Classic Psychedelic Drugs: Update on Biological Mechanisms

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ABSTRACT

Renewed interest in the effects of psychedelics in the treatment of psychiatric disorders warrants a better understanding of the neurobiological mechanisms underlying the effects of these substances. During the past two decades, state-of-the-art studies of animals and humans have yielded new important insights into the molecular, cellular, and systems-level actions of psychedelic drugs. These efforts have revealed that psychedelics affect primarily serotonergic receptor subtypes located in cortico-thalamic and cortico-cortical feedback circuits of information processing. Psychedelic drugs modulate excitatory-inhibitory balance in these circuits and can participate in neuroplasticity within brain structures critical for the integration of information relevant to sensation, cognition, emotions, and the narrative of self. Neuroimaging studies showed that characteristic dimensions of the psychedelic experience obtained through subjective questionnaires as well as alterations in self-referential processing and emotion regulation obtained through neuropsychological tasks are associated with distinct changes in brain activity and connectivity patterns at multiple-system levels. These recent results suggest that changes in self-experience, emotional processing, and social cognition may contribute to the potential therapeutic effects of psychedelics.

Introduction

Classic psychedelics, or serotonergic hallucinogens, comprise three main chemical classes: the *indoleamines* such as N,N-Dimethyltryptamine (DMT) contained in plants [1], psilocybin and its active metabolite psilocin contained in several mushroom species [2], the phenylalkylamines such as mescaline contained in several cacti [3], and synthetic "amphetamines" such as 2,5-Dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-bromoamphetamine, and the semisynthetic ergolines such as lysergic acid diethylamide(LSD) [4]. They produce profound alterations in perception, cognition, emotion, and self-consciousness [5–8]. Given these intense mind-altering properties, naturally-occurring psychedelics have been used by humans for millennia for spiritual and medicinal purposes [3, 9].

During the 1950s and 1960s, the clinical potential of LSD and psilocybin was extensively investigated for the treatment of different psychiatric disorders including depression and alcohol use disorder. Although these early clinical studies had serious methodological flaws by current standards, systematic reviews suggest that repeated low doses of psychedelics in combination with psychotherapy (psycholytic or "mind loosening" model) or a few high doses with psychological support (psychedelic or "mind-manifesting" model) resulted in impressive improvement rates in the treatment of various forms of depression, anxiety, and alcohol dependence [10–12]. The association of psychedelics with the counterculture and concerns over misuse led to the placement of LSD and related drugs in a restrictive regulated drug category (Schedule I) in 1976 in the United States and most other countries. Hence, human research with psychedelics declined, leaving many questions about the mechanism of action and clinical efficacy of classic psychedelics unexplored [13].

However, in the early 1990s, human psychedelic research with psilocybin, mescaline, and DMT resumed in healthy volunteers by employing different new brain imaging techniques and concepts borrowed from cognitive neurosciences [14]. Since then, an increasing number of molecular and neurophysiological underpinnings of various psychological effects of psilocybin, LSD, and DMT have been identified in healthy volunteers that allow firmer inferences about the potential mechanisms of psychedelic drug action.

Recent behavioral and neuroimaging studies demonstrated that psychedelics produce their psychological effects primarily via agonist action at 5-HT2A receptors in the brain [15, 16], although modulatory downstream effects upon the gamma-aminobutyric acid (GABA)ergic [17], dopaminergic [18] and glutamatergic [17] systems also seem to be implicated [19]. Current psychological and cognitive studies of psychedelics drug effects in combination with functional human brain imaging in healthy volunteers suggest that psychedelics can profoundly change the sense of self, often experienced as a dissolution of the ordinary boundaries between the self and the world, enhance mood and shift emotion processing to the positive, and facilitate prosocial behavior [19, 20] which is accompanied by modulation of neural circuits that are implicated in mood and affective disorders [21–25]. Psychedelics have also been shown to increase glutamate-driven neuroplastic adaptations in animals [26] which may provide a novel mechanism for the lasting beneficial outcomes reported in non-clinical and clinical populations [27].

In this review, we first outline the phenomenology and key psychological dimensions of psychedelic-induced altered states of consciousness as measured by standardized psychometric scales and then review potential state and trait predictors of the acute responses to psychedelics. We have summarized the potential mechanism of action of classic psychedelic drugs at the molecular, cellular, and circuitry levels. Then, neural correlates of psychedelic-induced alterations of self-consciousness and emotion regulation have been reviewed and the relevance of these findings for the treatment of affective disorders has been discussed. A better understanding of the biological and neurocognitive mechanisms underlying the psychedelic experience and their long-term impact on the mind and brain shall help to develop more specific intervention strategies for improving well-being in health and disease.

Phenomenology and Predictors of Psychedelic States

Classic psychedelics produce multifaceted altered states of consciousness, characterized by profound changes in self-consciousness and interrelated psychological functions: altered perception, including visual illusion, (pseudo-)hallucinations, and synesthesia, alterations in mood and cognitive capacities, and transcendence of time and space [6].

The profound transient alteration in self-consciousness, experienced as a dissolution of the sense of self/ego and a breakdown of the boundaries between the self and the world, appears to be one of the core features of the psychedelic experiences (the term self and ego are used synonymously in these studies) [28, 29]. However, the phenomenon of ego-dissolution is neither an all or nothing affair nor does it occur on its own [30, 31]. The experience of ego-dissolution arises dose-dependently along a perception-hallucination continuum associated with increased sensory and emotional arousal, distinct changes in cognitive functions, the release of emotions, often with the recall of emotionally loaded autobiographic memories, and increased capacity for introspection [6]. Empirical research has repeatedly shown that in a supportive and controlled setting, medium to high doses of psychedelics (i. e., psilocybin < 25 mg, LSD < 200 µg) can trigger with relatively high incidence a pleasurable self-dissolution associated with bliss, feelings of oneness, and insightfulness [32–36]. Such unitive experiences can sporadically also occur during deep mediative states or spontaneously in religious exaltation and have been referred to as states of selflessness [37] or mystical-type experiences, respectively [38–40]. Although in this dose range the sense of being a self, or "I" distinct from the world, is diminished or briefly abolished, some remnant "self-observer" (self-awareness) remains preserved in most, if not all, psychedelic states [6]. In fact, memories of such experiences can apparently be formed and reported [41, 42]. However, at larger doses, the same dose of a given psychedelic (e. g., psilocybin 30 mg) might induce a pleasurable "mystical-type" experience, or under certain circumstances, a more psychologically challenging or psychotic-like response characterized by fear of losing control over thinking and one's autonomy, delusions of grandeur, impairment of reasoning, and anxiety or panic [42–44]. This clinical observation is underscored by a recent placebo-controlled dose-response study with psilocybin demonstrating that a 30 mg/70 kg psilocybin dosage compared to 20 mg/70 kg markedly increased the incidence for fear and paranoid thinking [33]. Likewise, when comparing dosages of LSD, the ratings for pleasurable "oceanic" self-dissolution increased with dosages of 25, 50, and 100 µg of LSD but plateaued at the highest dose of 200 µg, which also substantially increased the ratings for anxious ego-dissolution [36].

Although the intensity of the psychedelic experience depends most critically on the dosage [32, 33, 36, 45, 46], it is generally thought that several non-pharmacological factors categorized as the "set" (i. e., the individual's expectations, personality traits) and the "setting" (i. e., the therapeutic interventions, the physical and social environment) are important in shaping the quality of the acute psychedelics experience [32, 42, 47–50].

To date, however, only a few prospective studies including controlled conditions [47–49, 51–55] and a meta-analysis pooling data

from 23 controlled studies involving 409 psilocybin administrations to 261 healthy volunteers [32], have investigated the impact of non-pharmacological predictors of the acute response to psychedelics. In most of these studies, the well-validated Altered State of Consciousness Questionnaire (5D-ASC) was employed to measure the broad spectrum of the psychedelic experiences along the five core dimensions (factors): ''oceanic self-boundlessness''(OB), "dread of ego dissolution''(DED) ''visionary restructuralisation''(VIS), ''auditory alterations''(AA), and ''vigilance reductions'' (VR). The dimension OB assesses the blissfully experienced self-dissolution including feelings of oneness and insightfulness, while the dimension DED assesses the more distressing reaction associated with thought disorders, fear of losing control, and anxiety. The dimension VIS measures altered perception, changed meaning, and facilitated recall of memories and imagination. The dimensions OB, DED, and VIS can be further described along 11 second-order scales (11-ASC) [31, 56].

The OB-related blissful "mystical-type" experience can also be measured by the Mysticism Scale (M-Scale) [57] or by the Mystical Experience Questionnaire (MEQ30) [58]. Both scales yield a total score for mysticism comprising various subscale scores, such as a sense of unity, ego-loss, transcendence of space and time, ineffability, deeply-felt positive mood, feelings of sacredness, and noetic insight [57. Notably, both the M-scale and MEQ30 total scores correlate highly with the OB score of the 5D-ASC scale [48, 61] suggesting that these scales assess an overall similar experience.

The results of these studies suggest that scoring high on the personality traits including openness to experience [47, 48], trait absorption [32, 54], optimism towards life [47, 48], being well and relaxed the day(s) before and during drug intake [32, 47, 48], and using a mindful attention and emotion regulation strategy involving a non-judgmental orientation of acceptance towards all emotions and thoughts arising in the present moment predicted the magnitude of positive self-dissolution (OB) or mystical-type experience (M-total score) [48] (▶ **Fig. 1a**). Pre-experience with altered states [47, 48], older age [32, 47], and a pleasant environment and the application of music during drug intake were also found to contribute to a blissful experience of OB [32, 62] or beneficial outcomes [51, 53]. Finally, scoring high on cognitive-emotional re-appraisal capacity seems to buffer from distressing aspects of psychedelic experiences indexed as DED in mediation experts during a group retreat, which may arise with higher doses of psilocybin [48]. However, further research in mediation novices is needed to disentangle the interaction of mindfulness training and group setting. On the other hand, high neuroticism, younger age, and an impersonal laboratory setting predicted unpleasant and anxious reactions to psilocybin [32]. A high absorption capacity also predicted heightened visual perception [54], reduced stimulus-color consistency during synesthetic-like experiences [55], and together with esthetic sensibility VIS, included facilitated imagination and changed meaning [32, 47] (▶ **Fig. 1a**). Notably, absorption has also been identified as a predisposing trait for hallucinatory and mystical-type experiences [63] and linked to the binding potential (BP) of the 5-HT2A receptor [64], suggesting that the assessment of 5-HT2A BP may provide a predictor of the overall psychedelic drug effects [65, 66].

However, given the current experimental limitations (e. g., small sample sizes, homogenous samples) further studies yet need to replicate these findings by using well-power, placebo-controlled designs, and more diverse populations. The impact of other important potential predictors, such as the participant's expectations, the experimenter's mindset, the number and quality of preparation sessions, or the influence of the psychological interventions during drug intake, is not known and needs to be empirically investigated.

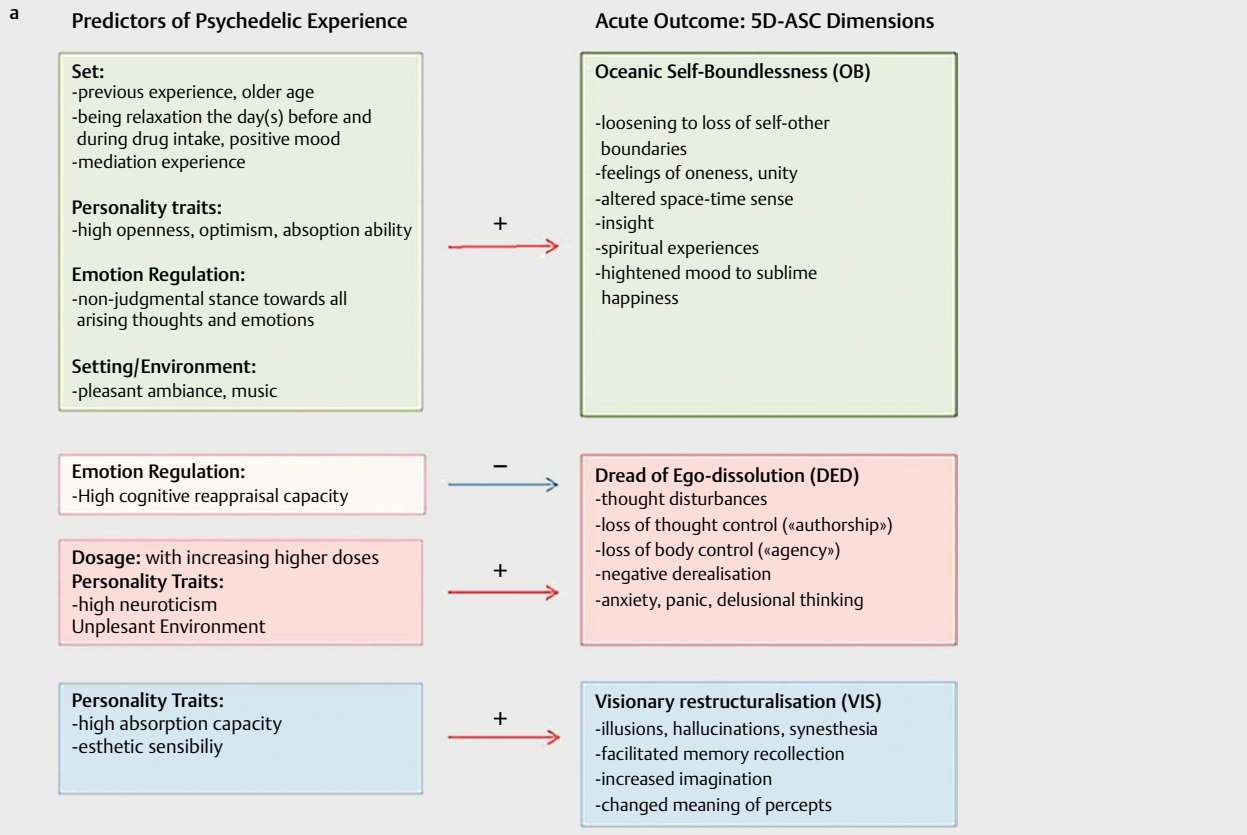
A better understanding of the influence of non-pharmacological variables seems not only to be crucial for the fine-tuning of the acute experience but also for producing enduring beneficial effects after drug intake [48]. A few recent studies have emphasized that the mystical-type experience (MEQ30, M-total or OB score) mediates the persisting positive changes in trait openness [67, 68], mood, well-being, attitudes, and psychosocial behaviors in healthy volunteers [48, 67, 69] as well as the enduring antidepressant effects in patients with major depression [70] and terminal cancer patients [71, 72] (▶ **Fig. 1b**). However, not every study found an increase in openness as a personality trait [73] or a correlation between the overall mystical experience and the enduring therapeutic effects in patients [74, 75]. A recent prospective study with psilocybin reported that the M-Scale subscale scores for 'unity' and 'sacredness' were the strongest predictors of the increases in "self-acceptance" and "appreciation for life" at a four-month follow-up in healthy meditation experts [48] (▶ **Fig. 1b**). Thus, the specific contribution of the different dimensions of the psychedelic experience, including the release and working-through of distressing emotions, to the long-term outcomes, remains to be systematically investigated [41, 70, 76–78].

Neurobiology of Psychedelics

Receptor activation and pharmacological effects of psychedelics

Classic psychedelics such as psilocybin, DMT, or LSD act as partial agonists upon 5-HT1, 5-HT2, 5-HT6, and 5-HT7 receptors [4]. LSD and other ergolines also act upon dopaminergic (D1, D2) and adrenergic receptors [4], while mescaline and DOI are selective agonists at 5-HT2A, 5-HT2B, and 5-HT2C sites [81]. Activation of 5-HT2A receptors located in cortical and subcortical structures seems to be a key mechanism in mediating many of the behavioral and psychological effects of psychedelics in animals [82] and humans [15, 16]. Blocking 5-HT2A/5-HT2C receptors with ketanserin abolished virtually all of the subjective effects of psilocybin, LSD, and DMT in humans [6, 15, 16, 83–87]. The intensity of psilocybin-induced subjective effects correlated with 5-HT2A receptor occupancy in the prefrontal cortex and other cortical regions [66, 88]. In addition, pre-treatment with the 5-HT1AR agonist buspirone significantly reduced the visual effects of psilocybin in healthy volunteers [89], while the 5-HT1AR antagonist pindolol significantly increased the psychological responses to DMT [90], suggesting a modulatory effect of the 5-HT1AR system on 5-HT2-mediated psychedelic effects. The 5-HT1AR has also been thought to contribute to the attention-disrupting effects of psilocybin in humans [91].

Psilocybin was also found to increase striatal dopamine concentrations, which correlate with euphoria and depersonalization phenomena in humans [18]. Blocking of D2 receptors with haloperidol partially diminished the psilocybin-induced positively experienced depersonalization but not the visual alterations and working mem-



▶**Fig. 1** Empirical described predictors of acute and long-term effects of Psychedelics. The Altered State of Consciousness Questionnaire (5D-ASC) [31,79] and the Mysticism Scale (M-Scale) [58,59] are usually administered shortly after the acute psychedelic experience. Red arrows = positive correlations; blue arrows = negative correlations: **a**: Scoring high on trait openness [47,48], absorption [32,54], and optimism about life [47,48], being relaxed the day(s) before drug intake intake [32,47,48], using a non-judgmental emotion regulation strategy [48], pre-experience with ASCs [47,48], older age [47], and a pleasant ambiance [32], supportive music [51,53,62], and meditation practice [49] were predictive for a positive psychedelic experience (e.g., "Oceanic Boundlessness") in healthy volunteers (HVs). High emotional re-appraisal capacity reduced the occurrence of distressing experiences (e.g., "Dread of ego-dissolution") [48]. On the other hand, high neuroticism, young age, and an impersonal laboratory setting predicted unpleasant and anxious reactions to psilocybin in healthy volunteers [32]. In addition, high absorption capacity and esthetic sensibility predicted changes in visual perception and altered meaning of percepts (VIS) [32,47]. **b**: Mysticism Total Score (M-Scale or MEQ30) predicted persisting increases in trait openness [67,68], mood, well-being, attitudes and psychosocial behaviors in healthy volunteers [48,67,69]. The M-Scale subdimensions "unity" and "sacredness" predicted persisting increases in self-acceptance and appreciation for life in healthy volunteers [48], while "ego dissolution" predicted lasting increases in openness and mood [80].

ory impairments, and even increased anxious derealization phenomena in healthy volunteers [15]. While psilocybin does not act directly on dopamine receptors, LSD shows high intrinsic activity at dopamine D2 receptors which may be responsible for the more psychotic-like effects in humans [4]. However, studies specifically blocking dopaminergic receptors after LSD administration are currently lacking. A recent animal study showed that high doses of LSD known to produce psychotic-like behavioral effects in rodents [92], but not low doses, modulated dopaminergic activity in the ventral tegmental area via activation of trace amine-associated receptors 1 (TAAR1) [93]. Hence, TAAR1 receptors may provide a novel target for the treatment of LSD-induced psychotic-like symptoms. In addition, hallucinogenic and non-hallucinogenic 5-HT2A receptor agonists such LSD and lisuride differentially activate intracellular signaling pathways in cortical neurons [94], and only hallucinogenic agonists such as LSD and DOI increased the expression of the early genes EGR1 and EGR-2 [95]. This functional selectivity remains to be further investigated and maybe a reference for the development of novel compounds with specific therapeutic properties.

Neuroplastic effects of psychedelics

Several preclinical studies have shown that LSD and DOI increase cortical glutamate levels and layer 5 pyramidal cell activity in the prefrontal cortex [96]. The increase in glutamate is due to recurrent network activity triggered by activation of postsynaptic 5-HT2A receptors located in deep layer 5 or 6 pyramidal neurons that project to layer 5 pyramidal neurons. This glutamate release subsequently activates postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors located in the apical dendrites in the same neurons which in turn is suggested to increase the gene expression of brain-derived neurotrophic factor (BDNF), a protein known to promote neuronal growth and neuroplasticity. DOI administration was found to increase BDNF expression in the prefrontal cortex and hippocampus in rodents [97]. In recent, DOI, LSD, psilocybin, and DMT produced both structural and functional neuronal plasticity in prefrontal cortical neurons in vitro and in vivo [98–102]. The increased synaptogenesis appears to be mediated through activation of 5-HT2A, tropomyocin receptor kinase B (TrkB), and mTOR signaling pathways [98], given that the spine remodeling in cortical layer V pyramidal neurons was abolished by antagonism of TrkB, BDNF's primary target, and activator or mTOR, or by blocking 5-HT2A receptors with ketanserin [98]. However, a recent study conducted in mice [102] showed that blocking of 5-HT2A receptors with a ketanserin dose (1 mg/kg), sufficient to completely abolish head twitch responses, did not block psilocybin-induced structural plasticity [102]. Another study similarly found that ketanserin (2 mg/kg) almost completely reduces the ability of psilocybin to induce head twitches but not its neuroplastic and antidepressant-like behavioral effects in mice [103]. The findings suggest that the spine remodeling and antidepressant-like effects of psychedelics in animals may not or only partially depend on 5-HT2A receptor activation but may also involve the activation of other serotonin receptors and signaling pathways [4]. However, given that different routes of administration and dosage were used in these two studies, further dose-response research may be necessary to clarify the role of the 5-HT2A receptor in these processes. Whether psychedelics exert their neuroplastic effects and potentially associated therapeutic consequences via 5-HT2A receptor agonism and/or polypharmacological action remains to be investigated.

To date, only a few studies have investigated the relevance of this psychedelic-induced increase of glutamate-driven AMPA receptor throughput and associated neuroplastic adaptations for the behavioral effects in animals and humans. In mice, low-dose psilocybin has been shown to facilitate the extinction of fear memory associated with a tendency to increase hippocampal neuroplasticity [104]. Similarly, DOI administration in mice led to fast-acting dendritic spine structural plasticity in prefrontal pyramidal neurons and acceleration of fear-extinction via the 5-HT2A receptor [100]. In another in vivo study, DOI produced a long-lasting depression of evoked AMPA excitatory postsynaptic currents in layer V pyramidal neurons in mice as an index of synaptic plasticity [105]. In a recent study on mice, repeated LSD administration (but not a single dose) selectively enhanced prosocial behavior without eliciting antidepressant effects by increasing medial prefrontal cortex (mPFC) excitatory neurotransmission through activation of 5-HT2A/AMPA receptors and mTOR signaling [106]. The inactivation of the mPFC excitatory neurons inhibited social interactions and nullified the social effects of LSD [106]. Using multiple measures of behavior, a recent study found that psilocybin produced fast antidepressant-like behaviors accompanied by strengthened synaptic transmission in the hippocampus of mice [103]. Intriguingly, neither the behavioral nor the electrophysiological responses were prevented by pretreatment with the 5-HT2A/C antagonist ketanserin, suggesting that the behavioral and synaptic effects of psilocybin are independent of 5-HT2A receptor activation, at least in these paradigms tested so far. The authors concluded that psilocybin may promote restoration of synaptic connectivity in cortico-mesolimbic circuits processing reward and emotions without involving 5-HT2AR-dependent psychedelic effects, which has to be confirmed in further studies. With regards to neuroplasticity effects in humans, one clinical trial of ayahuasca for depression found a correlation between BDNF plasma levels 48 hours post-treatment and symptom improvements [107]. However, in a recent study, 200 µg LSD significantly increased plasma BDNF levels 6 hours post-treatment, while there were only nonsignificant increases in plasma BDNF after 25, 50, and 100 µg LSD or after ketanserin with LSD treatment in healthy volunteers [36, 108]. A crucial limitation of such studies is that BNDF concentration cannot be directly assessed in the brain. Further studies including alternative approaches to brain plasticity are needed to investigate if and how the neuroplastic effects seen in animals relate to the long-lasting symptom improvements reported in recent clinical studies [27].

Functional Network Models of Psychedelic States

Recent human neuroimaging studies into psychedelic-induced changes in brain activity and connectivity patterns during resting state gave rise to various hypotheses regarding the neural underpinnings and widespread functional network disruptions underlying acute psychedelic states. Empirical evidence supports changes in thalamic gating, signal diversity of cortical activity, between- and within functional network integration, and temporal dynamics induced by psychedelic compounds.

Thalamic gating model

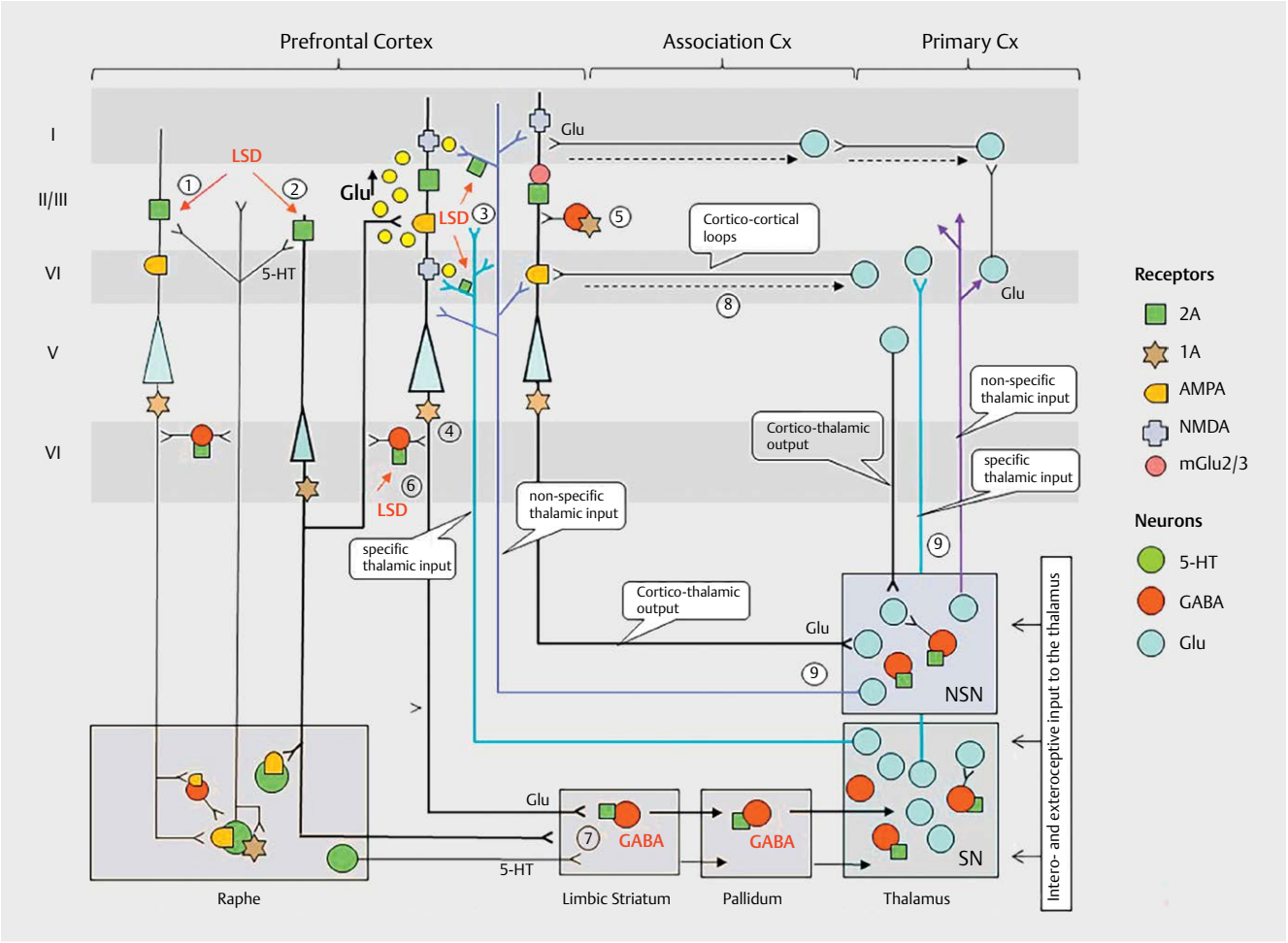
Alteration of information processing within cortico–striato–thalamo-cortical (CSTC) feedback loops is one mechanism that has been proposed to underly the psychedelic experience. The thalamus within this circuit is crucial in gating external and internal information to the cortex and, thereby, in the regulation of the level of consciousness and attention [109–111]). Thalamic gating is under the control of glutamatergic cortico–striatal and cortico-thalamic pathways that project to specific and nonspecific nuclei of the thalamus and under the modulatory influence of serotonergic and dopaminergic projections arising from the raphe and ventral tegmentum to several components of the CSTC loops. The CSTC model proposes that psychedelics disrupt thalamocortical information flow through the stimulation of 5-HT2A receptors located on cortical pyramidal cells and/or GABA interneurons in several parts of the CSTC loop, resulting in an information overload of the cortex and subsequent disruption of cortico-cortical integration of distributed neuronal activity. This could ultimately cause the increased sensory perception, cognitive disturbances, and ego-dissolution that arise in psychedelic experiences [109, 112] (▶ **Fig. 2**). This hypothesis is also compatible with the suggested increase of bottom-up information flow and relaxed priors proposed in the relaxed beliefs under psychedelics (REBUS) model described below [113].

The CSTS model is supported by the recent finding that LSD dose-dependently reduced the firing activity of reticular thalamus GABAergic neurons accompanied by disinhibition of mediodorsal thalamus relay neurons and increased firing activity of infralimbic prefrontal pyramidal neurons in mice [114]. Infusion of DOI into the dorsal pallidum in rodents and systemic administration of psilocybin, LSD, and DMT in humans disrupts sensorimotor gating and is associated with cognitive impairments in a 5-HT2A -dependent manner [34, 115–117]. Two neuroimaging studies reported that LSD increased functional connectivity between the thalamus and sensory-somatomotor cortical regions in healthy volunteers [118, 119]. LSD increased directed excitatory connectivity from the thalamus to the posterior cingulate cortex (PCC) and concomitantly decreased functional connectivity to the temporal cortex [120]. In line with the CTSC model, LSD also decreased control of the ventral striatum over the thalamus [120]. These results indicate that LSD differentially affects thalamo-cortical connectivity and does not lead to an undifferentiated increase in cortical information flow [120]. According to the hypothesis that disruption of thalamic gating may result in a sensory overload of the frontal cortex ("hyperfrontality") [121], two positron emission tomography studies reported increased prefrontal glucose metabolism after psilocybin administration in healthy volunteers [121, 122] which also remained evident after normalizing for global effects of psilocybin [123]. Similar frontal-dominated effects were shown with DMT and mescaline measuring cerebral blood flow (CBF) with single-photon emission computed tomography [124, 125]. However, using arterial spin labeling to investigate changes in brain perfusion, LSD was found to increase CBF in the visual cortex [126] while psilocybin produced brain-wide hypoperfusion in healthy subjects [127]. This latter result was replicated by Lewis et al. [128], but after adjusting for unspecific global effects, psilocybin was found to increase CBF in frontal and temporal regions and decrease CBF in subcortical and occipital regions. These findings are consistent with the hypothesis that reduced thalamic gating leads to overactivity of prefrontal brain regions, and also illustrate that the interpretation of such changes depends on the analytical methods used. It is also conceivable that modern imaging techniques are unable to determine the delay between changes in brain activity and signal acquisition and how temporally dynamic thalamic gating may be. Future studies are warranted to investigate whether differential effects on thalamic subregions or other subcortical structures may provide a more detailed model and their linkage with specific psychological alterations of psychedelic states.

The functional state of CSTC loops can be inferred by perturbational imaging (e. g., electroencephalography, EEG combined with transcranial magnetic stimulation, TMS) to assess drug-induced changes in brain state in real-time [146]. Perturbational imaging reveals the synchronized neuronal firing mediated by receptor kinetics [147] and can be used to describe the functional state of the brain. TMS-pulses induce a phase-reset of several endogenous cortical oscillations and can therefore also be used as a biomarker of the physiological state and to compare across physiological conditions [146]. TMS-EEG is currently being used to probe psychedelic-induced changes in cortico-thalamo-cortical dynamics in humans (unpublished). This unique approach to characterizing the effect of psychedelics on regional interactions at millisecond resolution is expected to clarify the relationship between phenomenological state and brain-state. The role of receptor kinetics in the TMS-evoked response, in combination with the ability to infer cortico-thalamo-cortical interactions using this technique, offers the possibility to model the relationship between pharmacodynamics and psycho-physiological responses.

Neural Entropy model

The "entropic brain hypothesis" (EBH) proposes that the variety of altered states of consciousness can be indexed through the information-theoretic measure of the entropy of key parameters of brain activity [113, 148]. The EBH together with the 'free-energy principle' has recently been integrated to formulate the "REBUS and the anarchic brain" model [113]. In brief, this model states that psychedelics increase the entropy of spontaneous cortical activity and consequently reduce the precision of high-level priors (expectations or beliefs about the world), and thereby liberating bottom-up information flow [113]. This renders recurrent cortical information processing more sensitive to the ascending information flow resulting in increased entropy or complexity of the underlying neuronal activity. Recent empirical research has identified increased entropy or signal diversity as a signature of psychedelic states [149]. Recent neuroimaging studies with magnetoencephalography (MEG) and EEG showed that LSD, psilocybin, and DMT increased the Lempel-Ziv complexity, a measure of signal diversity and approximation to entropy, which correlated with the overall intensity of the psilocybin and DMT-induced psychedelic experience [150, 151]. Furthermore, in an fMRI study, LSD increased sample entropy in sensory and some higher-order networks [80]. An increased repertoire of different brain states including rapid brain dynamics and functional connectivity was reported after the administration of psilocybin and LSD in the same set of healthy individuals [148, 152]. Increased Shannon entropy, broadly defined as the amount of information in a variable, was also reported in seven



▶ **Fig. 2** Working hypothesis of psychedelic drug effects on cortico-striato-thalamo-cortical and cortico-cortical circuits of information flow: The schema in ▶ **Fig. 2** comprises central brain networks on the effects of psychedelic drugs 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 model is based mostly on data obtained on the action of LSD and DOI in animals as well as from some studies with LSD and psilocybin in humans. The 5-HT2A receptors are highly expressed in the apical dendrites of layer 5 pyramidal (L5p) neurons in the cortex and are particularly enriched in the prefrontal cortex (PFC) [129–131]. A smaller proportion is located pre-synaptically on thalamocortical afferents projecting to the neocortex [96]. 5-HT2ARs are also expressed on GABAergic interneurons in the cortex and subcortical structures [131]. LSD and DOI both increase extracellular glutamate levels via activation of post-synaptic 5-HT2A receptors on deep layers 5 and 6 pyramidal neurons (L5p) (stage 1) and on Lp6 (stage 2) neurons projecting to L5p neurons [96, 132, 133] as well as via activation of pre-synaptic 5-HT2A receptors on specific (SP) and non-specific (NSP) thalamocortical afferents [96, 134]. Psychedelics such as LSD can also stimulate 5-HT1A receptors on the hillock on Lp5 and Lp6 neurons (stage 4) and cortical GABAergic interneurons (stage 5) resulting in both inhibition and disinhibition of prefrontal pyramidal cell activity [132, 135, 136]. Furthermore, LSD or DOI are also potent partial agonists at cortical (stage 6) and subcortical (striatal, pallidal or thalamic) (stage 7) 5-HT2A receptors in GABAergic interneurons [137, 138]. Despite this partially inhibitory mechanisms, this LSD- or DOI-induced increased glutamate release produces a striking net-excitatory effect on L5p neurons [139–141] and promotes synaptic plasticity via AMPA and NMDA receptor-dependent mechanisms [98, 105, 106, 133, 142]. L5P neurons affect both thalamic and cortical processing and have the unique ability to couple thalamo-cortical (stage 8) and cortico-cortical loops (stage 9) of information streams with each other [143]. This is thought to provide a mechanism through which the state and content of consciousness are functionally coupled [134]. Psychedelics appear to affect this extended thalamic-cortical broadcasting system and thus consciousness as a whole, by simultaneously producing sensory flooding and arousal via reduced thalamic gating of interoceptive and exteroceptive stimuli and by altering the meaning and attachment of percepts due to disrupted cortico-cortical interactions [19, 109]. In this model, thalamic gating is thought to be under the control of glutamatergic cortico-striatothalamic and cortico-thalamic loops projecting back to the cortex, in addition to being under the modulatory influence of serotonergic (and dopaminergic) projections from the raphe (and the VTA) to several parts of the CSTC.

participants after ayahuasca [153]. A recent mechanistic simulation model of the entropic effects of LSD suggests that 5-HT2A receptor activation leads to an increase in the overall entropy of the neural signals, but also that the entropy changes are not uniform across brain regions. Entropy increased in some cortical regions and decreased in some subcortical regions as a result of 5-HT2A receptor activation, suggesting a reconfiguration of the topographical distribution of entropy. Intriguingly, at the whole-brain level, this change was poorly explained by 5-HT2A receptor density, but correlated strongly with local connectivity strength [154]

The REBUS model proposes that the increase in entropy under psychedelics reflects a relaxation of the precision weighting of high-

level priors, leading to decreased top-down and increased bottom-up information flow. In support of this view, LSD reduced the electrophysiological responses to surprising stimuli in an auditory mismatch paradigm [155]. Analysis by Dynamic Causal Modeling (DCM) revealed that this effect was best explained by reduced top-down information flow from the frontal cortex [155]. However, other studies with psilocybin [156–158] or DMT [159] did not reveal reductions in auditory mismatch processing. On the other hand, a recent fMRI-EEG study using a tactile mismatch paradigm revealed that psilocybin reduced the blood oxygenation level dependent (BOLD) signal responses to surprising tactile stimuli in frontal cortex regions, visual cortex, and cerebellum, as well as the electrophysiological responses in frontal cortical regions correlating with the experience of disembodiment and altered meaning of percepts [160]. Hence, it is conceivable that increased bottom-up information flow, presumably by altered cortico-thalamo-cortical gating and impaired top-down cortical integration [109, 113, 149], may underlie the reduced sensation of body touch and thus the experience of disembodiment [160]. Further research is needed to unravel the extent to which alterations in bottom-up and top-down information transfer contribute to the topology of entropy changes and signal diversity observed in psychedelic states.

Models of this nature are an important tool for interpreting neurophysiological changes induced by psychedelic drugs. They act as a conceptual lens for explaining how the induced psychological states may be causally linked with physiological states. Distinguishing correlation from causation remains a challenge for neuroscience in general [161]. Approaches like the REBUS model, which conceptualize the brain as having properties of a Bayesian process (i. e., updating high-level priors), have proven to be predictive in many areas of cognitive research [162]. However, confidently mapping Bayesian objects, such as priors, onto the dynamic activity of neuronal populations remains ongoing research [163]. As models of information processing and neuronal population coding are developed and aligned, our understanding of psychedelic states will continue to expand. When borrowing nomenclature from other disciplines, such as “entropy”, “complexity”, “information” and “noise”, it is important to anchor terminology to signal properties and the experimental paradigm used. Experiments that investigate brain activity can either deliver a controlled stimulus and record the (causally known/trial-invariant) signals elicited, or they can record unconstrained (spontaneous) brain activity. Properties such as “signal” and “noise” are easier to define in the context of controlled stimuli because activity can be parsed based on stimulus invariance. Spontaneous activity, on the other hand, used to support the REBUS model, is the preferred terminology, and could be considered by these criteria to be structured noise and therefore a measure of signal diversity such as entropy. Entropy may be the most appropriate description for scenarios when brain activity changes in unpredictable directions and the only consistent outcome following drug administration is unconstrained change.

Effects of Psychedelics on Brain Network Integration

Several neuroimaging studies have investigated the impact of psychedelics on brain network dynamics by measuring resting-state functional connectivity changes between and within intrinsic networks [119, 126, 127, 164–168]. Two studies exploring the effect of LSD and psilocybin on global brain connectivity (GBC) using a graph-based measure of intrinsic whole-brain network connectivity and global signal correction (GSR) found that both drugs increased connectivity of brain region in sensory and somatomotor networks and decreased connectivity of brain regions in associative networks including the Default Mode Network (DMN) [119, 169]. The DMN is a large-scale network – consisting of brain regions such as the medial prefrontal cortex, posterior cingulate cortex, precuneus, and angular gyrus - that is activated when one is awake, but not involved in any specific mental exercise [170]. Moreover, the regional GBC changes correlated significantly with the topography of HTR2A gene expression [119]. These results are in line with the finding that psilocybin decreased expression of the frontoparietal control network (that is, a decreased probability of the occurrence of a recurrent phase-locking of BOLD signal over time), and concomitantly increased occurrence of a globally coherent brain state [171]. However, two other studies investigating the effects of LSD on GBC, although without using GSR, reported no overlapping results [118, 172], except for increased functional thalamic connectivity [118, 164, 172]. The decision to use or forgo GSR to adjust for shared variance across brain regions as well as for physiological-, movement- and scanner-related artifacts [173] remains a point of contention, and there is essentially no single "right" way to process resting-state data [173]. Together, these findings suggest that increased (bottom-up) sensory processing and reduced top-down integration capacity due to diminished associative network integrity may underlie psychedelic experiences. Notably, a recent whole-brain model using the dynamical mean-field quantitative description of excitatory and inhibitory neuronal populations as well as the associated synaptic gain function suggests that the effect of LSD on global brain connectivity can be best explained by the regional distribution and density of 5-HT2A receptors located on cortical pyramidal neurons [174]. A similar approach employing a transcriptomics-informed large-scale cortical model, including the expression level of various serotonergic and dopaminergic genes also found that modulation of pyramidal cell gain by 5-HT2A receptor activation accurately captures the LSD-induced GBC changes [119, 144, 145]. In addition, fitting to GBC in individual subjects revealed that the model also captures patterns of individual differences in LSD response that predict different aspects of the psychedelic experience [144]. Thus, it appears that the integration of bio-physical modeling and empirical neuroimaging data provides a promising framework to further unravel circuit mechanisms through which psychedelics alter cortical functional topography. Future work may also incorporate 5-HT2A receptors located in high density within the claustrum [175] and to a lesser extent in subcortical structures [138], but may also include other types of neuroreceptors such as the dopamine D2 [93, 138, 176], AMPA [98, 105, 106, 133] or NMDA receptor [142], all of which have been shown to contribute to the emotional and cognitive effects of psychedelics as described above.

Some studies also reported that psychedelics alter functional network connectivity which is the strength of typical anticorrelations between the DMN and other intrinsic networks [168]. Although psilocybin decreased DMN – Task Positive Network orthog-

onality [165], this finding was not replicated in another study after the administration of the DMT-containing drink Ayahuasca [167]. Psilocybin [166] and LSD [126, 168] were also found to induce widespread changes in between-network connectivity, although no uniform pattern of changes has emerged so far [168].

A consistent finding of several studies that have explored within-network functional connectivity (FC) is that psilocybin, LSD, and DMT decrease FC in or between structures of the DMN, [119, 126, 127, 167, 168, 177]. For example, psilocybin [69, 127] and LSD [126] decoupled FC between the medial prefrontal (mPFC) and the posterior cingulate cortices (PCC) - two major hubs of the DMN that have been implicated in self-other distinction, self-related cognition, and inward- versus outward-directed mentalizing [178]. Notably, a recent study found that the decrease in mPFC – PCC FC, two days after psilocybin administration, correlated with the intensity of the acutely experienced self-dissolution (OB) and predicted positive changes in psychosocial functioning in healthy volunteers four months later [69]. However, similar decreases in FC between the nodes of the DMN have also been reported after the administration of selective serotonin reuptake inhibitors [179] and the serotonin-releaser N-Methyl-3, 4-methylenedioxyamphetamine (MDMA) [180]. Changes in DMN activity have been reported for several conditions, including meditation [181] and task-positive behaviors [182]. Hence, identifying DMN changes specific to psychedelic drugs and the contribution of decreased DMN FC to the subjective effects of psychedelics remains to be further investigated.

The concerted interaction of brain networks and brain regions is also reflected by brain oscillations [183, 184]. They are characteristic features of the cortical dynamics implicated in the modulation of perception and cognitive functions, which can be measured via resting-state MEG/EEG recordings [185]. MEG/EEG studies reveal that psilocybin, LSD, and DMT reduce spontaneous oscillatory power of low-frequency signals including the delta, theta, beta, and alpha (1–12.5 Hz) frequency bands. The reduction of alpha power in the DMN including the ACC and PCC [177, 186], in parahippocampal regions [186], and parieto-occipital and posterior association cortices [177, 186–189] was the most consistent finding after administration of psychedelics. Alpha oscillations reflect cortical inhibition of neuronal ensembles [190]. Thus, the decrease in alpha power may indicate a bias of the cortical excitation/inhibition balance towards excitation. DCM applied to MEG data suggests that the reduction in PCC alpha power after psilocybin administration is consistent with increased L5p neuron activity, which also correlated with ego-dissolution [127]. In another study, lagged phase synchronization of delta oscillations between the orbitofrontal cortex, the parahippocampus, and the retrosplenial cortex correlated with the psilocybin-induced spiritual experience and insightfulness [186]. Psilocybin and DMT also increased low gamma oscillations in the PCC [186] as well as low and high gamma power in frontal, temporal, and parieto-occipital cortices [189]. However, decreases in gamma power in prefrontal, sensory and somatomotor areas have also been reported [177]. Gamma oscillations are thought to provide a neuronal mechanism to bind coherently distributed cooperating neuronal assemblies for representation, storage, and retrieval of information [184, 191]. The range of cognitive processes in which gamma synchronization has been implicated suggests that its presence may reflect an array of simultaneous processes at work [192]. Changes in gamma synchronization would then reflect changes in information processing, including endogenously-generated states. Hence, alterations in gamma synchronization may well contribute to changes in processes like autobiographical memory retrieval [193] and awareness of one's own internal state during the psychedelic experience [194, 195].

Neural Correlates of Altered Self- and Emotion-Processing in the Psychedelic States

Early clinical observations in psychedelic research suggested that psychedelics induce regression of the self, lowering of rational thinking, increased affectivity, and facilitated recall of memory blocks. This gave rise to the hypothesis that these are important psychological mechanisms that contribute to the restructuring of the self and self-related functions, as well as the changes in emotion regulation, and thus to the clinical efficacy of psychedelic-assisted psychotherapy [41, 76, 196–198]. Building upon these findings, several studies have investigated the neural correlates of psychedelic-induced alterations in self-experience, cognition, mood, and emotion processing.

Self-Processing

Psychedelics profoundly alter various aspects of the ordinary coherent self-experience [6]. This is often described as a loosening of self-boundaries, an experience of oneness, disembodiment, a loss of authorship of thought, emotions, and actions, and dissolution or disintegration of the experiential "I" or "ego" [6, 199]. To date, several studies have attempted to capture the neural correlates of these phenomena by correlating psychometrically assessed subjective alterations in self-experience with brain imaging data. So far, different constructs – ranging from dimensional (e. g. "oceanic boundlessness" [119, 200] to sub-dimensional (e. g. "unity" [6, 201] and to single item-based approaches (e. g., "I experienced a disintegration of my self or ego" [126, 172, 177, 202, 203] – have been used to measure the complex multi-layered alterations of self-experience in psychedelic states.

In an fMRI study, the LSD-induced loss of self-boundaries correlated with increased global brain connectivity in the somatomotor network [119], while in another study the subjective reports of ego-dissolution correlated with increased global FC in the angular gyrus and the insula [172]. In a subsequent analysis of the later study [172], the LSD-induced ego-dissolution also correlated with decreased seed-based functional connectivity within the DMN and between the parahippocampus and retrosplenial cortex as measured by fMRT and with decreased delta and alpha power as measured by MEG [126]. By focusing on the time-dependent effects of LSD on functional connectivity, another analysis of this study [172] revealed that the feeling of ego dissolution correlated with the increased weighted small-world propensity (organization) during the dynamic sub-state of high global integration [203]. Concerning the effect of psilocybin, one study noted that the self-reported ego-dissolution correlated with decreased alpha power in the PCC [177], and in the same participants, with a reduction of FC between the medial temporal lobe (MTL) and high-level cortical regions, a "disintegration" of the salience network (SLN), and a reduction of interhemispheric communication [202]. In another study, the Psilo-

cybin-induced spiritual experience and insightfulness – two subdimensions of OB – correlated with the lagged phase synchronization of delta oscillations between the retrosplenial cortex, the parahippocampus, and the orbitofrontal cortex [186].

Recent neurocognitive approaches to the self suggest that self-referential processing of internal and sensory stimuli in cortical midline structures constitute a core concept of one's self [204–206], a phenomenal self as the subject of experience, also referred to as a self-model [7, 28]. The representation of the self as a solid entity includes in parallel the processing of internal stimuli from one's own body with emotions and cognition which are also examined through self-reference and bound to that entity [7, 207]. This complex multi-layered representation of the self has various features such as a sense of being, ownership of a body, temporal order, spatial location, ownership and authorship of thoughts, emotions and actions, and a history [208]. Along this line, a recent EEG-ERP study using an auditory self-monitoring task found that psilocybin abolished self-stimuli encoding via a P300 mechanism associated with current source density changes in the supragenual anterior cingulate cortex and right insula [209]. Notably, the extent of the P300 effect significantly correlated with the intensity of the experience of unity ('oneness with the surroundings') and changed the meaning of percepts, assessed psychometrically. Moreover, in accordance with predictive coding principles [210], psilocybin also reduced tactile mismatch processing in prefrontal cortex regions that correlated with the extent of disembodiment and changed meaning in a combined EEG-fMRT study in healthy volunteers [160]. The phenomenon of reduced mismatch processing has been interpreted as reflecting an impairment of predictive coding or, more generally, the "Bayesian brain" notion that the brain continuously updates a hierarchical model to infer the causes of its sensory inputs [162]. Thus, this study provides the first evidence to the hypothesis that the profound alteration of the bodily-self as an aspect of self-dissolution during psychedelic states is due to a dysfunctional integration of bodily states and sensory inputs with prior beliefs [211]. However, more research is warranted to further investigate the detailed hierarchical and temporal dynamics of psychedelics-induced disruption of belief updating within the framework of predictive coding [212].

Taken together, these disparate findings regarding the neuronal correlates of altered self-experience or ego-dissolution appear to reflect different facets and layers of the dynamics of self-loss in psychedelic states, but may also be due to the different methods, metrics, and doses used across studies. The participant's widely different understanding of ambiguous terms such as "ego", "sacredness" or "spiritual experience" may also have contributed to the variability of present results [213, 214]. More differentiated operationalization and fine-grained psychometric instruments are needed to conclusively identify specific neural correlates of altered self-experiences across future studies. However, the present data also suggest that the self should be understood as a complex matrix of representations involving different structures and functions rather than a single entity that could be readily abandoned in psychedelic states. The investigation of self-referential processing may offer a promising alternative operationalized approach to unravel the neural correlates of altered self and ego-dissolution.

Beyond the scope of getting a deeper insight into the different organizing principles and processing levels that constitute our self, these studies are important because alterations in self-processing are considered to be crucial for the efficacy of psychedelic-assisted therapy [41, 197, 198]. So far, positively experienced self-dissolution (e. g., OB) or mystical-type experiences were correlated with the treatment success in an open-label study of major depression [215] and two controlled studies of depression and anxiety in palliative care [71, 72]. Clinical observations suggest that the transient dissolution of self-boundaries and the reduction of self-referential processing leads to decentering [41, 48, 216–218], which is a process of stepping outside of one's own immediate experience enabling a person to realize that their thoughts and emotions are not unchangeable facts, but only a constructed reality of the self [219, 220]. This shift in perspective facilitates more appropriate reactions and adaptions to one's own cognitions and negative attribution of emotions and reduces dysfunctional attitudes towards the self [48, 219]. Increased self-focus and reduced attention to others and the environment are characteristic features of depression - presumably due to increased DMN resting-state activity and altered balance between DMN and executive network activity [24, 221] – therefore, it is conceivable that the transient self-dissolution associated with reduced DMN activity leads to reduced and more flexible cognitive reactions, especially in depressed patients suffering from negative self-attribution and ruminative thinking [22, 23]. Consistently, LSD and psilocybin acutely increased emotional empathy [222, 223], facilitated social adaptation [224], and reduced rejection sensitivity and feelings of social exclusion [20, 201]. Hence, reduced self-processing may also promote improvements in social cognition [20], thereby contributing to the emotional attunement which is important in (psychedelic-assisted) psychotherapy of depressed patients [11, 41, 198]. However, these hypotheses remain to be tested in clinical studies.

Emotional Processing

Several studies in healthy volunteers have shown that psychedelics also acutely alter emotion processing, and particularly reduce the response to negative emotional stimuli. For example, psilocybin and LSD dose-dependently attenuated the recognition of negative facial expression in healthy volunteers [84, 223, 225, 226]. Intriguingly, psilocybin reduced both non-conscious and conscious structural encoding of fearful faces, although somewhat more pronounced during conscious processing [226], suggesting that emotional awareness may enhance psychedelic-mediated emotion regulation (for an opposite view see [103]). Furthermore, psilocybin and LSD reduced the neuronal response to negative stimuli in the amygdala correlated with the increase in the positive mood [227, 228]. Subsequent correlation analyses revealed that psilocybin reduced directed connectivity from the amygdala to the primary visual cortex during threat processing [229] and decreased the functional connectivity between the amygdala and the striatum during angry face discrimination [230]. In a recent study, reduced amygdala response to negative stimuli was observed one week after psilocybin administration but returned to baseline one month after administration [231].

Negative cognitive and emotional biases, as well as increased amygdala reactivity to negative stimuli, are characteristic features

of depression [22]. Hence, it is conceivable that psychedelics may acutely abolish this negative cognitive and emotional bias by reducing amygdala reactivity, allowing a cognitive-emotional readaption from a decentered stance. To what extent this process on its own or in combination with psychotherapy may contribute to the enduring symptom reductions reported in psychedelic-assisted therapy is hardly understood. So far, a recent open-label study in depression reported increased amygdala reactivity in response to fearful stimuli and decreased amygdala-prefrontal cortex FC one day after psilocybin administration [215, 232]. This discrepancy may be because increased amygdala reactivity in these depressed patients was measured prior to psychological integration work [215]. Further longitudinal studies are needed to explore the long-term effects of psychedelics on amygdala reactivity and its clinical relevance.

Conclusion

Elucidating the biological mechanisms of classical psychedelic drugs, while hindered by a complex socio-political history, persists as a promising research endeavor for neuropsychopharmacology. Realizing the full potential of psychedelic compounds as an effective and reliable clinical tool will require a continuous understanding of their interdependent effects at many biophysical and psycho-social levels. Psychedelic experiences have broadly defined phenomenological trajectories, which makes their contents accessible to researchers via psychometrics. Standardized questionnaires currently exist to quantify aspects of these drug-induced alterations in consciousness, which lends to quantification and correlation with biomarkers and measures of physiological state. The diversity of receptor targets is well-characterized, affecting primarily serotonergic receptor subtypes and mediated by several other neuromodulatory receptors. Through these known mechanisms, aspects of psychedelic experiences in humans can be modified by administering other drugs concomitantly to target specific receptor subtypes. The affected receptor sites are situated within neuronal pathways necessary for cortico-thalamic and cortico-cortical feedback circuits. By modulating excitatory-inhibitory balance in these circuits, psychedelic drugs can participate in neuroplasticity within structures critical for information processing in the brain. These insights have laid a foundation for several, non-conflicting, theories about the multi-system-level changes induced by psychedelic drugs. They predict altered pathways in brain structures associated with the integration of information relevant to sensation, cognition, emotions, and the narrative of self. These theories also converge to explanations inspired by biological (statistical) thermodynamics, using the concepts of entropy and information, in combination with the necessary receptor-mediated dynamics. Moreover, modern approaches to causal inference applied to imaging techniques (like DCM and perturbational imaging) are helping to forge models directly relevant to neuropsychiatry which will hopefully become prognostic tools. Neurophenomenological metrics for transient and long-lasting effects of psychedelic drugs on healthy volunteers and patients continue to be discovered, and those which best predict clinical outcomes of psychedelic-assisted therapies are an ever-expanding field and show great promise.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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