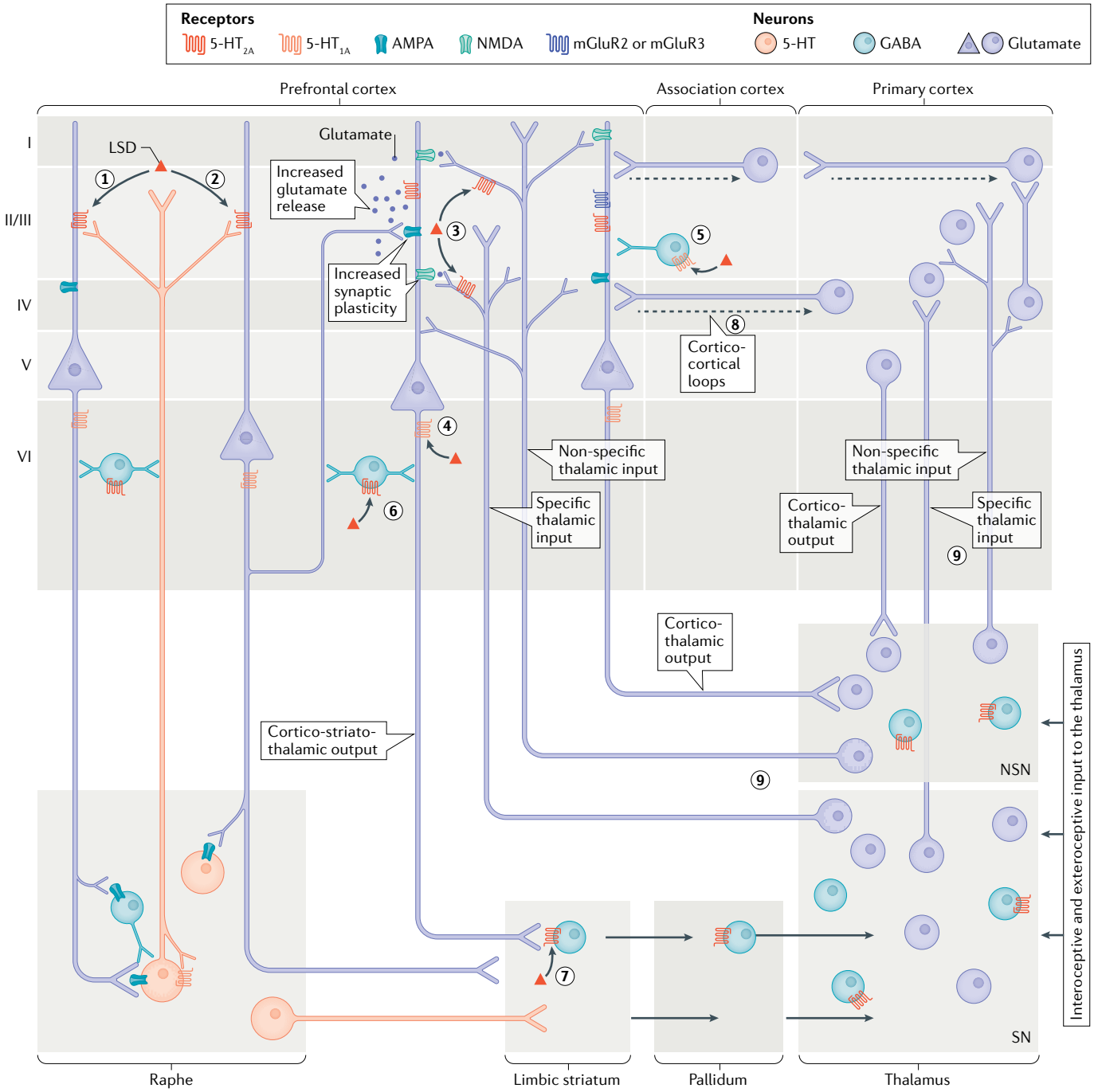
Neuroplastic adaptions
The brain's ability to reorganize itself by forming new neural connections throughout life. Neuroplasticity allows the neurons in the brain to compensate for injury and disease, and to adjust their activities in response to new situations or to changes in their environment.

Long-term depression
Long-lasting, activity-dependent decreases in synaptic strength.

Functional MRI
(fMRI). A neuroimaging technique that measures brain activity by detecting changes associated with blood flow.

Dynamic causal modelling
A framework for inferring the causal architecture of coupled or distributed dynamic systems, which allows the coupling between brain regions to be estimated.

Priors
The prior probability distributions in Bayesian statistical inference, which express one's beliefs before some evidence is taken into account.




somato-motor cortical regions[31,70]. In another study, dynamic causal modelling was used to assess effective connectivity between major hubs of the CSTC model[71]. Increased excitatory connectivity from the thalamus to the posterior cingulate cortex (PCC), consistent with the predicted increase in thalamo-cortical information flow, was demonstrated under LSD. In line with another prediction of the model, decreased control of the ventral striatum over the thalamus was detected. However, LSD also decreased the effective connectivity from the thalamus to the temporal cortex. These results together suggest that whereas LSD indeed increases 'bottom-up' thalamo-cortical information flow to certain cortical regions, it reduces information flow to others. Hence, psychedelics such as LSD, at least at the moderate doses tested, appear not to induce undifferentiated cortical flooding as originally hypothesized[71].

Consistent with the idea that psychedelics disrupt thalamic gating, two earlier human positron emission tomography studies reported that psilocybin markedly increased cerebral glucose metabolism in PFC regions (a phenomenon termed 'hyperfrontality') and, to a lesser extent, in adjacent cortical regions[72,73]. After normalizing to the global metabolic rate of glucose, a pattern emerged of hypermetabolism in prefrontal and tempomedial areas and hypometabolism in subcortical and occipital brain regions[74]. Similar hyperfrontality effects were shown after oral administration of DMT or mescaline

◀ Fig. 1 | **Effects of psychedelic drugs on cortico-cortical and cortico-thalamic circuits.** The known effects of psychedelic drugs on the neurons comprising the central brain networks responsible for bottom-up sensory input via the thalamus to the cortex and top-down cortico-striato-thalamic, cortico-thalamic and/or cortico-cortical control of information processing. The schematic is based on data mostly obtained from studies of lysergic acid diethylamide (LSD) and 2,5-dimethoxy-4-iodoamphetamine (DOI) in animals, as well as some studies of the actions of LSD and psilocybin in humans. LSD increases extracellular glutamate levels in the prefrontal cortex via stimulation of postsynaptic 5-hydroxytryptamine (serotonin) type 2A (5-$HT_{2A}$) receptors on deep layer 5 pyramidal (L5p) neurons[39,163] (stage 1) and on the L6p neurons (stage 2) projecting to L5p neurons as well as via activation of presynaptic 5-$HT_{2A}$ receptors (stage 3) on specific and non-specific thalamocortical afferents[41,43,61,164–166]. Psychedelics such as LSD can also stimulate 5-$HT_{1A}$ receptors located on the hillock of L5p or L6p neurons (stage 4) and on cortical GABAergic interneurons (stage 5), resulting in both inhibition and disinhibition of prefrontal pyramidal cell activity[34,39,167]. In addition, LSD and DOI are potent partial agonists at cortical (stage 6) and presumably also subcortical (striatal or palladial) (stage 7) 5-$HT_{2A}$ receptors in GABAergic interneurons[168]. Despite these partially inhibitory mechanisms, the LSD or DOI-induced increase in glutamate release produces a marked net excitatory effect on L5p neurons[34,39,164,169] and promotes synaptic plasticity via AMPA and NMDA receptor-dependent mechanisms[41,43,61]. L5p neurons influence both cortical and thalamic processing and play a central role in coupling cortico-cortical (stage 8) and thalamo-cortical (stage 9) loops of information streams with each other[51], providing a mechanism through which it is thought the state and content of consciousness may be coupled[42]. It has therefore been suggested that psychedelics affect this extended thalamo-cortical broadcasting system, and thus consciousness as a whole, by simultaneously producing sensory 'flooding' due to reduced thalamic gating of interoceptive and enteroceptive inputs and by altering the meaning of percepts due to disrupted cortical–cortical interactions[170,171]. In this model, thalamic gating is thought to be under the control of glutamatergic cortico-striatal and cortico-thalamic pathways projecting to the thalamus in addition to being under the modulatory influence of serotonergic projections from the raphe to several components of the cortico-striato-thalamo-cortical loops[51]. mGluR, metabotropic glutamate receptor; NSN, non-specific thalamic nuclei; SN, specific thalamic nuclei.

in studies that measured cerebral blood flow (CBF) via single-photon emission tomography[75,76]. More recently, two studies investigated CBF after the administration of psilocybin and LSD using arterial spin labelling[77–79], revealing increases in CBF in the visual cortex under LSD[79] and brain-wide decreases in CBF after psilocybin administration[78]. The latter result was corroborated in a third study that used two different doses of psilocybin[77]. However, after additionally controlling for unspecific global effects (see BOX 2), a divergent pattern with increases in CBF in frontal regions and decreases in subcortical and occipital regions was evident[77]. These results support the hypothesis that reduced thalamic gating leads to overactivity of prefrontal brain regions.

It is important to note that alterations in thalamo-cortical connectivity may not be a specific signature of the psychedelic state, as changes in the functional organization of these loops have also been reported in psychotic disorders such as schizophrenia[80]. However, they may represent an important component of the response to these compounds that, together with changes in the functional architecture of the cortex (discussed below), gives rise to psychedelic experiences. Whether the characteristic features of psychedelic states (such as ego dissolution) are due to a disruption of more specific thalamo-cortical projections and cortico-cortical interactions needs to be further investigated. Animal studies were able to show selective modulation of thalamic gating by attention during wakefulness[81]. The use of such animal models may therefore represent a promising scientific approach to shed further light on the role of thalamic gating in psychedelic states.

***Evidence for alterations in network integration.*** In recent years, various neuroimaging studies have investigated the impact of psychedelics on the network dynamics of the human brain[31,78,79,82–86]. Most studies used functional connectivity approaches to investigate changes in between-network and within-network connectivity.

Using functional global brain connectivity, a data-driven approach that measures the connectivity between each voxel and the rest of the brain, a concurrent increase in the integration of sensory and somato-motor brain networks and disintegration of networks of associative brain regions was reported after LSD[31] and psilocybin[87] administration. The pattern of brain regions affected by these functional connectivity changes correlated with those expressing the *HTR2A* gene in maps derived from the Allen Human Brain Atlas DNA microarrays[31] (which are highly consistent with positron emission tomography imaging data for the 5-$HT_{2A}$ receptor[88]), pinpointing the crucial role of this receptor also in systems-level changes induced by psychedelics. These results are in line with a recent study showing decreased expression (that is, a decreased probability of the occurrence of a recurrent phase-locking pattern in the blood oxygen level-dependent signal over time) of the frontoparietal control network, which overlaps with associative brain regions mentioned above, together with an increased occurrence of a globally coherent brain state under the influence of psilocybin[89]. Thus, it is conceivable that increased processing of sensory information that is not counterbalanced by associative network integrity may underlie or contribute to the multifaceted phenomenology of psychedelic states. FIGURE 2 presents an integration of these results with the reported changes in thalamic gating discussed above. However, it is important to note that FIG. 2 is not a comprehensive summary of all neuroimaging results obtained under the influence of psychedelics but, rather, represents a working hypothesis of the mechanisms that potentially underlie the psychedelic state and that should be tested in future studies. Two additional studies have investigated global brain connectivity after the administration of LSD and reported evidence for increased thalamic functional connectivity. However, with the exception of this finding, these studies — which, unlike the studies mentioned above, did not use global signal regression (GSR)[70,90] — did not show overlapping results[91]. For a detailed discussion of psychedelic-induced global effects on neuroimaging data and the advantages and disadvantages of GSR, see BOX 2.

In addition to these changes, several studies have demonstrated alterations in functional connectivity between nodes of different intrinsic brain networks after the administration of psychedelics; however, the results reported have often been inconsistent[91]. Resting-state fMRI studies in regular waking states have identified two orthogonal (anticorrelated) networks: the default mode network (DMN) and the task positive network[92]. This anti-correlation is suggested to support

Arterial spin labelling
An imaging method used to quantify cerebral blood perfusion by magnetic labelling of arterial blood.

Blood oxygen level-dependent signal
A signal detected in functional MRI and used to investigate regional brain activity changes.

Intrinsic brain networks
Brain networks determined by their spatially independent and temporally correlated functional connectivity.

Default mode network
(DMN). A brain network consisting of various large regions, such as the posterior cingulate cortex, precuneus, medial prefrontal cortex and angular gyrus.

Box 2 | **Psychedelic-induced global effects on neuroimaging data**

Across different imaging modalities, such as positron emission tomography, arterial spin labelling (ASL) and functional MRI, psychedelics have repeatedly been shown to induce unspecific global effects on resting-state data[15,31,72,77,86,87,89]. The global signal in functional MRI data is thought to represent a complex mixture of non-neural artefacts, such as head motion, cardiac and respiratory changes, changes in blood pressure and vasomotion[174], and additionally includes fluctuations in neuronal activity[175]. One approach to control for these unspecific effects is the use of global signal regression (GSR), in which the mean is computed across grey matter voxels and regressed from each voxel's time course. However, the utilization of GSR is still a matter of debate with advantages and disadvantages[175]. Not removing the global signal and related artefacts can induce spuriously high correlations across brain regions[175,176]. On the other hand, GSR may also remove interesting neuronal effects and has been reported to induce anti-correlations in modelling studies[175]. A detailed description of the advantages and disadvantages of GSR is presented in REF.[175]. The current consensus is that neuroimaging analyses should be repeated with and without GSR, to provide complementary insights into changes in the brain's functional architecture[175].

Although GSR has been shown to have negligible to small effects on the results obtained with certain analytic approaches, such as dynamic causal modelling[177], two studies have reported that the use or non-use of GSR has an impact on functional global brain connectivity measures obtained after the administration of psychedelics[31,87]. Global brain connectivity has been shown to produce replicable results in two different samples in which GSR was used[31,87], whereas the pattern of results across studies without GSR has been inconsistent to date[31,70,87,90]. To further improve the consistency of results, future studies should therefore pay attention to this preprocessing step and report results with and without GSR.

With regard to ASL data, global signal fluctuations have similarly been associated with temporal magnetic resonance signal variations, thermal noise or physiological variations[178]. These signals can vary across different scan sessions or subjects and are therefore insufficiently removed with regular filtering procedures. Using repeated ASL scans, it has been shown that controlling for the global signal resulted in better cerebral blood flow quantifications with a higher temporal signal to noise ratio, better test–retest stability and better cerebral blood flow map quality[178]. Controlling for the global signal is a routine procedure in ASL studies, and for most pharmacological ASL studies it is common practice to report analyses both with and without the global covariate[179,180]. Psilocybin has been shown to induce global changes in the ASL signal. Complementary to those results, additional insights have been reported after these changes have been controlled for[77]. This provides further support for the suggestion that future studies assessing the effect of psychedelics on cerebral blood flow continue to report results with and without controlling for global signal changes.

Selective serotonin reuptake inhibitors
A class of drugs increasing the level of serotonin by inhibiting the reuptake into the presynaptic cell, used to treat depression and anxiety disorders.

Predictive processing
A framework that views the brain as an organ of inference that is constantly generating and updating a mental model of the environment.

Entropy
A measure of uncertainty about a dynamical phenomenon (in this context, neuronal fluctuations across time).

Magnetoencephalography
An imaging technique used to map brain activity by recording magnetic fields produced by electrical currents in the brain.

the transition between internally directed thoughts and the external environment[92]. Although psilocybin decreased DMN–task positive network orthogonality[84], this result was not replicated after administration of the DMT-containing drink ayahuasca, regardless of preprocessing with or without GSR[86]. More widespread changes in between-network connectivity have also been reported after psilocybin[85] and LSD[79,83] administration; however, again, results have not yet revealed a congruent pattern[91]. The lack of consistency may be because most of the results are based on relatively small sample sizes (<20 participants), a potential limitation calling for larger studies and comparable methodological approaches[93–95].

The most consistent finding in all of the various studies that have investigated functional connectivity within the nodes of intrinsic brain networks has been reduced functional connectivity in or between structures of the DMN[31,78,79,83,86,96]. However, similar decreases in functional connectivity between the nodes of the DMN have been reported after the administration of selective serotonin reuptake inhibitors[97] and may therefore represent unspecific serotonergic effects[91]. The specific contribution of decreased DMN integrity to psychedelic effects should therefore be investigated in future studies.

***Evidence for altered entropy.*** The neuromodulatory effects of 5-$HT_{2A}$ receptors and their effects on synaptic efficacy can also be observed as changes in fast electrophysiological dynamics that result from specific alterations in neuronal excitability or postsynaptic gain in cortical microcircuits. Functionally, these changes can be expected to influence the precision of neuronal message transfer, especially in the context of predictive processing or hierarchical Bayesian formulations of perception[98]. In line with this, increased entropy has been suggested to be a neural signature of psychedelics. This has been formulated as the "entropic brain hypothesis"[99,100] and has recently been integrated together with the "free-energy principle" to produce the "relaxed beliefs under psychedelics (REBUS) and the anarchic brain" model[64]. In brief, this model states that psychedelics reduce the precision of high-level priors (expectations or beliefs about the world) and concurrently increase bottom-up information flow. This renders recurrent message transfer more sensitive to modulation by ascending afferents, thereby increasing the entropy and complexity of accompanying neuronal dynamics[64]. Empirical evidence that psychedelics such as LSD, psilocybin and DMT (but also the dissociative drug ketamine) increase the Lempel–Ziv complexity (a measure of signal diversity that quantifies the number of distinct patterns present in the data and an approximation to entropy) of magnetoencephalography and electroencephalography signals has been reported[101,102]. In an fMRI study, increased sample entropy (a measure indicating the complexity of a signal by representing the predictability of the signal over time) was also observed in sensory and some higher-order networks after the administration of LSD[103]. Furthermore, an increased repertoire of different brain states (rapid changes in brain dynamics and functional connectivity) was reported after psilocybin and LSD administration in the same set of healthy individuals[104,105]. Increased Shannon entropy, broadly defined as the amount of information in a variable, was also reported in seven participants after the ingestion of ayahuasca[106].

As noted above, the REBUS model hypothesizes that psychedelic-induced increased entropy reflects a relaxation of the precision weighting of priors, leading to decreased top-down and increased bottom-up information flow. Corroborating this model, reduced electrophysiological responses to the presentation of surprising stimuli have been found under the influence of LSD[107], as well as reduced top-down and increased bottom-up connectivity between different brain areas such as the thalamus and the PCC as described above[71]. However, other studies have not observed reductions in surprise responses[108,109]. This model therefore needs further testing to establish its specificity and generalizability. Future research should consider leveraging the advantages of technologies allowing the co-registration of electroencephalography recordings and transcranial magnetic stimulation to gain further causal insight into psychedelic-induced changes in connectivity and complexity.

Electroencephalography
An electrophysiological imaging method that records the electrical activity of the brain using electrodes placed on the scalp.

## Functional alterations

Numerous recent studies have investigated the impact of psychedelics on specific cognitive and emotional functions. Most studies were conducted while participants were engaged in specific tasks and under the acute influence of the substance. These studies have revealed psychedelic-induced alterations in emotional processing, self-processing and social processing that may have relevance for psychedelic-assisted therapy (summarized in FIG. 3) as well as perceptual changes and alterations in symbolic imagery.

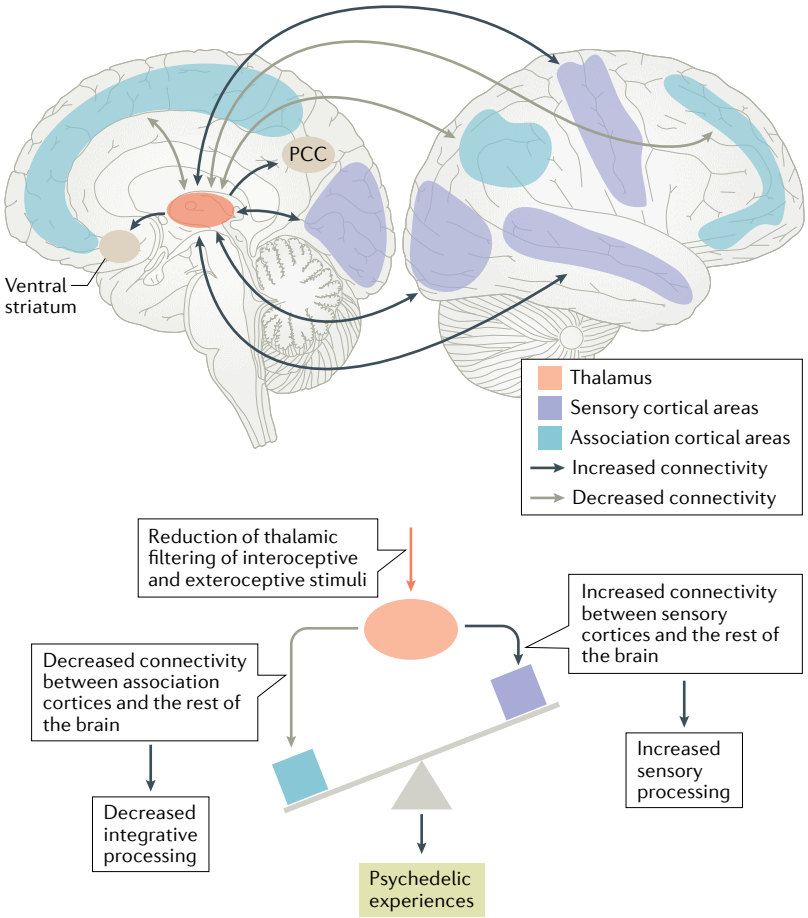



Fig. 2 | **A working hypothesis of psychedelic-induced changes in brain connectivity.** One model for the mechanism of action of psychedelics suggests that they exert their effects via the cortico-striato-thalamo-cortical loops that control thalamic gating of internal and external sensory and cognitive information to the cortex[51]. Consistent with this idea, it has been shown that these psychedelics disrupt pre-attentive sensorimotor gating in humans[66–69,84]. Furthermore, evidence from some human neuroimaging studies shows that psychedelics increase functional connectivity between the thalamus and sensory cortical regions[31,70] and decrease thalamic functional connectivity with association areas[31]. Lysergic acid diethylamide (LSD) has also been shown to increase effective connectivity from the thalamus to the posterior cingulate cortex (PCC) and the ventral striatum[71]. These findings support a reduction of thalamic filtering of interoceptive and exteroceptive information and increased information flow to particular areas of the cortex, and are also compatible with the hypothesis of sensory bottom-up overflow and relaxed priors as described in the REBUS model[64]. At the same time, increased synchronization of sensory cortical regions[31,87,154] and decreased integration of association regions has repeatedly been reported[31,78,79,83,86,87,89,96]. Therefore, as illustrated in the schematic, a reduction of thalamic filtering may lead to an increase in sensory processing that is not counterbalanced by integrative processing in association cortices. This dysbalance may be experienced as psychedelic symptoms[31,87,153]. This figure is not a comprehensive summary of neuroimaging results obtained under the influence of psychedelics (see main text for more details) but, rather, represents a working hypothesis of potential mechanisms underlying the psychedelic state that needs to be tested in future studies.

***Altered emotional processing.*** During the 1950s and 1960s, psychedelics were used as adjuncts to psychotherapy to facilitate the release of emotion and ease emotionally loaded memory blocks[110]. More recent studies in healthy volunteers as well as patients with different psychiatric disorders have confirmed that psilocybin and LSD increase both positive and negative mood, emotional excitation and sensitivity, and can lead to emotional breakthroughs (that is, the overcoming of challenging emotions or memories and thereby the experience of emotional release) in a supportive clinical setting[11,68,111,112]. Furthermore, psilocybin has been shown to augment subjective and neural responses to positive autobiographical memory cues in healthy participants[113].

Investigating the processing of emotions, various studies have shown that psychedelics can reduce the response to negative emotional stimuli in a controlled research setting. For example, LSD and psilocybin dose-dependently decreased the recognition of negative facial expressions in healthy participants[114–116]. In line with this, psilocybin reduced the subjective discrimination between fearful and neutral faces and the encoding of fearful faces[117]. In another study, the reduced processing of fearful faces was associated with decreased activity within limbic brain areas, whereas there was a reduction of activity in response to happy faces within limbic and right temporo-occipital brain areas[118]. Furthermore, psilocybin and LSD induced reduced neural responses to negative stimuli in the amygdala[119,120], an effect that correlated with an increase in positive mood[120]. Connectivity analyses showed that psilocybin reduced top-down directed connectivity from the amygdala to the primary visual cortex during threat processing[121] and decreased functional connectivity between the amygdala and the striatum during angry face discrimination[122]. Additionally, changes in positive mood after a low dose (microdose) of LSD have been shown to correlate with increased resting-state functional connectivity between the amygdala and the frontal cortex[123]. It is possible that a global reduction in concentration could influence the results of these studies testing the effects of psychedelics on specific cognitive or emotional tasks. That being said, all of the studies mentioned above controlled carefully for differences in performance and none of them revealed global impairments[114,115,119,120]. We therefore believe it is unlikely that the reduced processing of negative stimuli under the influence of psychedelics can be attributed to decreased attentional or cognitive capacities.

A negative cognitive and emotional bias is a core symptom of major depression disorder[46]. Hence, the findings above make it conceivable that classic psychedelics enhance positive mood in individuals with major depression disorder by acting as a modulator of the major connectivity hubs of the amygdala, therefore acutely reducing the processing of negative emotions. This, in turn, may allow patients with depression to inspect emotionally loaded self-relevant thoughts

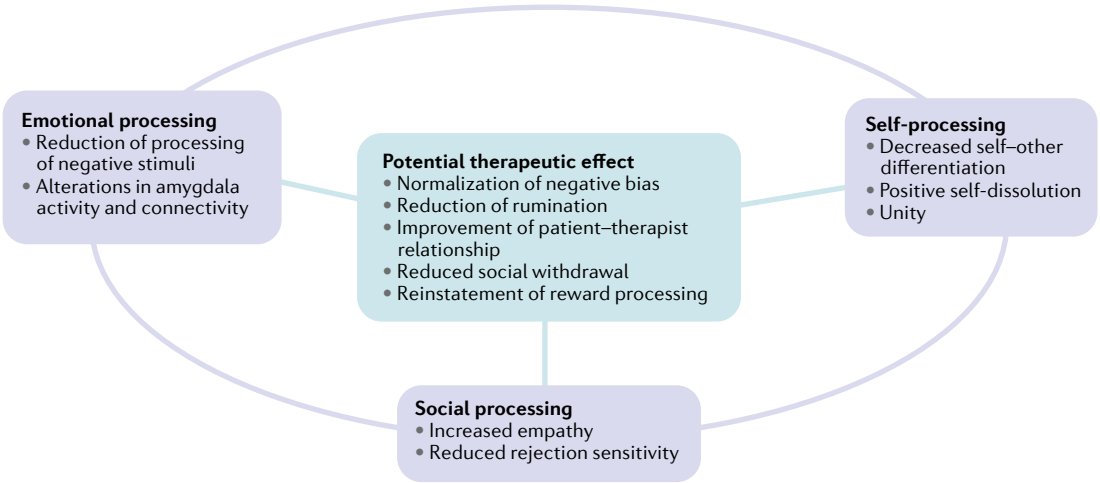



Fig. 3 | **Functional psychedelic-induced alterations that may underlie therapeutic effects.** Schematic shows changes in emotional processing, self-processing and social processing that have been measured acutely in controlled trials after the administration of psychedelics[11,12,20,120,138]. These acute effects may contribute to the potential therapeutic effects of these substances.

and memories from a less judgemental and decentred stance[4].

An important, yet scarcely addressed, question is whether psychedelics produce a sustained beneficial effect on emotional processing. In healthy participants, reduced amygdala reactivity in response to emotional stimuli has been reported 1 week after psilocybin administration, but returned to baseline 1 month after administration[124]. Similarly, negative affect was decreased 1 week after administration and returned to pre-administration levels after 1 month[124]. In individuals with treatment-resistant depression, emotion recognition showed continued improvement 1 month after treatment with psilocybin[125]. These results provide the first evidence that psychedelics may have a continued positive effect on emotion processing and mood that may normalize the negative bias observed in major depression. In contrast to these acute and sustained effects of psychedelics, one study reported increased amygdala reactivity in response to fearful faces in individuals with depression the morning after psilocybin administration[126]. The same group showed a reduction in amygdala–PFC connectivity[127]. One potential explanation for these findings is that acute, psilocybin-induced, facilitated processing of negative experiences may lead to increased reactivity and emotional processing post acutely. It is important to note that the increased amygdala reactivity in individuals with depression was measured prior to psychological integration work[126]. This may indicate that a therapeutic integration of the experience is necessary to achieve long-term reductions in the processing of negative emotions. Thus, the long-term effects of psilocybin on amygdala reactivity, their clinical relevance and the impact of post-acute psychotherapeutic interventions need to be determined in future studies. Additionally, further studies are warranted to evaluate whether specific emotion processing tasks may be useful to predict clinical efficacy of psychedelics in patients with different psychiatric disorders.

***Altered self-processing.*** Psychedelics can have a profound impact on various aspects of the experienced sense of self[128]. This is often described as a loosening of self-boundaries, oneness, unity or ego dissolution under the acute influence of the substance[111]. Experimentally, several studies have aimed at capturing these phenomena. During a social interaction task in human volunteers, LSD was found to reduce the differentiation between self and others via decreased differential activation in the cortical midline structures[12], which have repeatedly been shown to be involved in generating a model of the self[129]. Additionally, in another study, the administration of LSD led to increased perception of self-relevance as well as of meaningfulness of external stimuli[11].

By correlating psychometrically assessed subjective alterations in self-experience with brain imaging data, recent studies have attempted to identify the neural correlates of ego dissolution. So far, different results have been obtained with different methods. LSD-induced alterations in self-processing were correlated with altered global brain connectivity in the somato-motor network[31], as well as in the angular gyrus and the insula in a different study[90]. In a separate study that used the same data set as REF.[90], LSD-induced subjective ego dissolution correlated with decreased seed-based functional connectivity between the parahippocampus and retrosplenial cortex and within the DMN assessed with fMRI[79] and with decreased delta and alpha power assessed with magnetoencephalography[79] (potentially associated with increased excitability of brain networks[130]). In another study, psilocybin-induced self-reported ego disintegration correlated with decreased alpha power in the PCC[96] and — in the same participants — with decreased functional connectivity between the medial temporal lobe and high-level cortical regions, a 'disintegration' of the salience network and reduced interhemispheric communication[131]. These disparate findings suggest that a single neural correlate of ego dissolution may not exist. However, the various aspects of altered

Box 3 | **Psychedelics in the treatment of psychiatric disorders**

Since 2010, clinical research that examines the effects of psilocybin, lysergic acid diethylamide (LSD) and the plant-derived ayahuasca beverage (containing the psychedelic *N*,*N*-dimethyltryptamine (DMT) and the monoamine oxidase inhibitor harmaline) in the treatment of mood disorders and addiction has resurged[181]. Recent psychedelic-assisted therapy studies include three steps: a few intensive preparation sessions; one or two supervised drug sessions in which a medium or high dose of a psychedelic is administered in a supportive environment; and several post-drug integration sessions for the psychedelic experience. Based on the idea that psychedelics may facilitate the psychotherapeutic process, some clinicians combine this basic approach with evidence-based psychotherapy.

Two open-label trials using this approach showed that psilocybin, in conjunction with motivational enhancement therapy or cognitive behavioural therapy, reduced alcohol consumption in individuals suffering from addiction for up to 53 weeks and nicotine abuse for up to 6 months, outcomes that were linked to the intensity of the mystical-type experiences that the subjects reported[135,182]. Two additional open-label studies showed that a single dose of ayahuasca in individuals with recurrent major depression produced significant reductions in depressive symptoms, with a rapid onset and effects lasting up to the 3-week end point[183,184]. Neuroimaging revealed acute increases in cerebral blood flow in the left nucleus accumbens, right insula and left subgenual area, which might be relevant for the change in mood, after ayahuasca intake[184]. In another open-label trial, individuals with treatment-resistant major depression received two doses of psilocybin at a weekly interval with psychological support[185]. Significant improvements in self-rated depressive symptoms were observed up to 6 months, with a maximum at 5 weeks[186]. The reduction of depressive symptoms at 5 weeks was predicted by high scores of acutely experienced pleasurable self-dissolution and by low scores for dread of ego dissolution[137], supporting the hypothesis that the quality of the psychedelic experience is key for the positive long-term outcome[4]. The improvement at week 5 also correlated with the sum score for feelings of unity, bliss and spirituality. One day after psilocybin treatment, neuroimaging revealed that decreased amygdala cerebral blood flow and decreased parahippocampal–medial prefrontal cortex functional connectivity, as well as increased prefrontal cortex–bilateral inferior lateral parietal cortex resting-state functional connectivity, correlated with the reduction in depressive symptoms[187]. In contrast to previous studies reporting decreases in resting-state functional connectivity within the default mode network with psilocybin, LSD and DMT administration in healthy subjects[31,78,79,83,86,96], psilocybin increased default mode network resting-state functional connectivity in the patients 1 day post treatment[187]. This finding is somewhat surprising, given that increased resting-state functional connectivity within the default mode network has been repeatedly reported in depression, and associated with rumination[188]. Thus, longitudinal placebo-controlled studies are warranted to further elucidate the temporal dynamics of these changes in functional connectivity and their relation to depressive symptoms.

Five double-blind, placebo-controlled studies have also been conducted to investigate the effects of psychedelics in the treatment of depressive symptoms and/or anxiety[134,136,189–191]. Three of these studies used psilocybin and reported significant reductions in depression and anxiety in patients with advanced cancer[134,136,189]. The symptom improvement was correlated with the extent of the acute mystical-type experience reported by the patients[134,136]. Likewise, in another double-blind trial, two doses of LSD or placebo-like doses of LSD (20 μg) were given to patients with life-threatening diseases and anxiety. In combination with psychotherapy, this treatment was found to reduce state anxiety at 2-month follow up, enduring to the 12-month follow up[191,192]. In another double-blind study, a single dose of ayahuasca was reported to reduce depressive symptoms in treatment-resistant major depressive disorder[190].

self-experience — in particular, pleasurable versus anxious ego dissolution — have not been clearly distinguished in current studies. A more distinct definition and operationalization of altered self-experiences is needed to be able to conclusively identify their specific neural correlates.

In addition to the advantages of gaining an integral understanding of the neural basis of the self, these studies are important because alterations in self-processing are considered to be central to the efficacy of psychedelic-assisted therapy[4,128,132]. So far, positively experienced self-dissolution associated with feelings of oneness (often referred to as mystical-type experiences) has been shown to be positively correlated with treatment success in addiction, depression and anxiety in palliative care[133–136] and in major depression[137]. It is also conceivable that ego dissolution and reduced self-focus lead to a 'decentring', that is, a state allowing a broader spectrum of thought patterns and emotions, which may be beneficial especially in individuals with depression who suffer from ruminative thinking. Furthermore, alterations in self-processing have been linked to changes in social cognition — in particular, increased empathy and reduced rejection sensitivity[12,20,138]. Alterations in self-processing may therefore promote changes in social cognition that have been reported to be critical to therapeutic efficacy (see below).

***Altered social processing.*** LSD and psilocybin have been shown to acutely modulate social processing in healthy participants[12,20,114,138]. This is of particular interest given the impact of impaired social cognition in psychiatric disorders and the insufficiency of currently available medication to treat these deficits[139,140]. Most importantly for therapeutic application, both LSD and psilocybin increase emotional empathy (that is, the capacity to feel 'with' other people), although they have no effect on cognitive empathy (that is, the ability to take another person's perspective and the understanding of another person's mental state)[114,138]. Furthermore, psilocybin has been shown to reduce the feeling of social exclusion and social rejection processing in the anterior cingulate cortex[20]. These effects may reduce social withdrawal behaviour and improve the patient–therapist relationship during psychedelic-assisted treatment[4].

The long-term effects of psychedelics on social processing have currently scarcely been investigated. Self-reported increases in interpersonal closeness were described up to 14 months after one or two administrations of psilocybin[141–144]. Self-reported increases in positive and/or altruistic social effects were also reported 4 and 12 months after the administration of psilocybin and LSD in healthy participants[145,146]. Furthermore, self-reported increases in prosocial behaviour 4 months after psilocybin administration correlated with changes in medial PFC–PCC connectivity 2 days after psilocybin[146,147]. Emotional empathy has also been reported to be increased the morning after a psilocybin retreat and to endure up to 7 days for negative emotions[148].

In clinical studies with psilocybin (BOX 3), individuals with various psychiatric conditions identified social factors as contributing to their disease and reported improvements after psilocybin-assisted therapy. For example, participants in one study designed to promote smoking cessation reported psilocybin-induced feelings of love and of being reconnected with their environment and other people as important for quitting smoking[149]. In addition, they reported increased engagement in prosocial and altruistic activities after psilocybin administration[149]. This suggests that psilocybin-assisted therapy may reinstate social reward processing, helping people to overcome their addiction. In a study of individuals with depression, participants reported distressing

Alpha oscillations
Neural oscillations in the frequency range of 8–12 Hz that can be measured using electroencephalography or magnetoencephalography.

Synaesthesia
A perceptual phenomenon in which stimulation of one sensory modality leads to experiences in a second sensory modality.

Pharmacological challenge studies
Studies involving the administration of a pharmacological substance.

feelings of being disconnected before psilocybin-assisted therapy[150]. After psilocybin treatment, they felt reconnected with their social environment and identified this increased connection as one of the main changes induced by the treatment[150]. Taken together, these findings suggest that the beneficial impact of psychedelics on social cognition and behaviour may be an important mechanism contributing to clinical efficacy.

***Altered sensory processing.*** Perceptual changes are the most frequent and robust features of the psychedelic experience. Psychedelics, also called hallucinogens, have been claimed to produce a dream-like state characterized by alterations in visual processing, but have also been shown to impact auditory and tactile perception to a lesser degree[111]. At moderate doses, alterations in visual percepts rarely represent true hallucinations but, rather, illusions or pseudo-hallucinations that can be distinguished from real perceptions. A psilocybin, LSD and DMT-induced decrease in alpha oscillations — in particular, over posterior parieto-occipital brain areas – suggests that psychedelics increase the excitability of the visual pathway[21,102,130,151,152]. The amplification of internal-driven excitation may therefore underlie the visual alterations experienced in the absence of external input[153]. This is also in line with resting-state neuroimaging results obtained after LSD administration showing that connectivity within the visual cortex reflects the intrinsic retinotopic architecture, suggesting that activity within the visual cortex becomes more dependent on its intrinsic organization[154]. Furthermore, increased resting-state connectivity between the thalamus and the fusiform gyrus was shown to correlate with visual alterations under LSD administration[70]. During mental imagery, the blood oxygen level-dependent signal amplitude in the primary visual cortex after ayahuasca intake was reported to be comparable to natural image viewing[155]. In response to external stimuli, psilocybin increased the P1 component (the first positive component of an event-related potential observed around 100 ms after stimulus presentation and thought to reflect early visual information processing) in visual area V1 and concurrently decreased the visual N170 evoked potential (a negative event-related potential occurring 130–200 ms after visual stimulus presentation and thought to reflect altered global integration) in the lateral occipital complex[156]. This suggests that a dysbalance between perception and integration may explain psilocybin-induced illusions and hallucinations[153], and is in line with results obtained in resting-state connectivity studies described above (FIG. 2).

For other modalities, only slight perceptual changes have so far been recorded. A reduction in the N1 sensory evoked potential (the first negative component of an event-related potential observed around 150–200 ms after stimulus presentation) in an auditory paradigm was reported after psilocybin administration, suggesting reduced processing of the intensity of auditory stimuli[108]. Alterations in tactile perception are often associated with changes in self-experience and body experience[111]. Usually, alterations in these domains are experienced as synaesthesia, with mostly auditory stimuli being translated to the visual domain[157]. Under the influence of LSD, music-evoked visual imagery has been related to increased effective connectivity from the parahippocampal cortex to the visual cortex, suggesting that an increase in top-down information on early sensory regions may contribute to psychedelic-induced changes in perception[158].

The therapeutic relevance of alterations in sensory processing is currently not well understood. However, the content of psychedelic-induced mental imagery is often based on autobiographic memories[14] and the activation of related emotions[14,113]. Such subjective experiences of vivid imagery strongly resemble naturally occurring dreaming during the sleep–wake cycle and may have long-term beneficial effects on psychosocial functioning and well-being[14].

***Implications for health and disease.*** Pharmacological challenge studies with psychedelics not only elucidate their potential clinical effects but also offer the unique opportunity to investigate the role of the 5-HT receptor system in human perception, cognition and emotion[11], particularly when psychedelics are investigated in combination with specific 5-HT receptor antagonists. Psychedelics provide a significant advantage over other tools used to study the serotonin system, such as selective serotonin reuptake inhibitors or tryptophan depletion, which cannot reveal receptor-specific contributions.

The studies summarized above show that the 5-$HT_{2A}$ receptor system is critically implicated in emotional, social and self-processing. Blocking the 5-$HT_{2A}$ receptor with ketanserin before administering LSD showed that this receptor system is involved in the generation of self-relevance[11]. Whereas individuals with schizophrenia spectrum disorders often experience an increased attribution of relevance to their environment[159], those suffering from addiction or depression could benefit from changes in self-relevance attribution[160]. This suggests that treatment with 5-$HT_{2A}$ agonists may be effective in depression and addiction but not in schizophrenia spectrum disorders.

LSD also alters self-processing and social cognition[12]. These effects were also blocked with ketanserin, suggesting that aberrant 5-$HT_{2A}$ receptor-mediated signalling underlies these interdependent changes in self-perception and social processing. This association between self-perception and social perception suggests that individuals who suffer from incoherent self-experience and social withdrawal (as often encountered in schizophrenia) may benefit from treatment with 5-$HT_{2A}$ receptor antagonists. By contrast, 5-$HT_{2A}$ receptor agonists may be well suited to treat social deficits in individuals with increased self-focus, such as depression[161]. This is also in line with results suggesting that stimulating the 5-$HT_{2A}$ receptor results in a decreased processing of negative emotions[114–116], an effect that may be helpful in the treatment of depression[46]. Furthermore, it has been shown that this effect translates to a reduced processing of negative social interaction in the anterior cingulate cortex[20]. This was associated with decreased aspartate concentrations in the same brain area. The 5-$HT_{2A}$ receptor system and the aspartate system may therefore be implicated in

the pathophysiology and treatment of disorders characterized by increased rejection sensitivity, such as depression and borderline personality disorders[162]. In sum, these results implicate the 5-$HT_{2A}$ receptor system in various trans-diagnostic cognitive and emotional processes important for the treatment of depression, addiction and borderline personality disorder, and therefore provide rational targets for the development of novel medication.

## Conclusions

Scientific interest in the effects of psychedelics has risen sharply in the past decade. Preclinical and clinical studies leveraging modern neuroscientific methods have produced various novel results with significant implications for understanding the neuropharmacology of human cognition, emotion and self-regulation, discovering potential trans-diagnostic treatment mechanisms in psychiatry and the development of novel rapid-acting and long-lasting treatment approaches.

Pharmacological challenge studies investigating the acute effects of single doses of psychedelics in healthy human participants have revealed important insights into the role of the 5-$HT_{2A}$ receptor in human cognition, emotion and self-regulation. These studies have shown that this specific receptor system is implicated in modulating social functioning, mood regulation and coherent self-representations. Importantly, these studies have also revealed the importance of targeting and studying specific sub-receptor systems to be able to conclusively understand human psychopharmacology and eventually be able to inform the development of new pharmacological therapeutics.

Recent neuroimaging studies have furthermore started to increase our understanding of the ways in which psychedelics temporarily change the functional architecture of the brain. Although different analytical approaches often limit the comparability between studies (see BOX 2), some congruent patterns have started to emerge. Changes in functional and directed connectivity between the thalamus and cortical areas have been reported across different analysis techniques[31,70,71]. In addition, increased synchrony of sensory brain regions and decreased integrity of associative brain regions (including the DMN and the frontoparietal control network) have been reported after the administration of LSD, psilocybin and DMT[31,78,79,83,86,87,89,96,153]. However, it has to be noted that some of these effects are sensitive to GSR as outlined in BOX 2. Increases in various measures of entropy and signal complexity have also been reported after the administration of LSD, psilocybin and DMT[101,102,104–106]. Other analytical approaches, such as the investigation of between-network connectivity during the resting state, have so far revealed inconsistent results or still need replication. These results support hypotheses that are not mutually exclusive but, rather, reflect different aspects of changes in neuronal dynamics. It is conceivable that future studies will reveal a more detailed (in terms of both spatial and temporal resolution) pattern of psychedelic-induced changes in brain connectivity that will allow one to better associate these neuronal effects with specific psychedelic-induced subjective experiences.

Studies of the effects of psychedelics in healthy participants have shown that these substances modulate a person's self-focus, reduce negative emotional processing and strengthen social functioning[12,120,138]. Patients across different disorders who underwent treatment with psychedelics identified these effects as contributing to treatment success[149,150]. These experiences may therefore represent trans-diagnostic mechanisms for the treatment of psychiatric illnesses within and beyond the framework of psychedelic-assisted therapy. Additionally, preclinical results point to the potential of induced neuroplasticity as a promising neuronal mechanism that could be leveraged in psychotherapy[54].

Lastly, studies in patient populations show that psychedelics may constitute promising therapeutic agents that represent a novel treatment model in psychiatry: they have been shown to act rapidly and to have long-lasting effects after only a few doses. This is in stark contrast to the current treatment approaches in psychiatry, which usually consist of a regular intake of psychotropic medication. However, many open questions remain. The exact mechanisms underlying the therapeutic effects are still not well understood and beneficial clinical results need to be replicated in larger trials. It is unclear whether the therapeutic effects of these substances are due to their direct effects on brain activity and connectivity or due to the cognitive and psychological experience of an altered state of consciousness. In other words, it is unclear whether the conscious experience of the psychedelic-induced subjective effects is necessary for therapeutic efficacy. Furthermore, the field still needs to uncover individual predictors or biomarkers of treatment efficacy. The impact of different approaches to accompanying psychotherapy will also require empirical investigation. Accompanying psychotherapy may turn out to be of critical importance, if the proposed neuroplastic effects of psychedelics indeed contribute to their clinical efficacy. Using psychedelics in a clinical setting can therefore be understood as pharmacologically assisted psychotherapy that leverages the molecular, systems-level and functional alterations induced by psychedelic substances.

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