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REVIEW ARTICLE

Learned Helplessness As a Potential Transdiagnostic Therapeutic Mechanism of Classic Psychedelics

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Abstract

Background: Emerging literature suggests that classic psychedelics may have efficacy in treating mood and substance use disorders in humans. This has raised questions regarding the primary therapeutic mechanism of these compounds. Here, we hypothesize that the reversal of and resilience against learned helplessness may be an important driver of the therapeutic mechanisms of classic psychedelics. Furthermore, we argue that the learned helplessness paradigm can provide a robust model to investigate the behavioral and mechanistic effects of classic psychedelics in both clinical and preclinical experiments.

Opinion: We highlight the learned helplessness model and its potential utility in the psychedelic sphere for several reasons. First, learned helplessness is a robust phenomenon observed across multiple mammalian species including humans, and has been well described in terms of its neurobiology, behavioral effects, and clinical implications; current efforts in psychedelic research and theories of psychedelic mechanisms have yet to achieve this level of integration. Interestingly, there is substantial overlap in the neural circuits governing resilience against learned helplessness and psychedelic actions—such as those involving the dorsal raphe nucleus. Furthermore, our hypothesis that classic psychedelics can reverse helplessness behavior fits with much of the current preclinical data, which has shown that psychedelics improve performance in behavioral despair tasks in rodents. Here we make the case for bringing attention to these congruencies in an effort to advance toward mechanistic, behavioral, and transdiagnostic insights into the therapeutic effects of classic psychedelics, with the potential for learned helplessness to help explain some positive effects across levels of analysis.

Keywords: translational, serotonin 2A, psychopathology, therapeutic mechanisms

Introduction

Serotonin 2A (5-HT_{2A}) receptor-mediated or ''classic'' psychedelics,[1] which prominently include psilocybin and lysergic acid diethylamide (LSD), have been shown to exert substantial beneficial effects in patients with mood disorders such as depression and anxiety[2–11] as well as in patients with substance use disorders.[12–14] The potential efficacy of serotonergic psychedelics, particularly psilocybin, in treating mood and substance use disorders raises questions regarding their therapeutic mechanisms, which largely remain unknown.

Below we begin by highlighting the current literature that aims to answer these questions and indicate two primary perspectives—one that places emphasis on the

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neurobiological mechanisms, and the other that focuses on cognitive (and subjective) mechanisms. Interestingly, very few theories to date have been able to integrate across levels of analysis.

Some have described a mechanism of enhanced plasticity, even proposing the term ''psychoplastogen,'' which refers to the neuroplasticity resulting from these substances, to be more appropriate than the term psychedelic.[12–14] Although the neuroplastic effects of psychedelics are likely an important factor, some researchers have pointed out the lack of specificity in such a proposal—it is not well understood where exactly these psychedelic-mediated neuroplastic changes are happening in the brain, how long these changes last, and why such increased plasticity would necessarily lead to therapeutic outcomes of such substances.

Although there is a dearth of knowledge about the therapeutic mechanism of psychedelics, recent literature suggests that there have been attempts to answer some of these questions using preclinical models. To date, preclinical studies have primarily focused on cortical regions to understand neuroplastic changes associated with psychedelics.[15,16] Other groups have shown data that indicate the possibility of reopening critical period-like windows in the brain, which are associated with a heightened plastic state, as possible mediators of the therapeutic capacity of psychedelics[17] (Nardou et al., 2023, *in press*). Work in this area is still preliminary, and it is still not well understood how these effects might produce therapeutic capabilities.

Although preclinical studies have allowed us to probe the molecular and cellular underpinnings of the neurobiological changes associated with psychedelics, clinical studies have provided evidence regarding mechanisms described at the psychological level of analysis that would necessarily rely on more complex neurobiological models than those described above. Several studies have found that the extent to which a psychedelic experience is considered ''mystical'' by participants is correlated with a moderate-to-high degree with various treatment outcomes.[5,18–22] Here, mystical experience is operationalized based on conceptualizations from philosopher William James and others[23,24] in scales such as the Mystical Experience Questionnaire (MEQ).[25]

Other mental processes that have been proposed as mediators of the beneficial effects of psychedelics include insight,[18] psychological flexibility,[18] and emotional breakthrough.[26] According to this view,[22] the specific qualities of the acute subjective effects, context, salience, and significance of the experience itself are of paramount importance, and that various self-report constructs may help to clarify the persisting therapeutic mechanisms of psychedelics.

Few attempts have been made to integrate neurobiological and cognitive mechanisms or subjective effects into a coherent account.[27] One of the models that comes closest to such an integration is the thalamic gating account of psychedelic effects—cortico-striatal-thalamic-cortical model (CSTC).[28–30] This model attempts to explain the overwhelming sensorium as well as the reduction in elements of cognitive control characteristic of the psychedelic experience through the disruption of cortical striatal-thalamic loop that facilitate top-down control of sensory information. Preclinical studies strongly suggest that psychedelic-mediated cortically driven altered perception is gated through the thalamus with thalamocortical afferents expressing the 5-HT_{2A} receptors on presynaptic boutons.[31,32]

Psychedelic-mediated 5-HT_{2A} receptor activation can result in enhanced glutamate release from the thalamic afferents onto the primary sensory cortices, resulting in overexcitation of the cortex or ''sensory overload.'' This model can account for the acute effects of psychedelics, but largely fails to provide an explanation of the involvement of this circuit in mediating the therapeutic effects.

Another model that can facilitate arguments to integrate levels of analysis is the claustro-cortical network model, the claustrum-cortical circuit.[33] The claustrum is thought to coordinate the recruitment of cortical networks in response to changing task demands, especially in the case of increased cognitive demand, implicating a role for the claustro-cortical circuits in the initiation and engagement of psychological processes such as attention and cognitive control.[33] A recent study has also shown that the claustrum is causally involved in mediating stress-induced anxiety in mice.[34]

The claustrum is densely packed with 5-HT_{2A} receptors, which are targeted by almost all classic psychedelics. This raises an intriguing possibility that one of the therapeutic targets for psychedelic drugs may be the claustrum. This suggestion is further substantiated by a recent observation that the acute psilocybin-associated changes in the task-free functional connectivity or ''integrity'' of the default mode network (DMN) and the frontoparietal network are correlated with the changes in the claustrum.[35] However, it remains difficult to comment on the mechanism of therapeutic action of psychedelics across these networks given the preliminary nature of these studies and the lacking ties to behavior.

In addition, the balance of positive and negative affective processing and the neurobiological substrates of these processes,[36] as well as the overall capacity for cognitive flexibility and cognitive control,[37] have been offered as potential transdiagnostic therapeutic targets of psychedelics in both mood and substance use disorders, where negative affect[38,39] and cognitive flexibility[40–42] disruptions can be considered key components of the development and maintenance of both families of disorders. Psilocybin administration may reduce negative

affect and increase positive affect for weeks to months after a psilocybin administration session[20,36,43] and reduce amygdala reactivity for at least a week after psilocybin administration.[35]

It has also been shown that there is an increase in cognitive flexibility, associated with altered activity and connectivity of brain regions involved in executive control, for at least a week after psilocybin treatment in both healthy participants and patients with major depressive disorder.[36,37] However, these findings lack specificity as compared with other treatments.

Despite the above observations, there are hardly any robust models from the clinical and preclinical literature that can substantiate the mechanism for the therapeutic action and efficacy of psychedelics.[27] Ideally, a model of the therapeutic mechanisms would explain findings of therapeutic efficacy in humans *and* findings that suggest therapeutic efficacy in rodents, thereby relying on processes that do not necessitate language or abstract thought.

In this article, we suggest that learned helplessness may be a helpful concept going forward in understanding the beneficial effects of psychedelics across mammalian species. More specifically, the reversal of and subsequent resilience to learned helplessness could act as an underlying mechanism of the therapeutic effects of psychedelics. This hypothesis, if confirmed by future research, would also give us a robust model to study the effects of psychedelics in preclinical studies (as has been done in a select few cases discussed below[44]).

Although we focus on learned helplessness as the most prominent example in the current review, we will also discuss other models of stress-induced anxiodepressive behaviors wherever helpful, with an understanding that these models are related, yet distinct from the learned helplessness paradigm.

Learned helplessness has the virtue of being deeply theoretically grounded, which comports well with recent calls for robust efforts toward investigating the therapeutic mechanisms of psychedelics[45] and has the benefit of being relatively well specified with respect to the neural circuits involved. Intriguingly, recent findings in optogenetic studies on learned helplessness in rodents highlight a neural circuit featuring the ventromedial prefrontal cortex (vmPFC) and dorsal raphe nucleus (DRN)[46] that was also explored in earlier decades of psychedelic research but has since been largely neglected.[47]

Below we present the learned helplessness paradigm and the key studies that led to its development, and then show how current preclinical and neuroimaging findings on psychedelics demonstrate some overlap with this framework on both biological and behavioral levels. We conclude by proposing that learned helplessness could be a productive model in psychedelic research.

Learned Helplessness

Learned helplessness is a phenomenon describing an organism's failure to avoid an escapable aversive situation after having experienced inescapable aversive stimuli in a different previous context.[48] The now classic experiment demonstrating learned helplessness exposed two groups of dogs to the exact same series of foot shocks—the only difference being that the first group could press a panel to turn off each shock (escapable), whereas the second group simply received the same shock pattern as the first regardless of behavior (inescapable). A third group received no shocks at all (control).

The next day, animals from each condition were individually put into a different environment—called the shuttlebox escape—where foot shock *is* escapable (by jumping out of the box). The replicated result is that the animals that were exposed to the previously inescapable condition will now fail to escape in the new environment, whereas the group who experienced the escapable condition and the group who received no shocks (control) will both tend to successfully escape the shuttlebox.[48] The authors called this behavior ''learned helplessness'' since it seemed that those in the inescapable condition learned to expect that aversive stimuli will be independent of their response.

In the decades since learned helplessness was initially formulated, the phenomenon has been replicated many times across several species, including in cats,[49,50] rodents,[51–55] as well as in humans.[56–58] Learned helplessness has been associated with various animal models of depression,[56–58] as well as depression in humans,[59–62] overlapping with eight of the nine symptoms listed for major depressive disorder in the *DSM-5*.[63] Given that learned helplessness is a phenomenon characterized across multiple mammalian species and relatively well described at the neurobiological level, it becomes a good example to assess the mechanism and efficacy of drugs against stress-induced mood-related disorders.

Interestingly, the literature associated with learned helplessness overlaps with the literature on the mechanism of action of classic psychedelics across at least two domains: (1) the neural circuits involved as seen in both clinical and preclinical studies and (2) altered molecular and cellular signatures as seen predominantly in preclinical studies. We first address the mechanisms underlying learned helplessness, and then illustrate the substantial overlap with psychedelic actions.

The Neurobiology of Learned Helplessness

Substantial work has now been done to elucidate the basic neural circuit responsible for learned helplessness,[63] which is described as follows:

First, repeated aversive shock activates serotonergic neurons in the DRN—the locus of serotonergic neurons in the central nervous system. This central node projects

to numerous regions, including the periaqueductal gray (PAG), striatum, and the amygdala. In the PAG, serotonin (5-HT) release from the DRN inhibits active escape behavior (i.e., resulting in passivity), whereas in the amygdala 5-HT potentiates fear/anxiety. Specifically, Maier et al. showed that lesioning the amygdala reduces freezing behavior.[64]

A related effect was found for humans with bilateral damage to the amygdala: these patients had reduced defensive behavior in response to an aversive stimulus, despite intact memory that the stimulus was aversive.[65] Although Maier et al. showed that lesioning the amygdala reduced freezing behavior, they further showed that lesioning the DRN reduced both freezing *and* escape behavior, presumably because the DRN projects to both the amygdala and the PAG. It should be noted that lesioning a region is not comparable to simply inhibiting a circuit and may result in drastic and unexpected changes in behavioral response, which may be compensated for by other circuit mechanisms.

It is further interesting to note that 5-HT neuronal dynamics in the DRN can switch depending on the intensity of environmental threat, wherein activation of the DRN can result in reduced locomotion and escape behavior in a low-threat environment, but the same stimulation of the DRN can account for enhanced escape response in a high-threat environment.[66] Past work has demonstrated that electrical stimulation of the PAG produces stereotypical escape behavior.[67–69] More recently, it was also shown to encode key aspects of escape and avoidance behavioral responses with precision, assessing threat or risk, and predicting escape behavior in advance.[70,71]

Thus, activation of 5-HT neurons in the DRN leads to the key outcomes of helplessness: heightened anxiety and passivity through its actions on the PAG and the amygdala. The activation of the DRN by aversive shock causes a sensitization of these neurons, leading to several days of persistent effects, which explains the later failure to escape from the shuttlebox.

Second, the *detection* of control (i.e., from turning off the shocks by pressing the panel) can modulate the DRN activity that normally leads to helplessness. Control is detected by a reciprocal circuit connecting a population of neurons in the ventromedial prefrontal cortex (vmPFC) and the dorsal medial striatum. Once control is detected by this circuit, a unique population of cells in the vmPFC are activated and cause the inhibition (through GABAergic interneurons in the DRN) of those serotonergic neurons that are crucial in causing helplessness. Thus, it is the detection of control that drives a change in circuit activity and subsequently alters behavior (i.e., successfully escaping the shock in the escapable context).

Third, if the vmPFC to DRN pathway is activated by the detection of control, there can be a persisting change in circuit function that leads the organism to *expect* control in sufficiently similar circumstances in the future. If this circuit change occurs, stressors are then treated by organisms as if they were controllable, even if this is not the case. *The activation of this vmPFC to DRN circuit provides a resilience against helplessness responses in similar contexts going forward.*

This brief summary provides a simplified understanding of the phenomenon as it has been elaborated in rodent models[63] (Fig. 1). A substantial amount of work has been done in both human and animal models to support this mechanism.

Abstractly, the ability to determine whether a stressor is controllable or not is often key to action selection in stressful environments. In the learned helplessness paradigm, determining controllability leads to one of two behavioral outcomes: a controllable context prompts proactive goal-directed actions, whereas uncontrollable contexts prompt reactive ''spectator'' models that rely on

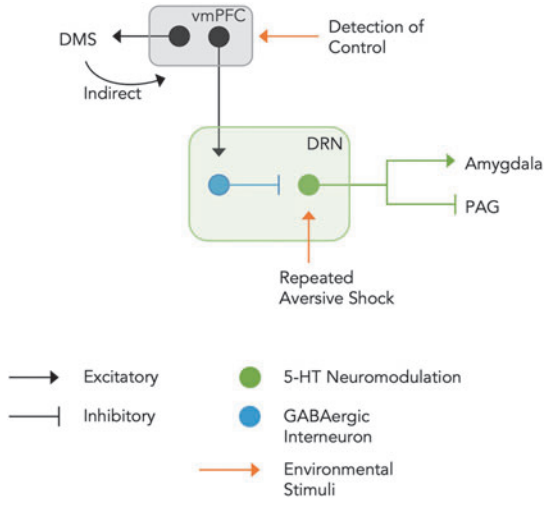

Fig. 1. Neurocircuitry of learned helplessness. Repeated aversive shock activates serotonergic neurons in the DRN, leading to an elevated fear/anxiety response mediated by the amygdala and diminished escape behavior (passivity) through the PAG resulting in learned helplessness. Detection of control, in contrast, leads to a top-down activation from the vmPFC of inhibitory interneurons onto serotonergic DRN cells, blocking the helplessness response. The DMS may be another input capable of activating the vmPFC through cortico-striatal-thalamo-cortical loops. PAG, periaqueductal gray; vmPFC, ventromedial prefrontal cortex; DMS, dorsal medial striatum; DRN, dorsal raphe nucleus.

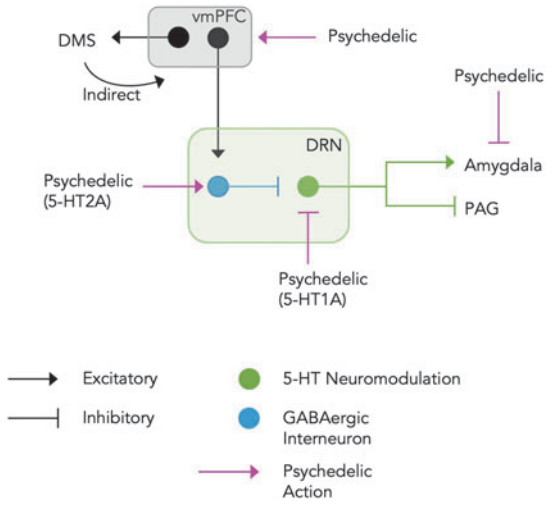

Fig. 2. The neurobiology of psychedelics and the learned helplessness circuit. Psychedelics could modulate the learned helplessness circuit in several ways. Some psychedelics directly inhibit DRN activity either through activation of 5-HT_{1A} autoreceptors on serotonergic DRN neurons, or by stimulating 5-HT_{2A} receptors on GABAergic interneurons of the DRN. Psychedelics may also influence top-down control of the DRN by modulating vmPFC activity. Finally, psychedelics may inhibit the amygdala either through direct agonism at 5-HT_{2A} receptors on parvalbumin-containing GABAergic interneurons or through top-down modulation of cortical regions.

an innate repertoire of behaviors. In one model of this process previously described,[72] the determination of controllability and the subsequent behavior (proactive or reactive) can be understood as an organism's estimation of its own agency, given the context.

When the stressful context is determined to be controllable, and thus the organism can exert agency, proactive reward-driven behaviors are triggered. When the stressful context is determined to be uncontrollable, and thus the organism cannot exert agency, reactive defensive behaviors are triggered.

This can also be understood from models that force a defeat-like state, where an individual eventually fails to save themselves, resulting in an enhanced anxiety and despair-like behavioral state, as well as enhanced passive avoidance response. In addition to the learned helplessness model (which itself is based on an inescapable stress paradigm), another classic example is social defeat stress, where a social confrontation between two male conspecifics results in a social defeat in the subordinate animal. This causes the defeated animal to ''learn loss,'' resulting in enhanced despair-like state on the forced swim test (FST).

Although this paradigm only accounts for the stress-related response in males, it is rather interesting that just witnessing the social defeat stress, without actively getting involved in the paradigm, is often enough to evoke enhanced anxiety and despair-like state in female rodents.[73,74] Even though both learned helplessness and chronic social defeat models account for the uncontrollability of the environment, which perhaps is instrumental in establishing negative behavioral states, it is important to acknowledge that these two paradigms are strikingly different in their design approach as well as the timing of exposure of animals to the stressful environment.

The passive stressed response of learned helplessness generalizes beyond the inducing uncontrollable environment and appears to be governed by a feedback mechanism within the DRN.

In the DRN, 5-HT_{1A} receptors are expressed on the soma and dendrites of 5-HT cells. 5-HT_{1A} receptors are inhibitory autoreceptors—that is, when they are activated, they inhibit 5-HT neuronal activity. Since axon collaterals from neighboring 5-HT cells release 5-HT onto these 5-HT_{1A} receptors, the DRN is effectively under self-restraint. In the helplessness model,[63] intense 5-HT activity during inescapable shock (but not escapable shock) desensitizes 5-HT_{1A} receptors, leading to a disinhibition, or sensitization, of DRN serotonergic neurons that persists for several days, leading to the behavioral traits of learned helplessness.[75]

Notably, the DRN receives most of its cortical input from the vmPFC,[76,77] an input that inhibits DRN activity (when control is detected) and blocks associated passive avoidance strategies. When the stressful environment is controllable, however, persisting passive behaviors do not develop. It has been suggested[63] that estimates of controllability are detected by a reciprocal circuit connecting a population of neurons in the vmPFC and the striatum.

Consistent with this model, it was shown that adopting proactive coping strategies exhibited greater vmPFC activity in the context of encountering stressors.[78] Moreover, it was shown that stimulating an area slightly above the mPFC through high-definition transcranial direct current stimulation increased adaptive behavior in environments with reduced controllability, providing causal evidence regarding the role of mPFC in mediating controllability estimates.[79] Optogenetic activation of specific neurons projecting from mPFC to DRN, a circuit strongly implicated in the regulation of despair-like behavior, results in the reversal of immobility on the FST, which is routinely used to assess for despair-like behavior in rodents (explained in more detail below).[80]

However, estimates of controllability require making statistical inferences about the environment[81] and likely

involve the coordination of multiple brain regions that are responsible for cognitive control (e.g., there is evidence that the DMN more widely plays an important role in determining controllability).[82–84]

Thus, greater estimates of controllability in the face of stressors are associated with the engagement of mPFC circuitry, which can then determine whether proactive agentic coping strategies are recruited.[72] As was shown in the original learned helplessness experiments, if an organism has previous experience with controllability, this reduces the occurrence of a helplessness response when exposed to subsequent inescapable shocks, a phenomenon termed ''immunization.''[63] This protective effect is both enduring and generalized (e.g., the escapable shock prevents learned helplessness not only from future inescapable shock but also from other stressors, like social defeat[85]). Importantly, immunization appears to occur through a persisting change in the same circuitry that governs controllability.[86]

For example, glutamatergic signaling in the mPFC through NMDA receptors is implicated in controllability-related behavioral response on the passive avoidance task in rats.[87] More specifically, Amat et al. showed that blocking vmPFC–DRN projections during escapable shock disrupted the generalization of active coping strategies in an uncontrollable context.[88] Furthermore, increased levels of proteins associated with neuronal function and plasticity, like phosphorylated extracellular signal-regulated kinases, were associated with enhanced immunization, whereas inhibiting the mitogen-activated protein kinase in the prelimbic region of the mPFC prevents immunization response.[87]

These results strongly suggest that the vmPFC–DRN circuit is modified after experiencing control during an aversive stressor, which then predicts an *expectation* of control in future environments—which could be considered a form of resilience.[87,88]

Overlap Between Psychedelic and Helplessness Neurocircuitry

There are several intriguing overlaps between the effects of classic psychedelics on the brain and the helplessness neurocircuitry described in the previous section. *Foremost of these is the activity of the DRN, which is responsible for eliciting helplessness behavior, and appears to be directly affected—in a way that could theoretically reverse helplessness—by classic psychedelics. In fact, the ability of psychedelics to reduce DRN firing is so apparent that early investigators initially proposed that this suppression of raphe cell firing may be the key underlying mechanism eliciting psychedelic effects.*[89–96]

However, further investigations have specified more distinct biological effects from different classes of psychedelics on the DRN, which reduced the theoretical emphasis on DRN inhibition. Indeed, there are some studies[97] that provide evidence to argue against DRN suppression-mediated effects of psychedelics on acute behavioral responses. However, its early prominence underscores the magnitude and reliability of the effect of classic psychedelics on the DRN.

Prior studies strongly suggest that the psychedelic-evoked inhibition of the DRN happens through 5-HT_{1A} autoreceptor activation on the serotonergic neurons in the DRN. Although Maier and Seligman propose that strong 5-HT_{1A} activation due to aversive shock may disinhibit the DRN (through 5-HT_{1A} desensitization), there is also evidence, as mentioned, that 5-HT_{1A} agonists strongly inhibit DRN firing.[63,98,99] Therefore, one of the possible mechanisms through which psychedelic compounds can affect change in learned helplessness behavior may be through their inhibitory action on the DRN through 5-HT_{1A} receptor activity.

For example, Haigler and Aghajanian investigated how serotonergic neurons in the DRN and neurons postsynaptic to this population respond to LSD.[100] They found that postsynaptic areas were relatively insensitive to LSD as compared with DRN cells, suggesting a direct inhibitory action on DRN neurons by LSD (which would primarily involve 5-HT_{1A} autoreceptors). Further studies found that LSD hyperpolarized DRN neurons in rat brain slices in a similar manner to 5-HT, suggesting shared action on the serotonergic autoreceptors.[47]

However, this theory does not hold true for all classes of psychedelics, as psychedelic phenethylamines have very little affinity for the 5-HT_{1A} receptor as compared with their affinity for the 5-HT_{2A} receptor (e.g., 2,5-dimethoxy-4-iodoamphetamine [DOI]), yet can still modulate the activity of the DRN.[91,93,101] In particular, phenethylamines have been shown to suppress DRN firing, especially in the ventral portion. Even though the 5-HT_{2A} receptors are not present on the serotonergic neurons in the DRN, blockade of 5-HT_{2A} receptors with MDL100907 was shown to completely curb the DOI-evoked inhibition of DRN firing activity.[101]

The inhibitory action of DOI on DRN firing may occur through the 5-$HT_{2A/2C}$ receptors reported to be present on the GABAergic neurons in the DRN.[102–104] This was further elucidated by Liu et al., who found that DOI greatly inhibits serotonergic neurons in the dorsal raphe (more so than 5-HT itself) through the activation of GABAergic interneurons, an effect that is largely reversed by a 5-HT_{2A} receptor antagonist. Finally, another study confirmed that DOI inhibits DRN neurons and showed that DOI increases the firing rate of a subset of 5-HT neurons in the mPFC.

This could suggest a potential modulation of serotonergic DRN cells through activation of mPFC neurons projecting to DRN interneurons.[105] These studies raise the possibility of a compelling connection between psychedelics and the helplessness circuit, with the possibility

of 5-HT_{2A}-mediated modulation of DRN activity. However, it does not preclude the possibility that DOI (like other classical psychedelics) may exert notable functional effects through action on other receptors, including the 5-HT_{1A} receptors, despite having lower affinity to them as compared with the 5-HT_{2A} receptors.

Studies have also shown that the induction of learned helplessness is associated with 5-HT_{2A} upregulation in cortical areas.[106] Curiously, 5-HT_{2A} receptors are known to readily internalize with both agonism and antagonism,[107] and psychedelics, as 5-HT_{2A} agonists or partial agonists, have been shown to cause both a transient downregulation of 5-HT_{2A} receptors[108] and a substantial slowing of the re-expression of these receptors.[109] Although the above observations may undermine the original clean story around a psychedelic-evoked 5-HT_{1A}-mediated mechanism of DRN inhibition, the involvement of an indirect mechanism through postsynaptic 5-HT_{2A} receptor activation could explain the seeming contradiction.

The other key aspect in regulating learned helplessness behavior is the neural circuit involved in the estimates of controllability, which include the mPFC and the striatum. These regions can function, potentially through the activity of the vmPFC, to inhibit the DRN by activating GABAergic interneurons and thus reverse helplessness behavior, indicating the role of control estimates on action selection in the face of threat. With this understanding, it is important to note that psychedelics have been shown to activate both GABAergic interneurons in the DRN and the excitatory neurons of the mPFC.[103,105] Thus, it is plausible that the serotonergic psychedelics may activate inhibitory DRN interneurons through activation of the vmPFC in a manner similar to natural estimations of control.

The PFC more broadly is strongly influenced by the actions of psychedelics in multiple ways. Serotonergic psychedelics significantly enhance PFC activity, seen as increased frequency and amplitude of spontaneous excitatory postsynaptic potentials in the apical dendrites of layer V pyramidal neurons (including mPFC), which is believed to be mediated through an increase in glutamate release.[110–116] Imaging studies have also shown enhanced prefrontal activity under the influence of psychedelics, a phenomenon termed ''hyperfrontality.''[117–122]

Increased prefrontal activity is seen even 1 week after psilocybin administration in the dorsolateral prefrontal cortex while performing cognitive tests such as the Stoop task (which involves naming the color of the word when the text and color of the word do not match).[36] Acute DOI has been shown to influence cortical plasticity, such that there is an increase in the expression of cAMP-response element binding protein-mediated neuroplasticity associated genes.[123]

Research by Ly et al. has shown that serotonergic psychedelics elicit increases in spinogenesis, neuritogenesis, and synapse number and function, both *in vitro* and *in vivo*. Furthermore, this augmentation of neural plasticity may be mediated by overlapping pathways with ketamine, including mTOR.[12,124] Enhanced structural plasticity in the neocortex has been observed with a single dose of psilocybin, an effect that does not seem to be effectively blocked with ketanserin (a 5-HT_{2A} receptor antagonist). However, whether ketanserin can effectively block 5-HT_{2A} receptors in the mouse cortex remains to be determined and its efficacy was questioned by the authors in this study.[44]

Repeated ketamine, in turn, has been shown to reverse helplessness behavior[125] and can also spur plasticity, including the growth of dendritic spines and an increase in synaptic proteins (e.g., BDNF) when administered acutely.[124,126] Interestingly, chronic stress-induced reductions in cortical spine density can also be reversed by repeated LSD administration.[127] Finally, preliminary data have shown that both MDMA[17] and psilocybin (Personal communication; Gül Dölen) have the capacity to reopen critical periods of plasticity.

Lastly, the amygdala, as a region involved in threat detection[128] is a crucial mediator of fear/anxiety, has been implicated in the processing of and response to emotional stimuli (especially negative emotional stimuli[129]), and is a downstream target of the DRN. It has been reported that learned helplessness disrupts amygdala function by downregulating 5-HT_{2A} receptors in the basolateral amygdala (BLA).[130] 5-HT_{2A} receptors in this region are primarily localized to parvalbumin-containing GABAergic interneurons, the downregulation of which causes an overall increase in amygdala sensitivity and excitability.

Seeing that 5-HT administration to the BLA causes an increase in 5-HT_{2A} receptor-mediated spontaneous inhibitory postsynaptic currents (sIPSCs), which seem to be impaired by stress,[130] one possibility is that psychedelics act in a similar manner, enhancing sIPSCs through direct 5-HT_{2A} receptor activation, thereby acutely reducing amygdala activity and thus reducing the fear/anxiety behavior crucial to both learned helplessness and depression. It has been shown that acute administration of psilocybin as well as LSD can reduce amygdala activity in response to negative stimuli, which is often associated with enhanced positive mood state.[131,132]

Although lacking precise specificity to the BLA, a previous report reports a significant enduring decline in both right and left amygdala activity 1 week after psilocybin administration using regions of interests that are heavily influenced by the BLA.[36] The authors suggest that this may be mediated by a change in top-down control, a possibility that fits with our delineation of recovery from learned helplessness, but it is also possible, though

speculative, that direct 5-HT_{2A} activation by psychedelics in the BLA may result in enduring changes in receptor expression or downstream signaling that rescues sIPSC response to 5-HT that was impaired by stress.

Although the above data are suggestive, the underlying mechanism by which classic psychedelics lead to enduring changes in the helplessness circuit remains unknown. The effects of psychedelics on neural plasticity and circuit activity resemble those required by immunization in learned helplessness, but we are yet to make a causal link between this potential protective adaptation related to resilience in stress-induced maladaptive behavior and the therapeutic actions of classic psychedelics. Brain-wide mapping of activity-dependent gene markers, such as c-fos, may be resourceful in understanding the change in neuronal activation pattern in animals susceptible to learned helplessness under the effect of psychedelics, and whether it phenocopies the neuronal activation pattern as seen in resilient animals.

Although a compelling study addressing this precise question is yet to be done, there are resources that independently provide important insights about brain-wide neuronal activity in animals prone to the learned helplessness paradigm, and the changes associated with psychedelic administration. A previous study showed that when compared with resilient animals, those susceptible to learned helplessness showed a significant reduction in c-fos activation in almost all brain regions examined, except for locus coeruleus, the center for noradrenergic neurons and release of the monoamine neurotransmitter norepinephrine, which is implicated in regulating the ''flight-or-fight'' response.[133]

It is interesting that in helplessness prone animals, c-fos activity in medial prefrontal cortical regions, amygdalar nuclei, as well as multiple subfields of hippocampal formation is significantly reduced. These regions show a robust increase in c-fos activity under the effect of psilocybin.[134] Psilocybin also results in reduced c-fos activity in the DRN, suggesting yet again that DRN activity may be suppressed under the influence of psychedelics. These two studies also show opposing c-fos activity patterns for ''helpless'' animals as compared with animals with psilocybin administration in areas that are not directly implicated in regulating learned helplessness response but are essential in processing other emotional valences.

For example, the insular cortex, which plays a key role in social cognition and is known to link the sensory percept to emotional responses, implicating its role in introception and emotional valence,[135,136] shows a reduced c-fos activation pattern in susceptible animals,[80] but shows significantly enhanced activity under the effects of psilocybin.[134] Although c-fos activity does not necessarily correlate with neuronal excitation/inhibition pattern, it definitely lays the groundwork for understanding the key regions that may be therapeutic targets for psychedelics against stress-induced maladaptive changes, specifically learned helplessness.

Taken together, the current literature and findings suggest that classic psychedelics may produce therapeutic effects as plasticity-promoting compounds that can restructure the brain dynamically, while altering network activity to provide a mechanism by which positive psychedelic effects on the helplessness circuit may endure.

Behavioral Tests of Learned Helplessness with Psychedelics

Preclinical

Few studies address the effects of psychedelics on learned helplessness in preclinical models. Shao et al. exposed group-housed mice to repeated inescapable foot shocks over two induction sessions, and then tested the animals for active avoidance behavior in an escapable foot shock paradigm 1 day before and 1 day after treatment with either saline, psilocybin (1 mg/kg), or ketamine (10 mg/kg). Within individuals, psilocybin significantly reduced the proportion of escape failures (e.g., learned helplessness reversal was achieved), but comparison between saline, psilocybin, and ketamine groups failed to demonstrate a treatment effect.[44]

In contrast, administration of 1 mg/kg psilocin did not show reversal of learned helplessness behavior in single-housed animals that were subjected to a learned helplessness paradigm for over 2 weeks, intermittently accompanied by unpredictable stress of wet bedding and food restriction.[137] Although this study does not show reversal in learned helplessness, it does provide evidence that 1 mg/kg psilocin administration can alleviate stress-induced despair-like behaviors, as seen with the sucrose preference test as well as the tail suspension test. The difference in the outcome of these two studies can perhaps be attributed to the design and timing of the experiments, which underscores that further investigation is needed to better understand the scope of effects of psychedelics on learned helplessness behavior.

Although follow-up to the above studies will be crucial, there have been several *indirect* tests of the effects of classic psychedelics on learned helplessness in preclinical research. Although these other studies either tested nonclassical psychedelics (e.g., ketamine) or do not conform exactly with the learned helplessness paradigm as described in the Seligman and Maier studies,[63] they strongly suggest that future studies of this type may be worthwhile. Importantly, ketamine has now been shown to reverse helplessness behavior in multiple studies.[125,138] Interestingly, it was also found that ketamine successfully restores glutamate-evoked spinogenesis in mice mPFC after learned helplessness-induced blunting, in line with our discussion of plasticity earlier.[138]

Studies looking at classic psychedelics have shown that repeated LSD administrations can lead to the

amelioration of a host of chronic stress-induced anxiety-like behavioral responses in rodents, paralleled by an increase in cortical spinogenesis.[127] Interestingly, no effects were seen on anxiety or depressive-like behaviors in nonstressed animals.[127] Furthermore, psilocybin has been tested in the preclinical rodent depression paradigm called the FST. In this task, the amount of time the animal spends immobile in the tank is considered to be a measure of behavioral despair (for a review on FST, see Ref.[139]).

Previous studies have reported that ketamine and psilocybin both produced enhanced escape behaviors in rats in the FST 1 week after administration compared with control, *but only psilocybin produced improved FST performance that persisted for 30 days after drug administration*.[140]

Clinical

The effects of classic psychedelics on stress-induced changes in behavior have not been tested in humans. However, experimental paradigms recreating learned helplessness in human subjects have been established. In addition to analogous shock-based helplessness protocols as used with rodents,[141] human paradigms include exposure to aversive tones or unsolvable puzzles.[142] In the aversive tone setup, subjects are exposed to a series of unpleasantly loud noises, and can either escape the tone by pressing a button or cannot escape the tone but experience the same series of noises. Later they are presented with a new task that they can complete to escape from the aversive tone.

The unsolvable puzzle setup presents its subjects with a cognitive pretreatment task wherein they are presented with puzzles. For one group, some of the puzzles are solvable and some are not, whereas for the other group the puzzles are not solvable at all. Both groups are later tested in solving a series of solvable puzzles. Consistent with what is seen in other organisms, those subjects who experienced the unavoidable pretreatment show passivity in the new escapable/solvable environment. However, the validity of these paradigms remains uncertain, with issues such as persistence needing to be resolved[143] and few if any recent replications. Although the paradigms for testing helplessness in humans have not been used in recent years or extensively replicated, we reiterate that helplessness tasks in the rodent literature are extremely well replicated and represent a thriving research subject.[144,145]

Learned helplessness thus offers a concrete animal model that correlates well with human outcomes. Currently, animal models for psychedelic research are fraught and human therapeutic outcomes are largely survey based. More research is needed that is aimed toward testing the efficacy of classic psychedelics directly on learned helplessness paradigms in both rodents and humans. Several clinical trials have demonstrated some efficacy of psilocybin in reducing depression,[2–5,7] so helplessness as a model of stress-induced depression could provide a basis to explore the efficacy of psychedelics in future clinical trials.

Learned Helplessness As a Productive Theory for Psychedelic Research

Learned helplessness appears to be a useful theory and productive hypothesis in the context of psychedelic research, largely because it is replicable across species, falsifiable, has well-described neural mechanisms, holds transdiagnostic therapeutic implications, and bridges several levels of analysis. We address each of these strengths below.

In the midst of an on-going replication crisis in the psychological sciences that has just begun to be apparent in medicine,[146] learned helplessness is a highly replicated effect. Seligman and Maier review dozens of studies that have replicated the effect and examined the underlying neural mechanisms.[63] As shown throughout this review, learned helplessness has also been replicated across mammalian species, which is important as psychedelics have also shown to have efficacy across both humans and rodents.

As a robust model with established clinical correlations, the learned helplessness paradigm could be a valuable tool for future psychedelic research. As previously mentioned, current theories on the therapeutic mechanisms of psychedelics largely fall into neurobiological or psychological explanations, with little integration between the two. Furthermore, current preclinical research with psychedelics has been hindered by poor translational models, and clinical research into psychedelics has relied heavily on subjective, rather than behavioral, outcomes. Learned helplessness, as a potential driver of psychedelic effects, could to a great extent improve these issues in the field of psychedelic science.

Learned helplessness is also a theory that provides a falsifiable hypothesis in this context: psychedelics produce their therapeutic effects in large part due to reversing or building resilience to helplessness. This can be tested through several helplessness paradigms and across multiple mammalian species on both behavioral and biological (mechanistic) levels. If the hypothesis is false, this will be quickly established—although there are already several studies providing indirect evidence both on a circuit and behavioral level to support the theory.

Conclusion

Unlike most psychological phenomena, learned helplessness has well-described neural mechanisms. As has been outlined,[63] activation of the DRN during aversive circumstances is necessary and sufficient to cause a helplessness response—and activation of a vmPFC–DRN circuit, either through the detection of control or in the

laboratory using optogenetics or other stimulation, is necessary and sufficient to reverse helplessness and can help inoculate against it in similar circumstances in the future. The neural mechanisms of learned helplessness have substantial overlaps with those associated with psychedelic drug action.

Psychedelics also activate the vmPFC and inhibit the DRN, so it is possible that psychedelics impact this circuit in a positive way. Learned helplessness is basic enough to occur across mammalian species but also could drive some of the more sophisticated behaviors and thought patterns reported by humans. It is important to further characterize individual differences between resilience to and susceptibility against learned helplessness across species to better understand and predict specific responses to this paradigm. Indeed, the individual differences are not well studied.

Although there is evidence to show that animals can respond differentially to the same stressor paradigm by exhibiting either vulnerability or susceptibility toward mood-related disorders, the underlying factors governing such individual responses are not yet understood. Such work holds the potential to advance understanding of the helplessness phenomena in general and could enhance clinical practice by developing more personalized medicine approaches to psychedelic treatments. Thus, learned helplessness could provide a bridge between several levels of analysis in psychedelic research and a possible therapeutic mechanism to explore.

Authors' Contributions

P.T., A.P.B., C.S., M.K.D., F.S.B., and D.B.Y. contributed to the writing and editing of the article.

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