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Journal

Neuropsychopharmacology, 49(1)

ISSN

0893-133X

Authors

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Publication Date

2024

DOI

10.1038/s41386-023-01666-5

Peer reviewed

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REVIEW ARTICLE

Therapeutic mechanisms of psychedelics and entactogens

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Recent clinical and preclinical evidence suggests that psychedelics and entactogens may produce both rapid and sustained therapeutic effects across several indications. Currently, there is a disconnect between how these compounds are used in the clinic and how they are studied in preclinical species, which has led to a gap in our mechanistic understanding of how these compounds might positively impact mental health. Human studies have emphasized extra-pharmacological factors that could modulate psychedelic-induced therapeutic responses including set, setting, and integration—factors that are poorly modelled in current animal experiments. In contrast, animal studies have focused on changes in neuronal activation and structural plasticity—outcomes that are challenging to measure in humans. Here, we describe several hypotheses that might explain how psychedelics rescue neuropsychiatric disease symptoms, and we propose ways to bridge the gap between human and rodent studies. Given the diverse pharmacological profiles of psychedelics and entactogens, we suggest that their rapid and sustained therapeutic mechanisms of action might best be described by the collection of circuits that they modulate rather than their actions at any single molecular target. Thus, approaches focusing on selective circuit modulation of behavioral phenotypes might prove more fruitful than target-based methods for identifying novel compounds with rapid and sustained therapeutic effects similar to psychedelics and entactogens.

Neuropsychopharmacology (2024) 49:104–118; https://doi.org/10.1038/s41386-023-01666-5

INTRODUCTION

In sharp contrast to their unrestrained use in the 1960s, psychedelics are re-emerging in the 21st century as regulated medical therapies, delivered in controlled settings with close therapeutic monitoring. Psychedelic-assisted therapy is beginning to show promise, as several clinical trials have demonstrated that a single or a few administrations of drugs like 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin yield benefits that can last for months, and possibly years [1–8]. In fact, these clinical results are likely specific use cases for a class of drugs that can harness plasticity mechanisms to produce long-lasting beneficial effects with applications to learning [9], memory [10], mood [11], creativity [12] and perhaps even enhanced recovery from neurological injury [13]. And yet, psychedelic medicine is in its infancy. As an example, the widespread adoption of MDMA will be limited by its well-known potential for abuse [14], the high cost of a rather complex therapeutic package [15], and a host of neurological, psychiatric, and cardiovascular complications associated with long-term use [16]. Psilocybin faces similar challenges related to scalability and integration into current healthcare ecosystems that could limit patient access [17]. These therapies are intended to treat disorders like post-traumatic stress disorder (PTSD), depression, and substance disorder (SUD)—conditions that afflict hundreds of millions of people worldwide. Despite their promise, the psychedelics and entactogens we know today may quite possibly be the crudest tools to achieve that end, as their therapeutic mechanisms remain opaque, and they have not been optimized to maximize efficacy and scalability while minimizing adverse side-effects.

These early, highly promising clinical results have already inspired major industrial efforts [18] to identify psychedelic derivatives optimized for pharmacokinetics, toxicity, and more manageable subjective effects. However, the challenge of improving on drugs like MDMA and psilocybin to develop safe, scalable treatments for millions of patients requires an understanding of mechanisms that bridge pharmacology, large scale neural dynamics, and behavior. Yet, many aspects of human therapeutic trials are not well captured in animal models. Here, we review how psychedelic and entactogen mechanisms have been conceptualized in preclinical models, and the remaining gaps in these approaches. In that context, we consider our current understanding of how circuit-level processes contribute to the putative therapeutic properties of this broad class of small molecules, defined primarily by their rapid and sustained therapeutic effects and their abilities to produce often profound experiences in humans.

In several passages below, the reader will find references to "therapeutic" or "therapeutic-like" effects in rodent models. This shorthand is convenient for a discussion focused on forward and reverse translation between species, but we acknowledge the imprecision of these terms. Disease states like depression, PTSD, and SUDs occur in humans, and treatment outcomes are defined in humans. While noting the considerable controversy [19–22] surrounding the use of rodent behavior as surrogate markers for

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Received: 9 March 2023 Revised: 10 July 2023 Accepted: 11 July 2023
Published online: 24 July 2023

human disease and their generally poor predictive performance for novel treatments, we do not yet know which animal models will best predict human efficacy for psychedelics and entactogens. Rather, in this review, we seek to establish a framework for animal experimentation that may help arrive at that answer.

WHY GROUP PSYCHEDELICS AND ENTACTOGENS?

Psychedelics and entactogens are pharmacologically diverse classes of compounds, but they share two key features that have been demonstrated in humans and modeled in laboratory species —rapid onset subjective effects and persistent effects on behavior [23]. These core attributes may reflect changes in a convergent set of neural circuits that drive sustained behavioral effects. Circuit-level mechanistic similarities that unite these otherwise dissimilar compounds may therefore yield particularly valuable insights. Nonetheless, it is important to distinguish the differences between substances that are often generally categorized under the broad umbrella term "psychedelics". *Classical psychedelics* (i.e., "mind manifesting"), including lysergic acid diethylamide (LSD) and psilocybin, are hallucinogens that target serotonin 2 A receptors (5-HT2ARs) in the brain and have powerful dose-related effects on perception, cognition, and emotion. *Entactogens* (i.e., "touching within") are a distinct drug class, so named for their reported ability to allow subjects to retrieve repressed and often traumatic memories [24, 25]. Entactogens indirectly impact the serotonergic system by primarily stimulating the release of serotonin, though other monoamines and neuromodulators may make substantial contributions to the net subjective and therapeutic effects. The terms entactogen and empathogen refer to the same class of compounds that produce effects on self-perception, social interaction, and fear memory, while generally not possessing hallucinogenic properties [26–28]. The latter term was used to emphasize the ability of these molecules to elicit prosocial behaviors and feelings of empathy, though it fell out of use as some researchers suggested that, in a therapeutic setting, an enhanced ability to retrieve otherwise unavailable memories, rather than evoked empathy, drove lasting benefits [24]. While a number of amphetamine and cathinone derivatives are classified as entactogens [29], including N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) [25, 30], and 3,4-methylenedioxy-N-methyl-cathinone (methylone) [31], MDMA is by far the most prominent and best studied in multiple species. *Dissociative anesthetics*, such as ketamine, can cause altered brain states, and impact perception in some ways that overlap with psychedelics [32–34], but their classification as psychedelics is controversial. Mechanisms of ketamine for psychiatric indications are extensively reviewed elsewhere in this issue [35], but we will compare the effects of psychedelics and entactogens to ketamine throughout this review when appropriate.

In this review, we consider both classical psychedelics and entactogens together, as they face similar scalability challenges and the key unresolved questions about their respective mechanisms are largely applicable to both drug categories. For one, current therapeutic delivery models for drugs in both categories involve carefully controlled settings for drug administration and some degree of concomitant psychotherapy. This complex care model suggests that the subjective state and environment in which psychoactive drugs are taken are strong determinants of therapeutic outcome, an idea enshrined in psychedelic culture as "set and setting" [36, 37], popularized by Timothy Leary. Whether, and to what extent, "set and setting" determines clinical therapeutic outcomes has distinct implications for how putative therapeutic effects are modelled in animal species where we have limited insight into subjective state. We consider the translational challenges in modeling these and other non-pharmacological aspects of psychedelic and entactogen-assisted therapy in the final section of this review.

Classical psychedelics and entactogens also share an apparent and remarkable ability to induce long-lasting changes in behavior and cognition beyond the immediate and rapid onset effects. Despite substantive differences in pharmacology and subjective effects, this shared property may represent a convergent mechanism of action. Emerging evidence suggests that these drugs may cause structural and functional changes in the brain, which could underlie the therapeutic benefits seen in some neuropsychiatric conditions. These changes, however, remain poorly understood and require further investigation to better understand their nature and underlying mechanism.

WHAT HAPPENS DURING DOSING?

Perhaps the most straightforward-seeming aspect of psychedelic therapy to model in animals is the drug experience itself, as the way that drugs enter the brain is similar across mammalian species, even when accounting for differences in how the drugs are metabolized. However, in human studies, a great deal of attention has been paid to establishing a particular environment (the "setting" in "set and setting") for a patient to experience the profound psychoactive effects of the substance under investigation. The vast majority of controlled clinical trials are performed in environments where patients are typically laying on a couch, and auditory and visual information is limited or carefully controlled (e.g., eyeshades and headphones conveying curated music set lists) [38]. Conversely, for psychedelics and entactogens, the role of non-drug factors in the acute and persistent behavioral effects has generally received less attention in animal studies than clinical ones, despite well-known context dependent effects of, for example, psychostimulants and opioids in rodents and humans [39–42]. The potential importance of the acute drug experience suggests two alternative explanations for how the resulting therapeutic effects might arise.

The psychoplastogen model

Psychoplastogens. Drugs may directly affect receptors and the circuits in which they are embedded to induce long-lasting changes to the structure and function of the central nervous system. The extent to which accompanying subjective effects are required is debated [43, 44], however all models in this framework rest on an assumption that long-term changes in behavior (e.g., therapeutic outcomes in humans) are the result of drug-induced plasticity that strengthen and/or weaken adaptive and maladaptive circuits, respectively. The drugs that induce these changes are known as *psychoplastogens* [45].

In most studies, it is difficult to distinguish between biochemically driven plasticity and effects that might derive from a combination of direct stimulation of neuroplasticity pathways and acute subjective effects of the drug. It appears that the plasticity-promoting properties of psychedelics and their subjective effects result from activation of the same receptor (i.e., 5-HT2AR) [46]. In addition, 5-HT2AR occupancy may be a key factor regulating the intensity of subjective effects and potentially plasticity [47]. As both the intensity of subjective effects and magnitude of the plasticity effects appear to be initiated by the same receptor and are likely to be dose-dependent, therapeutic effects cannot be easily attributed to one or the other factor in a straightforward way.

The association between experiences on-drug and therapeutic outcome may not reflect a causal relationship at all. To understand which factors are causally related to therapeutic effects, experiments must be designed to eliminate either the subjective experience or the neuroplasticity effects while leaving the other intact. One recent powerful set of experiments probing the mechanism of ketamine's sustained antidepressant effects in mice took the latter approach [48]. Following ketamine administration and subsequent spine growth in the prefrontal cortex (PFC), a

photoactivatable Rac1 targeted to activated synapses was used to selectively photoablate ketamine-induced dendritic spines. Long-lasting antidepressant-like effects were absent following spine ablation, establishing a causal role for cortical spinogenesis in the sustained therapeutic effects of ketamine. Similar studies have not yet been conducted for serotonergic psychoplastogens.

Non-hallucinogenic psychedelic analogues present another powerful tool set to probe the relationship between subjective effects and plasticity [49–57]. Preclinical experiments with these compounds have found that persistent behavioral changes do not depend on acute psychoactive effects, but rather induction of neuroplasticity in key circuits, particularly involving the prefrontal cortex (see below). While several compounds in this group of non-hallucinogenic psychedelic analogues indeed appear non-hallucinogenic in humans, many are novel compounds that have not undergone clinical testing. Given that limited inferences can be made regarding subjective states in nonhuman species, the putative non-hallucinogenic nature of these novel compounds, as well as their putative therapeutic effects, must be verified in people.

The behavioral catalyst model

Behavioral catalysts. An alternative model explains long-term changes in behavior and associated changes in neural circuitry as the result of an accelerated natural course of recovery. In this model, a drug given during psychotherapy helps to overcome obstacles that otherwise impede successful therapy, thereby catalyzing a transformative therapeutic experience. Here, the experience itself, rather than the pure pharmacological effect of the drug, is central to producing long lasting changes in behavior and symptomatic relief [58]. Corresponding plasticity observed in neural circuits may thus reflect experience-dependent, learned adaptative change rather than an experience-independent drug effect.

For example, in healthy subjects, MDMA acutely disables recognition of otherwise aversive stimuli [59–64]. In the setting of MDMA-assisted psychotherapy, this state ostensibly allows for previously unsustainable recall of traumatic memories; this temporarily enhanced engagement with traumatic material allows the patient to finally digest and "move past" these memories. A similar process has been suggested for classical psychedelic therapy, wherein drugs may temporarily weaken the certainty of previously held beliefs, potentially making the individual more open to revising those beliefs [65]. Studies conducted on both healthy humans and rats provide some evidence supporting the hypothesis that psychedelics temporarily increase cognitive flexibility [9, 66] and reinforcement learning [67]. Cognitive flexibility is typically assessed using tasks where rules for correct responses are established and then changed. Adapting efficiently to these rule changes or probabilistic reversal learning tasks is seen as evidence of cognitive flexibility. Although the immediate effects of psychedelics on these tasks have not been definitively linked to therapeutic outcomes, a temporary boost in cognitive flexibility could catalyze a change in perspective during psychedelic administration, ultimately leading to therapeutic benefits.

In testing a model where the drug acts as a behavioral catalyst, the behaviors and physiology induced during its acute effects are of prime importance to understanding its putative therapeutic effect in humans. Several groups have focused on the mechanisms underlying acute prosocial effects of MDMA [68–70], on the basis that these same effects in humans enhance the patient-therapist bond and catalyze therapeutic transformation [71–73]. Remarkably, the hallmark social approach behavior induced by MDMA in humans [59, 61] could be largely reproduced by mimicking MDMA's serotonin-releasing properties in a single major reward processing area, the nucleus accumbens (NAc) [68, 74]. Other groups have modeled MDMA therapy as extinction learning, where, again, an acute experiential process is considered crucial for therapeutic outcome. Supporting this idea, MDMA administered immediately prior to, but not after, extinction learning resulted in robust extinction memory measured the following day [75, 76]. However, two recent studies in healthy human volunteers using behavioral paradigms similar to those used in rodent studies found that MDMA does *not* facilitate extinction of a conditioned fear-potentiated startle response [64, 77], though Vizeli et al. found that MDMA enhanced extinction of a fear-conditioned skin conductance response [64]. These data suggest either a PTSD-specific effect of MDMA, or that the fear extinction paradigm does not fully capture the processes underlying therapeutic effects of MDMA in humans. Future work could further probe the fear extinction hypothesis in patients with PTSD by administering MDMA prior to Prolonged Exposure therapy [78] in the absence of specific preparation, integration, or therapist support, though the ethical considerations of such an experiment ought to be carefully weighed. In addition, identifying molecular determinants of these distinct MDMA-evoked behavioral processes (see below) will be crucial to generate mechanistic hypotheses that can be tested in patients.

The psychoplastogen and behavioral catalyst models of psychedelic/entactogen therapeutic mechanisms are not mutually exclusive, but rather they describe two distinct physiological processes driving plasticity, both of which may contribute to therapeutic outcomes. In the psychoplastogen model, drug induces plasticity and results in a therapeutic response. No therapy is required; the drug and structural/functional changes are sufficient. In the behavioral catalyst model, a more conventional psychotherapeutic process mediates recovery, facilitated by a drug which, on its own, would not be predicted to have the same therapeutic effect. These processes seem likely to work in concert to produce particularly robust effects—drug-induced biochemical plasticity mechanisms could prime the brain for subsequent experience or psychotherapy to strengthen and weaken adaptive and maladaptive circuits, respectively. Nonetheless, the psychoplastogen and behavioral catalyst models emphasize substantially different areas of focus for preclinical behavioral research.

CIRCUITS IMPACTED BY PSYCHEDELICS AND ENTACTOGENS

The traditional industry-standard method of screening small molecules for high affinity interactions at a given receptor may not accurately predict the persistent changes in brain structure/function and behavior induced by drugs as pharmacologically dissimilar as MDMA, psilocybin, and ketamine. Indeed, as we deepen our understanding of various forms of functional selectivity including biased agonism [79], location bias [80], and GPCR crosstalk via heterodimerization [81], it becomes clear that psychedelics cannot be described simply as "5-HT2AR partial agonists."

Probing for convergent neurobiological effects at the level of circuit physiology may prove highly informative. Advances in systems neuroscience and circuit dissection now enable this broader view of drug mechanism and therapeutic discovery. This approach further suggests the possibility of separating the therapeutic versus undesirable attributes of psychedelics and entactogens based on differential modulation of the various circuits engaged following drug administration. Advances in tissue clearing, whole-brain imaging, high-density multi-site electrophysiology and well established opto- and chemogenetic methods for characterizing and interrogating neural circuits have the potential to reveal similarities and differences between the circuits modulated by psychedelics, entactogens, and nonhallucinogenic psychoplastogens. In this section, we focus on what is currently known about circuits impacted by psychedelics and entactogens, and how they might be involved in therapeutic responses. In many cases, the acute drug effects described here may depend on the context in which they are given, a property with potentially

important translational implications, discussed in more detail in the section *The Gap Between Clinical and Preclinical Studies*.

Psychedelics

Studies in both humans and animals have demonstrated that psychedelics can induce widespread alterations in neural activity [82]. However, mechanistic preclinical studies have tended to focus on brain areas and circuits that already have established roles in the pathophysiology of the specific neuropsychiatric disorder being modeled. For classical psychedelics, controlled human studies have enrolled patients with depression [3, 4, 6, 8, 83], alcohol use disorder [84, 85] or tobacco use disorder [86]—all of which are associated with cortical atrophy and dysfunction [17]. As a result, most mechanistic studies of psychedelics, whether modeling depression or alcohol use disorder, have focused on various areas of the cortex. These studies have consistently found that multiple psychedelic compounds can impact cortical neuron structure and function [87, 88].

Cortical changes. Psychedelics reliably induce the expression of immediate early genes (IEGs) in the cortex [89–102], and the induction of c-Fos is correlated with transcript levels of *GRIN2A* and *GRIN2B* [89] which encode NMDA receptor subunits (2A and 2B) heavily implicated in many forms of synaptic plasticity [103]. In addition to increasing cortical expression of IEGs, psychedelics also promote the growth of cortical neurons. Cellular studies have revealed that psychedelics from a variety of chemical classes can promote the growth of dendrites, increase dendritic spine density, and change dendritic spine morphology [104–109]. Ex vivo experiments have demonstrated similar increases in spine density in the PFC of rodents long after the drugs have been cleared from the body, with concomitant changes in functional plasticity such as increased frequency and amplitude of excitatory post synaptic currents and cortical long-term potentiation (LTP) [80, 108, 110–112]. In vivo studies using two-photon microscopy have also revealed enhanced cortical spine formation following administration of DOI [113], psilocybin [114], ketamine [115], and 5-MeO-DMT [116]. Remarkably, a single administration of psilocybin can increase spine density for up to a month [114].

Currently, it is unclear if IEG expression is required for psychedelic-induced neuroplasticity or is simply a molecular marker of subjective effects. The hallucinogenic drugs ketamine and psilocybin produce similar c-Fos expression patterns in the cortex [89], but direct comparisons to structurally-related nonhallucinogenic psychoplastogens are lacking. One study demonstrated that LSD, but not its nonhallucinogenic analogue lisuride, increased *egr-1* and *egr-2* expression in the cortex [90]. Both compounds increased *c-fos* expression, though the magnitude of that change was substantially greater following treatment with LSD [90]. Increased c-Fos expression may be a direct result of elevated glutamatergic transmission. Several hallucinogenic drugs including LSD, DOI, and ketamine have been shown to induce a glutamate burst in the cortex [117–121]. Currently, it is unknown if nonhallucinogenic psychoplastogens produce similar changes in cortical glutamate levels.

Downstream from the cortex. Given that the PFC projects to a variety of subcortical regions that regulate mood, fear, and reward, the rescue of cortical dysfunction is one hypothesis that can potentially explain why psychedelics seem to ameliorate symptoms associated with several neuropsychiatric disorders. Direct optogenetic stimulation of the PFC or direct injection of psychoplastogens into the PFC can produce beneficial behavioral responses in rodents [122]. For example, optogenetic stimulation of the PFC increases social interaction and ameliorates anhedonia as measured by the sucrose preference test [123]. Interestingly, the prosocial effects of repeated LSD

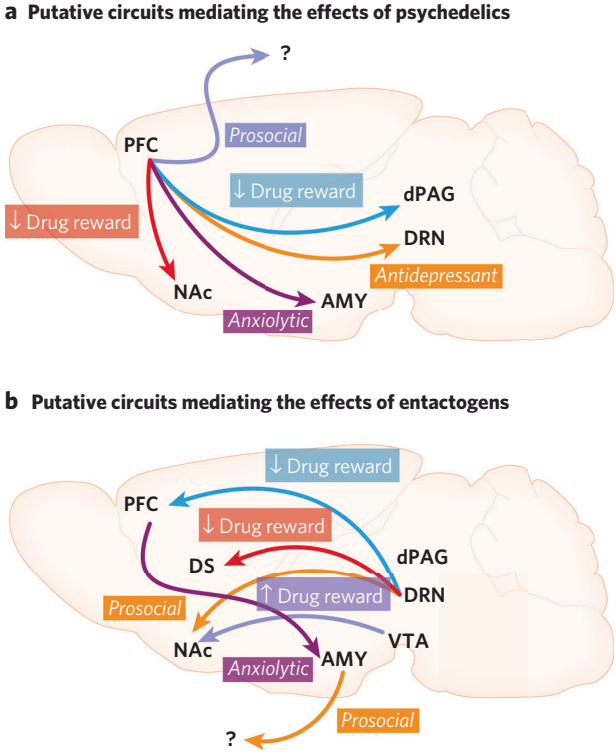

Fig. 1 Potential circuits mediating the effects of psychedelics and entactogens. a Several circuits involved in the pathophysiology of various neuropsychiatric disorders have been identified via opto- and/or chemogenetic studies. Given that psychedelics increase structural plasticity in the PFC, these circuits might underlie their therapeutic properties. However, specific experiments testing those hypotheses are lacking. While the PFC and AMY have been implicated in the prosocial effects of LSD and MDMA, respectively, those specific circuits have yet to be elucidated. **b** Potential circuits mediating both the therapeutic and addictive effects of entactogens are shown. Serotonin efflux from DRN projections play a key role in many of MDMA's beneficial effects. PFC prefrontal cortex, dPAG dorsal periaqueductal gray, DRN dorsal raphe nucleus, NAc nucleus accumbens, AMY amygdala, VTA ventral tegmental area, DS dorsal striatum.

administration are blocked if excitatory neurons in the PFC are photoinhibited [112].

Opto- and chemogenetic studies have revealed much about which PFC circuits mediate specific therapeutic-like responses (Fig. 1). Projections from the PFC to the dorsal raphe nucleus reduce immobility in the forced swim test [124], while those that innervate the amygdala have been implicated in the control of fear expression and extinction learning [125, 126]. Circuits from the PFC to the NAc have been implicated in the regulation of cocaine-seeking behavior [127–129], and optogenetic experiments have revealed that similar circuits may suppress compulsive alcohol consumption [130]. In addition, PFC projections to the dorsal periaqueductal gray may also contribute to the suppression of compulsive alcohol-seeking behavior [131].

While it is reasonable to hypothesize that the PFC circuits outlined above mediate various therapeutic responses following the administration of psychedelics, this hypothesis has not yet been rigorously tested and the exact circuits involved in the therapeutic effects of these drugs remain unknown. Genetic deletion of psychedelic targets within these circuits and/or selective inactivation of these circuits would certainly shed light on their roles in the therapeutic mechanisms of psychedelics. Alternatively, global knockout of psychedelic targets followed by selective restoration to PFC neurons projecting to various

subcortical regions could lead to a deeper understanding of the exact circuits mediating the antidepressant, anxiolytic, prosocial, and antiaddictive effects of psychedelics.

Beyond the cortex. While the PFC has been a major focus of psychedelic research given its high density of 5-HT2Rs, other brain regions might also be important. Advances in high resolution brain imaging using a combination of tissue clearing, c-Fos immunostaining, and light-sheet microscopy have enabled brain-wide mapping of cells activated by psilocybin, which may also facilitate comparisons between rodents and humans [89, 132]. Echoing findings with older methods of c-Fos quantitation after psychedelic administration [100], two whole-brain studies found robustly enhanced c-Fos expression in multiple neocortical areas. Region-based analysis found increased c-Fos expression in non-cortical regions such as the habenula and claustrum [89]. Using voxel-based comparisons, which are more sensitive to heterogeneous changes within brain subregions, Rijsketic and colleagues also found marked areas of decreased c-Fos expression after psilocybin, most notably in the hippocampal formation and hypothalamic nuclei regulating circadian rhythms and energetic homeostasis [132]. The contribution of these brain regions to the therapeutic effects of psychedelics are unknown.

Role of 5-HT2ARs. The leading hypothesis for how classical psychedelics such as LSD, psilocybin and DMT induce changes in cortical neuron structure is through activation of 5-HT2ARs [80, 82, 110, 133]. However, these drugs also have affinity for other serotonin receptor subtypes, such as the 5-HT1A and 5-HT2C receptors, as well as other neurotransmitter receptors like dopamine and adrenergic receptors. Recently, two groups were unable to completely block the physiological and behavioral changes associated with psilocybin administration using a 5-HT2R antagonist [114, 134]. However, it is unclear if these studies employed sufficient doses of the antagonist to fully occupy the receptor. Interestingly, Kaplan and colleagues also found that another 5-HT2AR antagonist, MDL100907, and a 5-HT2C antagonist, SB242084 also evoked antidepressant-like responses in one mouse model [54], highlighting that even nominally selective pharmacological tools to dissect serotonergic pharmacology may be insufficient to make well-founded conclusions about psychedelic mechanisms [135]. For a more complete discussion of the pharmacological mechanisms of psychedelic compounds, we refer the reader to the accompanying excellent reviews [79].

Network effects. The expression of 5-HT2ARs is quite high in layer 5 pyramidal neurons of the cortex [136], and this expression pattern likely plays an important role in the effects of psychedelics on cortical network dynamics, which have been studied using electrophysiological and functional imaging techniques. Both 5-MeO-DMT and DOI decrease the amplitude of low frequency cortical oscillations in a 5-HT2AR-dependent manner [137, 138]. In contrast, these drugs produce distinct effects on high frequency gamma oscillations in the cortex [139, 140]. Psilocybin may also decrease the power of low frequency cortical oscillations, while increasing gamma power [141]. A separate study found that local field potential power was decreased by DOI across a wide frequency range [142]. In contrast, a different phenethylamine 25C-NBOMe increased the power of high frequency cortical oscillations in rats via a 5-HT2AR-dependent mechanism [143]. In freely moving rats, electroencephalography studies have shown that LSD, psilocin, DOB, and mescaline all decrease spectral power in the 1–40 Hz frequency band [144]. Decreases in the amplitude of low frequency cortical oscillations seems to be a hallmark of psychedelics, though the potential role of these acute network changes in their therapeutic effects is unknown. Several studies have investigated the action of psychedelics in humans using imaging techniques that include functional magnetic resonance imaging (fMRI) and resting state MRI. Despite a variety of techniques, these studies consistently demonstrate a disintegration of connectivity within association networks after classical psychedelic administration [82], a finding which is remarkably reproduced by drugs which produce psychedelic-like effects through a variety of mechanisms [33]. Data in non-human species using these techniques is still sparse, and we refer the reader to excellent recent reviews on this topic [82, 145, 146].

Entactogens

Most randomized controlled studies of MDMA have tested it as an adjunct to therapy for PTSD [1, 71], as early data suggested that MDMA's effects were particularly well suited to helping patients recall and process aversive and traumatic memories [147]. Two small studies have also tested MDMA assisted therapy for social anxiety in autistic adults [148], and for alcohol use disorder [149] respectively. Mechanistic preclinical studies have mostly focused on the NAc, involved in prosocial and reward-related behavior [150], and the basolateral amygdala, involved in fear learning and PTSD [151] (Fig. 1), all behavioral processes theorized to play a role in MDMA-assisted psychotherapy.

NAc plasticity. In several species [68–70, 152], MDMA can produce an array of affiliative and prosocial behaviors. MDMA may also modify the sensitivity to social reward in mice, an effect lasting weeks after a single dose [153], reminiscent of the integration therapy process after an MDMA experience [147]. Insight into relevant social circuitry came from a seminal series of studies on the mechanism of pair-bonding in voles which focused attention on oxytocin, a neuropeptide known to play critical roles in social and affiliative behaviors [154, 155]. The importance of the NAc, a major reward processing center, was demonstrated by showing that direct infusion of an oxytocin receptor antagonist into this area prevented pair bond formation in prairie voles [150], and subsequent work in mice demonstrated that oxytocin in the NAc enhanced social reward learning through the downstream release of serotonin, and ultimately by activation of the 5-HT1B receptors on excitatory inputs to the NAc [156]. Remarkably, serotonin in the NAc, whether released optogenetically or by local infusion of MDMA, was sufficient to evoke comparable prosocial behaviors as systemically administered MDMA [68, 74, 156]. However, a recent mouse study challenges this simple model, showing that prosocial effects of MDMA can be induced by infusing MDMA directly into the basolateral amygdala, an effect blocked by local infusion of a 5HT1a antagonist [157]. While these respective studies require independent replication, it appears likely that the network governing social approach behavior can be manipulated through multiple nodes.

The leading candidate for plasticity that could explain the persistent effects of MDMA on social reward is long-term depression (LTD) at excitatory synapses onto medium spiny neurons in the NAc [68, 156, 158]. In ex vivo brain slice recordings, LTD at these synapses obeys all the same pharmacological properties as the prosocial behaviors under investigation: both can be triggered by oxytocin and MDMA, and blocked by a 5-HT1b antagonist. However, this form of LTD is unlikely to be specific for prosocial behavior as this same phenomenon is associated with behaviors related to mood, addiction, and motivation [159–161]. Moreover, plasticity in vivo may have strong context dependence, in that MDMA may only evoke certain forms of circuit physiology and plasticity when administered in a social setting. We speculate that future studies will find that behavioral output strongly depends on which excitatory inputs to the NAc undergo LTD, and plasticity is furthermore likely to depend on multiple neuromodulators acting in concert within the NAc, like for example, dopamine, which has a known role in both prosocial behavior and social reward learning [150, 162, 163].

Inputs to the NAc. Previous reports suggest that both dopaminergic and serotonergic receptor-targeting drugs can depress excitatory synaptic transmission within the NAc [68, 156, 164, 165]. These early finding have been greatly refined through a comprehensive study of four major glutamatergic inputs to the NAc, including basolateral amygdala, prefrontal cortex, ventral hippocampus, and paraventricular thalamus [158]. Importantly, there was a clear parallel in the pattern of synaptic filtering resulting from bath-applied dopamine or serotonin as compared to drugs, methamphetamine (METH) and MDMA, that release the same neuromodulators, respectively. Despite the internal consistency of these electrophysiological findings in the NAc, using optogenetics to apply similar patterns of input-specific suppression within the NAc in vivo was not, on its own, sufficient to explain simple behaviors like social approach or conditioned place preference. The limits of translating ex vivo slice recordings into behavior are well known, most notably caused by the need to cut afferent pathways, and the need for tight electrical and chemical control of the postsynaptic cell being recorded. Explaining the unique prosocial effects of MDMA requires a more sophisticated, comprehensive, and unbiased approach than conventional surveys of ex vivo synaptic physiology in a brain area of interest. Future work using brain-wide imaging techniques may reveal a more extensive network of circuits involved in both the acute and persistent prosocial effects of MDMA.

Basolateral amygdala. A substantial body of work has linked abnormal fear learning and PTSD to pathological changes in the function of the amygdalar complex [125, 126, 151]. MDMA disrupts fear memories in a widely used rodent model for PTSD [75, 166, 167], wherein a conditioned fear memory is extinguished by re-cueing the memory in a safe context. Two research groups, working in mice and rats respectively, have found that administering MDMA during extinction training resulted in a persistent reduction in both contextual and cued expression of learned fear [75, 76, 166]. Interestingly, direct infusion of MDMA into either of two key nodes of fear learning circuitry, the amygdala and infralimbic cortex, could recapitulate the effect of systemic MDMA, highlighting the relevance of this circuit for fear extinction. In one study, the authors linked MDMA action in the amygdala to the peptide brain-derived neurotrophic factor (BDNF), showing that infusing an antibody to BDNF in the amygdala, but not in another brain region, blocked MDMA's enhancement of fear extinction [75]. Further supporting a role for plasticity in MDMA-enhanced fear learning comes from histological analyses showing marked bidirectional changes in the morphology of neurons from the amygdala after trauma conditioning versus after treatment with MDMA [76].

Studies of MDMA in fear extinction models are still sparse, and not always consistent. Contrasting with prior results, Hake and colleagues did not find that MDMA impacted fear extinction, but rather, when given right after re-exposure to a traumatic cue or context, disrupted memory reconsolidation [167]. Further animal modeling studies may clarify the parameters needed to replicate the effect of MDMA on fear extinction in human subjects [64, 77].

Importance of 5-HT. Investigators consistently find that SERT-mediated 5-HT release is necessary [68, 153, 166], and potentially sufficient [74], to account for the putative therapeutic mechanisms of MDMA across disease models. Notably, these models' differences could inform human mechanistic trials. Fear extinction does not involve any particular social context, and mouse data suggest that 5-HT release in either the infralimbic cortex or basolateral amygdala can fully account for MDMA's effect on fear memory [75]. In contrast, social behavioral models find that 5-HT release in the NAc [68, 74, 153] or basolateral amygdala [157] explain MDMA's effects. Various 5-HT receptor subtypes appear necessary [68, 153], though it is unclear if any one subtype's activity can reproduce MDMA's prosocial effects. Finally, though MDMA and oxytocin actions overlap [28, 153, 156], available data in rodents [68, 168], and humans [28, 64] suggest oxytocin receptor signaling is not required for MDMA's acute effects, but may be involved in longer-term processes initiated by MDMA effects [153, 169].

MDMA modulation of dopaminergic reward circuits. Despite its reputation as a drug of abuse itself [16], MDMA may have a role in treating SUDs [149]. The abuse liability of MDMA, like many other psychostimulants, can be attributed to its release of dopamine in the NAc, in part by action at the dopamine transporter (DAT) [68, 170–172]. Yet, the psychological and behavioral effects of MDMA in human subjects contrast strongly with the closely related psychostimulant, METH. While MDMA and METH share similarities in structure and pharmacological mechanisms [173, 174], METH has a higher abuse liability in preclinical models [175] and, accordingly a more devastating societal impact. The unique prosocial properties of MDMA, specifically serotonin release into the NAc, may be mechanistically linked to its comparatively lower abuse potential. Recent work defining the circuit mechanisms that link opioid craving and social deficits further supports targeting serotonergic mechanisms in the NAc as a novel, viable treatment strategy for SUDs [176].

Alternatively, the prosocial effects of MDMA might simply correlate with its reduced abuse potential relative to METH given that the ratio of serotonin to dopamine elevation in various brain regions could be a key determinant of a compound's abuse liability [177]. In fact, the serotonin elevating properties of cocaine appear to suppress its full addictive potential [178]. Drugs that elevate serotonin levels, but lack MDMA-like prosocial effects, can decrease compulsive lever pressing leading to stimulation of dopaminergic neurons in the ventral tegmental area (VTA) [178]. Serotonin appears to reduce compulsive drug-seeking behavior by stimulating 5-HT1B receptors on neurons in the orbitofrontal cortex projecting to the dorsal striatum [178]. Furthermore, stimulation of 5-HT2C receptors can reduce compulsive drug-seeking behavior [179] and decrease dopamine release into the striatum [180]. The exact circuits mediating the antiaddictive effects of 5-HT2CR stimulation have not been precisely identified, though the PFC and VTA have been implicated [181, 182]. Complicating matters further, genetic deletion of the 5-HT2BR, or a systemically administered antagonist, completely abolishes the psychomotor stimulating and reinforcing effects of MDMA, as well as both MDMA-evoked serotonin and dopamine release in the NAc [183, 184]. These findings suggest that, at least in the NAc, serotonin and dopamine have a complex regulatory relationship that may not be easily amenable to pharmacological dissection. Rather, identification and control of circuits impacted by the serotonin-releasing properties of MDMA may ultimately lead to strategies to reduce its addictive liability and potentially endow it or its derivatives with antiaddictive properties [185].

THE GAP BETWEEN CLINICAL AND PRECLINICAL STUDIES

In the modern era, the largest controlled studies of drug-assisted therapy involve psilocybin or MDMA. Most clinical trials with MDMA and psilocybin have a similar structure involving three phases: preparation, drug administration, and integration therapy [186, 187]. This structure has been applied to therapy for a range of conditions including depression [3, 6, 8, 83], PTSD [1, 71], eating disorders [188], and multiple SUDs [84, 149, 189, 190]. Preparation involves an examination of personal goals and expectations for treatment [191], and is often tailored to the patient's disease condition [191, 192]. The drug administration itself is the focal point of the therapeutic process, as it produces both direct biochemical effects and profoundly altered states of awareness, as we have discussed in a previous section. Integration therapy

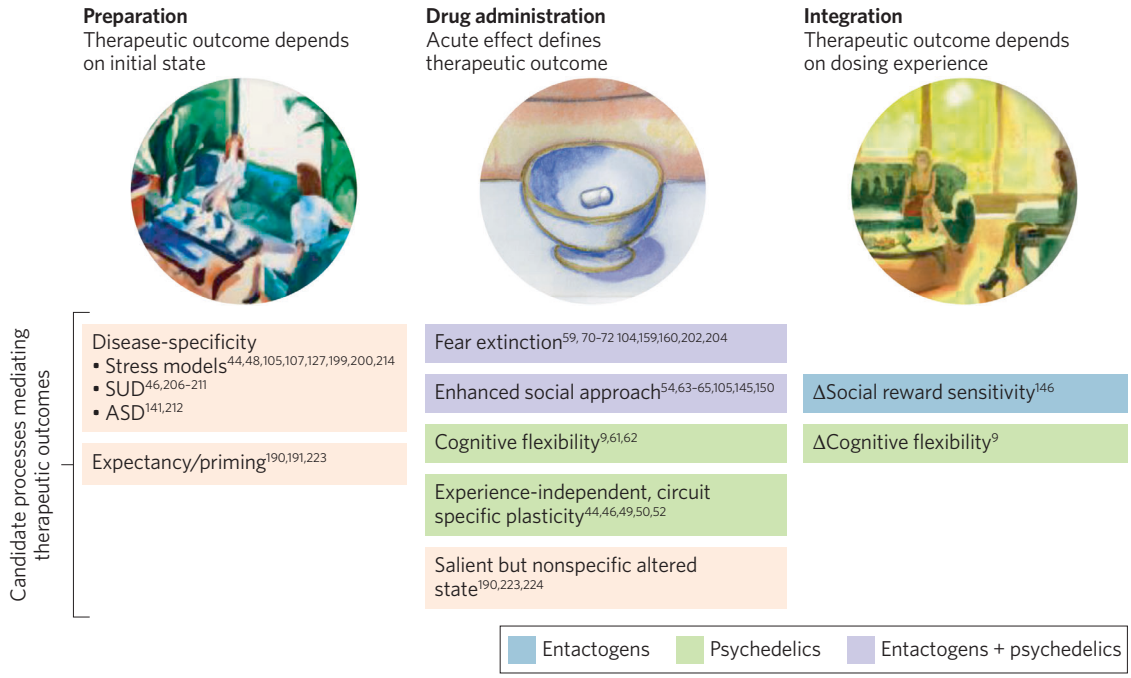

Fig. 2 Candidate processes mediating therapeutic outcomes. Most clinical trials testing psychedelics and entactogens employ a common structure of preparation, drug administration and integration. These phases of care may all contribute to clinical outcomes, but there are few clinical studies where these factors are clearly dissociated. Preclinical (non-human animal) studies model various aspects of this overarching therapeutic structure. *Preparation* includes psychological states prior to dosing that are influenced by expectancy, intent, and underlying psychiatric disease. *Drug Administration* includes the acute behavioral and subjective effects induced by the drug, which may be influenced by the setting in which they are administered. *Integration* includes behavioral changes that may be leveraged for further therapeutic benefit. These cognitive, emotional, and behavioral processes have been evaluated for entactogens (blue), classical psychedelics (green), or both (purple).

occurs after the drug experience and aims to provide a cognitive and emotional understanding of the experience, an understanding which may be incorporated into one's life for lasting therapeutic benefit.

While it is believed that the best therapeutic outcomes result from the combined effect of these three phases of therapy [192, 193], this hypothesis has not been rigorously tested. In fact, treatment of depression with ketamine often does not involve preparation or integration phases [194], and it is unclear if ketamine and psychedelics are distinct in this respect. There is little clarity on how preparation, drug administration, and integration phases interact with each other, and whether all elements must be present for each drug-assisted therapy and clinical indication. This lack of understanding is a major impediment to reducing the cost, increasing accessibility, and developing alternative therapeutic strategies with improved safety and efficacy [17]. Though the challenge of unraveling the tangle of drug-specific and non-pharmacological factors involved in psychedelic-assisted therapy is well known [23, 36, 195–199], definitive answers are still scarce. First, there are technical hurdles, including how to design convincing active placebos and maintain treatment masking for both patient and practitioner [200], all the while maintaining a semblance of similarity between how care is delivered in a clinical trial setting, versus how psychedelic and entactogen-assisted therapies are delivered in actual practice. Moreover, there are major ethical considerations for studies aiming to manipulate non-pharmacological factors like expectancy and integration therapy. In addition to the need for transparent informed consent, arguably a non-pharmacological intervention in its own right, therapeutic support is often considered an important safeguard for patient safety, especially when dealing with high-risk patient populations [38]. Furthermore, that "support" may in itself be a highly active treatment with its own attendant risks that are still poorly characterized and underreported [201–203]. For the near-term future, clinical trials and clinical practice with psychedelics and entactogens are very likely to continue incorporating non-pharmacological elements. In our attempts to understand how these complex therapeutics work, researchers ought to be cognizant of how these factors may translate into preclinical models, if not actively testing their impact.

Mechanistic studies in nonhuman subjects can shed light on these respective processes through controlled manipulations of identifiable, evolutionarily conserved behavioral and physiological processes. Here we give special focus to animal models, both in terms of the mechanisms they help illuminate and the predictions they can make for human therapeutic research (Fig. 2).

Modeling therapeutic preparation

Among the phases of psychedelic-assisted therapy described above, "preparation" may be the most difficult to reproduce in nonhuman subjects. During this preparatory period, patients are encouraged to reflect on their experiences, emotions, and motivations. Preparation helps to set the stage for the drug experience and is believed to have a significant impact on the outcome of the therapy. Notably, expectations in and of themselves have a powerful modulating effect on many types of therapeutic outcomes, and as part of a broader "placebo effect", may account for a significant portion of observed effect sizes in psychedelic trials [196, 198, 204]. A recent unpublished clinical study demonstrated that when complete masking integrity ("blinding") was achieved with surgical anesthesia, the antidepressant response in control and ketamine-treated arms was equivalent [205], and comparable to the large effect sizes observed in previous ketamine studies [11]. At present, expectancy is rarely if ever measured in psychedelic trials, therefore its

precise moderating effect on outcomes is unknown. While it seems far-fetched to suggest we can instill expectations in rodents about the effects of psychedelics on stress-induced symptoms, some innovative attempts to model placebo effects in mice have been attempted [206]. This field is relatively unexplored.

The importance of mental preparation rests on the assumption that psychedelic experiences have a sensitive dependence on the initial state of the subject. While we may not have access to the internal state of a mouse, we can ask whether perturbations of internal state, such as through stress paradigms, alter the effects of psychedelics or entactogens. In patients, this may correspond to asking whether drug effects depend on the presentation of particular disease symptoms. For classical psychedelics, the most well-powered clinical studies have dealt with major depressive disorder [3, 6, 8, 83] and alcohol use disorder [84, 207]. For entactogens, MDMA-assisted therapy for PTSD has the strongest evidence [1, 208]. Does the outcome of administering a psychedelic or entactogen depend on the diagnosis of a specific psychiatric indication? Scales used in clinical trials are primarily designed to detect presence or absence of a disease state rather than a dimension of behavioral change and are thus poorly equipped to answer this question. However, studies of healthy volunteers and secondary analyses of therapeutic trials suggest that for psychedelics and entactogens, respectively, similar acute and long-term behavioral effects occur regardless of the initial disease state [26, 83, 147, 209, 210].

Psychedelics. Controlled animal studies shed some further light on the role of an initial disease-like state on treatment with psychedelics. Stress models are commonly used to recreate a behavioral state that has features similar to human depression, in that they reproduce some of the same deficits in discrete behavioral domains such as reward processing, prosocial behavior, and threat detection [211, 212]. Taking ketamine as an example, several studies, including one from a multi-lab consortium, found that inducing significant stress prior to ketamine administration altered the persistent effect of the drug on simple behaviors including the forced swim test, sucrose splash test, novelty-suppressed feeding and escape from foot shock [213–215], though other groups have found similar results in non-stressed animals [213, 216, 217]. Ketamine is also reported to reverse specific stress-induced structural changes to cortical dendrites [48] as well as dopaminergic system function [218]. With respect to psychedelics, several groups have demonstrated therapeutic-like behavioral changes on measures such as forced swim, tail suspension, fear extinction learning, sucrose preference, learned helpless, light/dark box, social interaction and novelty-suppressed feeding [49, 110–112, 114, 133, 134, 216, 217, 219, 220], though only some of these assays involved stress paradigms. For alcohol use disorder, at present, animal models have mixed success in capturing psychedelic-induced reduction in use [221–226].

Entactogens. In preclinical studies of MDMA, PTSD is modeled with fear-learning and extinction paradigms in which the outcome of interest is the extent of freezing behavior [75, 76, 166, 167]. Freezing, a fear-related response, is not usually expressed in untrained rodents. As a wide variety of fear conditioning training procedures are often employed (e.g., different numbers of foot shocks and shock intensities), it is often unclear which training procedures lead to typical Pavlovian conditioned responses and which result in pathological fear memories—memories that are resistant to normal extinction processes and better model PTSD. Thus, it is difficult to assess the extent to which MDMA-enhanced fear extinction represents a disease-specific process versus a general enhancement of extinction learning.

The disorder-specific (or nonspecific) effects of MDMA are easier to discern for another emerging clinical indication for MDMA, social anxiety associated with autism [148]. Across several mouse models of autism, MDMA shows an enhancement of sociability [227] that is comparable to its effects in wild-type mice [68, 69, 227] and rats [70], in contrast to a more specific 5-HT1B agonist, which restores sociability in rodent models of autism but does not have prosocial effects in wild-type mice [227]. While MDMA might be useful for treating neuropsychiatric conditions with social components, it clearly produces prosocial effects in healthy individuals as well [28].

Thus, the available data suggest that both psychedelic compounds like psilocybin and entactogens like MDMA can exert measurable effects regardless of the initial state of the subjects depending on the specific assay employed. Notably, the sensitivity of these behavioral measures depends on the species under investigation [228]. An ideal test of state-dependence would involve direct comparison of behavioral effects and neurophysiology induced in both stressed and unstressed rodents, though few studies have attempted to implement this experimental design [229]. Cellular studies, prepared from presumably unstressed animals, have revealed that psychedelics from a variety of chemical classes can promote the growth of dendrites, increase dendritic spine density, and change dendritic spine morphology [104–109]. An intriguing recent study demonstrated that repeated administration of LSD increased cortical neuron spine density in both stressed and unstressed mice, though the magnitude of the effect appeared to be greater in stressed animals [111].

Modeling setting

Complementing "set", "setting", or the environment in which a psychedelic drug or entactogen is taken, is widely believed to shape the subjective experience [36, 230]. In turn, these shaped experiences are thought necessary for therapeutic outcomes [187, 231, 232], implying that some therapeutic psychedelic states might be preferentially accessible in specific environments. This belief has led clinical researchers to administer psychedelics in controlled environments, often in conjunction with psychotherapy [8, 233]. We are unaware of any controlled studies where environmental variables during psychedelic trials are systematically manipulated and therapeutic outcomes are measured. Most evidence supporting a role for setting comes from human observational studies and a small number of randomized controlled trials wherein changes in the quality of psychedelic experiences are associated with variables like the context of use (e.g., recreational versus religious) and environmental features (e.g., music playlists) [36, 230, 234].

On the other hand, randomized, controlled trials suggest that the context in which psychedelics are delivered may alone be responsible for some psychedelic-like subjective effects [235], as well as a drug-independent therapeutic effect [236]. Furthermore, psychedelic use in uncontrolled, naturalistic environments such as mass gathering events, may similarly elevate mood and promote social connectedness [209, 237]. These latter studies call into question whether setting determines the efficacy of psychedelic therapy or simply represents an independent effect on therapeutic outcome. Recent imaging experiments in mice tested the interaction of psilocybin and environment in mice by quantifying brain-wide cFos expression [132]. Against intuition, the authors found that despite large effects of environment and drug, interactions were quite sparse. How this sparse interaction at the level of neural activity relates to psilocybin-evoked behavior is still unclear. In contrast, for MDMA, rodent studies have clearly demonstrated context-specific effects. When MDMA is administered in a social setting versus a nonsocial setting, mice subsequently express a lasting enhancement of social reward sensitivity [153].

Thus, it is unclear whether psychedelic or entactogenic states, and their underlying neural dynamics, represent two independent effects of drug and setting, or if these factors interact to create setting-specific therapeutic effects. In principle, chronic stress

models could be used to alter 'set' in animals, while administration of psychedelics or entactogens during an acutely stressful or non-stressful situation might model 'setting.' Clearly, more data on the interaction of environmental context and psychedelic drug effects are needed, and it will be important to define these interactions for each drug and context. If carefully controlled settings are intended to constrain the chaos of psychedelic subjective effects, it would be reasonable to wonder why reported sessions seem as likely to result in 'blissful' versus 'terrifying' trips, either of which may ultimately be deemed meaningful and therapeutic [203, 231, 238].

Modeling integration

Integration. The third phase of therapy in most modern psychedelic trials is termed "integration". The importance of integration therapy has long been appreciated by therapists—in testimony to the DEA regarding scheduling MDMA under the Controlled Substances Act, George Greer, an early pioneer of the use of MDMA as an adjunct to psychotherapy, wrote: "I believe that long term beneficial results are entirely dependent on the person following through with ongoing therapeutic work…" [239]. In terms of specific therapeutic practices, integration therapy is still a loosely defined concept, however most definitions involve implementing and incorporating into one's life the key insights gained during the psychedelic experience [240]. Framing this phase of therapy explicitly in reference to a psychedelic experience differentiates integration from more conventional psychotherapy like Cognitive Behavioral Therapy, although many of the same psychotherapeutic concepts may be employed [192]. Implicit in the concept of integration is that the drug experience, while necessary, may not be sufficient to produce treatment benefit. This concept is most consistent with the drug-as-behavioral catalyst model (introduced above), wherein a psychedelic or entactogen enables movement through an ongoing therapeutic process, lowering the barrier to achieving a desired treatment outcome. Changes in behavior and neurophysiology during and after drug administration are not therapeutic per se, but rather facilitate therapeutic changes. In contrast, in a drug-as-psychoplastogen view, drug-induced plasticity within select neural circuits is essentially synonymous with therapeutic behavioral plasticity. Here, as with conventional selective-serotonin re-uptake inhibitor (SSRI) treatment, integration therapy is not necessary to achieve behavioral changes, though of course additional psychotherapeutic support may confer added or synergistic benefits. Once again, these two models of therapeutic efficacy lead to substantially different designs for preclinical experiments, and predictions from mechanistic experiments will need to be tested for each drug and indication in humans.

Metaplasticity. A psychedelic or entactogenic experience may have long-lasting effects on the brain's ability to adapt to future experiences, a concept known as metaplasticity. Integration may take advantage of this unique metaplastic state. For example, Doss and colleagues found that, in depressed patients, psilocybin enhanced cognitive flexibility, which may reflect metaplasticity, for a period of weeks [9]. Remarkably, these changes did not necessarily predict improvement in symptoms of depression, and the relevance of persistently altered neural dynamics to alleviation of symptoms of depression is still strongly debated [9, 241, 242], further highlighting the need for translational models where more precise manipulations can be made.

A clear example of metaplasticity in preclinical research comes from studies of social reward learning in mice conducted by Nardou and colleagues. They found that a single dose of MDMA, LSD, psilocybin or ibogaine in adult mice enhanced the ability to express social conditioned place preference for several weeks, a trait that usually disappears in adult mice [153, 169, 243]. While this effect of MDMA and psychedelics may not be therapeutic on its own, it can enable subsequent social learning to take place, which could have therapeutic benefits. It is important to note that this process differs from other models of MDMA's therapeutic mechanism, where for example the acute prosocial effect of MDMA is therapeutic in itself, potentially by facilitating engagement with traumatic memories [58, 68, 70, 72, 244]. Similarly, in animal models where PTSD is modeled as fear learning, MDMA appears to facilitate fear extinction only when it is administered during presentation of the cue or context associated with an aversive experience [75, 76]. Given existing safety concerns associated with studying psychedelics and entactogens in clinical therapeutic trials, many investigators have opted to include integration as a potential means to prevent adverse outcomes. An interesting exception to this pattern is an early study testing the efficacy of the N,N-dimethytrypamine (DMT)-containing brew, called ayahuasca, for depression [245]. Palhano-Fontes et al. reported large and persistent antidepressant effects in the absence of any structured post-drug integration therapy. Similarly, Reckweg and colleagues observed a robust antidepressant response following administration of a single dose of 5-MeO-DMT to patients with treatment-resistant depression even in the absence of psychotherapy [246]. These studies suggest the need for controlled studies where outcomes are measured with varying degrees of post drug integration therapy.

A ketamine counterexample. Some inferences about the role of integration can be drawn from therapeutic studies of ketamine, noting again that there are important differences in the subjective effects [32] and potential mechanisms [35] as compared to psychedelics and entactogens. Most trials of intravenous ketamine for depression do not employ any particular integration therapy [194]. In these studies, patients report, on average, a 1–2 week treatment response from a single infusion and a potentially more durable antidepressant response after a series of treatments [11, 247–251]. These data suggest that therapeutic responses can be driven by drug effect alone (consistent with the *psychoplastogen model* of efficacy), though these effects may be enhanced in the context of psychedelic-style psychotherapy. Unfortunately, there are still few controlled studies investigating ketamine in this latter context [252–254], and no head-to-head comparisons of intravenous ketamine with and without integration (or other psychotherapy components) have been published. Preclinical studies on the mechanism of ketamine support a ketamine-as-psychoplastogen model [48, 109]. In particular, findings by Moda-Sava et al. have demonstrated a causal link between ketamine-induced cortical spinogenesis and therapeutic-like behaviors associated with resilience to stress.

The simplest psychoplastogen model of therapeutic efficacy, illustrated above by ketamine, predicts that drug-evoked changes in structural plasticity within adaptive circuits (e.g., cortical spinogenesis [80]) are directly coupled and virtually synonymous with therapeutic behavioral changes, as no additional integration-like process is modeled in studies which show antidepressant-like effects of psychedelic compounds [49, 51, 54, 114, 133, 216, 217]. While psychoplastogens appear to produce particularly robust changes in cortical neuron structure after only a single dose, drug-induced changes to neuronal morphology are not unique to psychoplastogens, and may not be therapeutic per se. Most, if not all, psychotropic drugs can affect structural plasticity in certain brain regions. However, it is important to consider the totality of a drug's plasticity effects on all neural circuits when assessing its usefulness as a therapeutic. For example, psychostimulants like amphetamine and cocaine can increase spine density in the PFC, but they also produce profound structural plasticity effects in mesolimbic circuitry, which has been hypothesized to underlie their addictive properties [255]. Moreover, these compounds can even display distinct effects on brain subregions, with self-administered amphetamine increasing and decreasing dendritic

spine density in the mPFC and orbital frontal cortex, respectively [256]. The widespread nature of plasticity changes following drug administration suggests a nuanced relationship between structural and functional changes in specific circuits and precise behavioral outputs that correspond to human therapeutic processes. The emergence of new techniques to manipulate regional plasticity [48] will undoubtedly aid in establishing causal relationships between discrete structural/functional changes and behavioral endpoints. Interestingly, it is possible that psychoplastogen-induced structural plasticity might be more selective than is currently appreciated. Studies with the psychoplastogens ketamine and TBG have demonstrated that a large portion of psychoplastogen-induced spine growth occurs at sites where stress had previously led to spine retraction [48, 53].

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

It is important that we construct meaningful animal models as we identify circuits, receptors and genetic changes that result from the administration of psychedelics and entactogens. In reviewing the conceptual frameworks and animal models above, we arrive at several pressing questions that are worth considering as we continue forth to investigate the circuitry and pharmacology underlying putative therapeutic effects of these compounds.

- To what extent does the subject's state prior to drug administration influence long term effects of a drug administration?
- Does the environment in which a psychedelic or entactogen is administered matter?
- What do the acute drug-induced experiences and biochemically induced neuroplasticity effects contribute to therapeutic effects?
- How critical is integration in improving or maintaining therapeutic response?

Answers to these questions are critical for maximizing the potential benefits of psychedelic and entactogen treatments while reducing the cost and complexity of such treatments and improving patient access. The mechanisms of action for psychedelics and entactogens are not fully understood, but they share key features that suggest a convergence of neural circuits driving rapid plasticity that has yet to be fully elucidated. Both drug classes face similar challenges in scaling up therapeutic delivery and require further investigation to understand the long-lasting changes they may induce in the brain. The role of set and setting, as well as the environment in which the drugs are taken, will require creative, novel approaches both in human and animal experiments. Psychedelics and entactogens are crude, yet powerful tools that have the potential to drive lasting psychological transformations. Understanding their mechanisms may well lead to new therapeutic avenues for a range of psychiatric conditions.

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AUTHOR CONTRIBUTIONS

BDH: Writing—original draft, Writing—review & editing. DEO: Writing—original draft, Writing—review & editing.

FUNDING

BDH acknowledges support from the National Institute of Mental Health under award R01MH130591. DEO acknowledges support from the National Institute of General Medical Sciences and the National Institute on Drug Abuse under awards R01GM128997 and R01DA056365, respectively.

COMPETING INTERESTS

BDH is on the scientific advisory boards of Osmind and Journey Clinical and is a consultant for Clairvoyant Therapeutics and Vine Ventures, all unrelated to the present work. DEO is a co-founder of Delix Therapeutics, Inc., serves as the Chief Innovation Officer and Head of the Scientific Advisory Board, and has sponsored research agreements with Delix Therapeutics. Delix Therapeutics has licensed technology from the University of California, Davis.

ADDITIONAL INFORMATION

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