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The Emerging Neurobiology of Psychedelics: Critical Periods, Metaplasticity, and Extracellular Matrix Remodeling

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Abstract

Psychedelics are a broad category of compounds that induce altered states of consciousness. These drugs have shown remarkable promise for the treatment of debilitating disorders ranging from posttraumatic stress disorder to depression and addiction. Although early studies focused on linking binding targets of psychedelics to their therapeutic effects, these pharmacological and biochemical explanations fail to account for the diversity, durability, and context dependence of psychedelics' clinical and acute subjective effects. More recently, neurobiological explanations offer fresh insights and demonstrate that a unifying property of psychedelics is that these compounds reopen critical periods, induce metaplasticity, and reorganize the extracellular matrix. Here we review this evidence and argue that the neurobiological and therapeutic effects of psychedelics challenge the biochemical imbalance model that has dominated translational neuroscience since the 1950s and favor instead a learning model that better accounts for psychedelics' unique therapeutic profile.

Contents

1. INTRODUCTION

The term psychedelic was coined in 1956 (Bisbee et al. 2018) by psychiatrist Humphry Osmond from the Greek words ψυχή (*psyche*), meaning the mind or soul, and δήλος (*delous*), meaning to manifest or show (Osmond 1957). Today, psychedelic is used to describe drugs that induce "alterations in sensory perception, sense of time and space, and sense of self [that] are so alien to everyday experience that they shed new light on the workings of these every day mental functions" (Snyder 1986, p. 183). This umbrella term describes a broad group of drugs that include ketamine, phenylcyclohexyl piperidine (PCP), lysergic acid diethylamide (LSD), psilocybin, mescaline, *N*,*N*-dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 3,4-methylenedioxymethamphetamine (MDMA), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), ibogaine, and salvinorin A. These psychedelics can be subcategorized based on the subjective character of the altered state they induce, for example, dissociative psychedelics (ketamine, PCP), hallucinogenic psychedelics (LSD, psilocybin), empathogenic psychedelics (MDMA, 2C-B), and oneirogenic psychedelics (ibogaine, salvinorin A) (González et al. 2021, Hartogsohn 2022, Marguilho et al. 2023, Stocker & Liechti 2024). Some have argued that the subset of psychedelics whose subjective effects are similar to LSD should be distinguished as "classical psychedelics," thereby designating this group as the exemplary standard, discounting all others as atypical (Glennon 1996, Nichols 2016). This terminology is favored by pharmacologists and biochemists who prioritize receptor binding affinity [in this case to the serotonin 2A receptor (5-HTR_{2A})] as the organizing mechanism that defines their function (Jain et al. 2025). However, we contend that the term "classical psychedelic" should be abandoned for a number of reasons. First, it is confusing because the umbrella term that has been used to describe all psychedelics, including ketamine, MDMA, and ibogaine (Osmond 1957; Shulgin 1986; Shulgin & Shulgin 1991, 1997; Snyder 1986), predates (by decades) the introduction of the qualifier "classical," which, therefore, cannot be a reference to the traditional and long-established meaning of the term psychedelic. Second, it is historically inaccurate because the best anthropological evidence available indicates that psychedelics such as ibogaine (excluded from the so-called classical group) have been in use by human cultures for at least as long as psychedelics such as psilocybin (included in the so-called classical group) (Kaaronen 2025, Samorini 2025). Finally, as we discuss below, growing evidence supports the view that therapeutic and neurobiological properties cohere the category of psychedelics, independent of their principal binding target.

2. CLINICAL RESEARCH

Since the introduction of antibiotic treatments for syphilis in the 1940s, translational neuroscience has been captivated by the idea that neuropsychiatric illnesses could one day be cured with a single magic pill (Ghanem 2010). Building on this framework, the discovery of monoamine oxidase

inhibitors and tricyclic antidepressants in the 1950s and 1960s ushered in a long period dominated by the biochemical imbalance model of neuropsychiatric disease. According to this model, depression is conceptualized as a biochemical imbalance in serotonin, and selective serotonin reuptake inhibitors (SSRIs) reverse this imbalance. Despite the preeminence of the biochemical imbalance model for over a half century, there is growing awareness of its limitations. For example, SSRIs produce serious side effects (e.g., emotional blunting, metabolic disruptions, reproductive hormone impairments) caused by interfering with the normal function of the serotonergic neuromodulatory system, especially with chronic use (Atmaca 2020, Masdrakis et al. 2023, Sepúlveda-Lizcano et al. 2023, Strawn et al. 2023). Moreover, these interventions do not address root causes, providing symptom relief that is not sustained after discontinuation, and produce severe withdrawal symptoms often leading to lifetime medicalization (Cartwright et al. 2016, Zhang et al. 2025). As we argue below, the recent clinical successes with psychedelics circumvent these limitations and challenge the biochemical imbalance model in favor of a learning model, which better accounts for the diversity of conditions psychedelics treat, the durability of the therapeutic response, and the context dependence of their effects. According to the learning model, psychedelics are not the therapy itself but rather adjunct interventions that enhance the efficacy of the therapy delivered in conjunction with these medications. In this framework, transdiagnostic efficacy is the consequence of delivering psychedelics in different therapeutic contexts, while the durability of the therapeutic response is the lasting consequence of reconfiguring learned patterns of behavior. In subsequent sections, we discuss recent neurobiological insights that offer a mechanistic explanation supporting the learning model of psychedelics' therapeutic profile (see also Lepow et al. 2023).

As shown in **Figure 1**, psychedelics show therapeutic promise for a diverse array of neuropsychiatric conditions, including posttraumatic stress disorder (PTSD), depression, addiction, and anxiety, as well as trauma-related psychological and cognitive impairment and headache (Blest-Hopley et al. 2025, Bogenschutz et al. 2022, Cherian et al. 2024, Davis et al. 2025, Duek et al. 2023, Holze et al. 2023, Krupitsky et al. 2002, Kvam et al. 2026, McGowan et al. 2025, Mithoefer et al. 2013, Savage & McCabe 1973, Schindler et al. 2024, US Food and Drug Administration 2024, Veraart et al 2026, Yermus et al. 2024). Early theories attempting to explain the therapeutic efficacy of psychedelics focused on serotonin and were supported by their therapeutic overlap with SSRIs, which were originally approved for major depression but have also been used for PTSD, anxiety, and addiction. Indeed, several psychedelics, including LSD, psilocybin, MDMA, and mescaline, share structural similarities with serotonin and bind to its receptors (especially 5-HTR_{2A}) or the serotonin transporter (SERT) with high affinity (McClure-Begley & Roth 2022, Snyder & Reivich 1966). Nevertheless, this mechanistic overlap fails to account for therapeutic properties of psychedelics such as ketamine, which has low affinity for 5-HTR_{2A} and is instead thought to function through the *N*-methyl-D-aspartate receptor (NMDAR) (Autry et al. 2011). Similarly, ibogaine and its active metabolite noribogaine bind to the kappa opioid receptor (KOR), the vesicular monoamine transporter 2 (VMAT2), SERT, and the organic cation transporter 2 (OCT2), demonstrating complex matrix pharmacology not dependent on serotonin receptor binding (Hwu et al. 2026). Some have proposed that ibogaine's therapeutic efficacy might be a direct consequence of interrupting addiction, perhaps by a KOR-mediated mechanism (Havel et al. 2024); however, this account fails to explain the therapeutic potential of ibogaine for other neuropsychiatric disorders (Cherian et al. 2024; Davis et al. 2020, 2023; Rocha et al. 2023; Valdez et al. 2024), nor does it recapitulate patient narratives that focus on the importance of identifying root causes (e.g., trauma, adverse childhood experiences) and the cognitive reappraisal engendered by those insights (Heink et al. 2017, La Torre et al. 2025). Thus, it has become increasingly clear that a mechanistic understanding of the therapeutic effects of these compounds will involve discovery of novel unifying neurobiological properties.

Indication	Psychedelic	Context	Durability	Source
PTSD	Ketamine	No therapy	1 week	Feder et al. 2014
		Psychological intervention/support	At least 3 months	Duek et al. 2023
	Psilocybin	Psychological intervention/support	At least 3 months	McGowan et al. 2025
	MDMA	No therapy (recreational use)	No therapeutic response*	US Food and Drug Administration 2024
		Psychological intervention/support	At least 3.5 years	Mithoefer et al. 2013
Depression	Ketamine	No therapy (under anesthesia)	No therapeutic response†	Lii et al. 2023
		No therapy	1 week	Zarate et al. 2006
		Psychological intervention/support	At least 6 months	Yermus et al. 2024
	Psilocybin	Psychological intervention/support	At least 5 years	Davis et al. 2025
	MDMA	Psychological intervention/support	At least 7 months	Kvam et al. 2026
Addiction	Ketamine	No therapy	1 week	Dakwar et al. 2017
		Psychological intervention/support	At least 2 years	Krupitsky et al. 2002
	Psilocybin	Psychological intervention/support	At least 8 months	Bogenschutz et al. 2022
	LSD	No therapy	No therapeutic response‡	Cohen 1960
		Psychological intervention/support	At least 12 months	Savage & McCabe 1973
	Ibogaine	Psychological intervention/support	At least 2 years	Davis et al. 2017
Anxiety	Ketamine	No therapy	1 week	Taylor et al. 2018
	LSD	Psychological intervention/support	At least 4 months	Holze et al. 2023
Traumatic brain injury	Psilocybin	Psychological intervention/support	At least 1 month	Blest-Hopley et al. 2025
	Ibogaine	Psychological intervention/support	At least 1 month	Cherian et al. 2024
Cluster headache	Psilocybin	No therapy	At least 2 months	Schindler et al. 2024

Figure 1

Overview of psychedelic clinical trials highlighting the relationship between therapeutic context and response durability. The psychedelics were administered in 1–3 doses. For context, psychological intervention/support included a range of circumstances from formalized therapist and psychiatrist visits to informal therapeutic coaching before, during, and after the psychedelic intervention. Common factors that are shared across different psychotherapy styles include a therapeutic relationship, healing settings (e.g., eye masks, music, inner-directed trip), rationale, and ritual (Gukasyan & Nayak 2022). We have therefore chosen to group any mention of intention setting, therapist intervention (both formal and informal), and integration sessions as constituting a "psychological intervention/support" context. Conversely, "no therapy" contexts included sterile, impersonal clinical settings (no headphones, no eye masks, no supportive interactions), recreational settings, surgical settings (under anesthesia), and clinical settings solely focused on the collection of biometric data. Regarding durability, the qualifier "at least" denotes the longest time point reported by the study, though the efficacy may have persisted beyond this point. Otherwise, the time point denotes the termination of the clinical effect measured. The asterisk indicates that subjects with prior recreational MDMA use had continued PTSD symptoms sufficient to qualify for the clinical trial; following MDMA-assisted psychotherapy, these subjects, like drug-naïve subjects, showed significant symptom reductions lasting at least 6 months (US Food and Drug Administration 2024). The dagger indicates that the comparison was to the placebo + anesthesia group (Lii et al. 2023). The double dagger indicates that subjects showed increased symptoms of anxiety and depression (Cohen 1960). Abbreviations: LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, posttraumatic stress disorder.

Another feature of the therapeutic response to psychedelic drugs that has been difficult to reconcile with a purely pharmacological account is their therapeutic time course. Specifically, the therapeutic benefits of psychedelics persist well beyond their acute effects, and considerable variation exists across compounds in the durability of the therapeutic response. For example, ketamine's therapeutic effects are transient, with significant effects lasting only 1 week (Dakwar et al. 2017, Feder et al. 2014, Taylor et al. 2018, Zarate et al. 2006). In contrast, MDMA-assisted psychotherapy produces highly durable reduction of PTSD symptoms, lasting through the longest end point reported at 3.5 years (Mithoefer et al. 2013, US Food and Drug Administration 2024). Likewise, the decrease in depression symptoms following psilocybin-assisted psychotherapy is maintained for at least 5 years (Davis et al. 2025). Recent studies suggest that ibogaine's therapeutic effects are also remarkably durable, since a single ibogaine treatment reduces opioid withdrawal symptoms and achieves opioid cessation in dependent individuals for over 2 years (Davis et al. 2017, Noller et al. 2018). Importantly, unlike SSRIs, which are taken daily, psychedelics show durable therapeutic effects after one to three treatments, and as we discuss below, this durability appears to be dependent on their pairing with psychotherapy (see also **Figure 1**). Indeed, growing recognition of the synergy between psychedelics and psychotherapy has given rise to using ketamine in conjunction with psychotherapy (i.e., ketamine-assisted psychotherapy), which may extend the durability of ketamine's therapeutic effects (Duek et al. 2023, Krupitsky et al. 2002, Mathai et al. 2022, Wilkinson et al. 2021, Veraart et al. 2026, Yermus et al. 2024). The mechanisms underlying the variability in the duration of therapeutic effects of psychedelics are unclear, but recent advances described below offer important clues.

The internal and external circumstances under which psychedelics are delivered (the so-called set and setting, referring to mind set and situational setting) have a profound influence on the subjective character of the acute effects (Johnson et al. 2008). Although, to date, the context dependence of psychedelics' therapeutic effects has not been explicitly tested, decades of clinical evidence support this view (see also **Figure 1**). For example, clinicians emphasize the importance of establishing a therapeutic alliance, defining a therapeutic intention in preparation for taking psychedelics, as well as a prolonged period of integration after the acute effects have worn off (Alpert et al. 2024, Bogenschutz 2024, Deckel et al. 2024, Earleywine et al. 2024, Le et al. 2022, O'Donnell et al. 2024, Schenberg et al. 2024, Zamaria et al. 2025). Furthermore, since spontaneous remission of PTSD, depression, and addiction following common recreational use of these drugs has not been reported in the clinical literature, it seems unlikely that such use provides the appropriate set and setting for the therapeutic effects of psychedelics. Similarly, ketamine's antidepressant effects are absent when given under anesthesia (Lii et al. 2023). More recently, direct evidence to support the context dependence of psychedelics' therapeutic effects comes from Phase III clinical trials of MDMA-assisted psychotherapy for PTSD. Specifically, PTSD symptoms persisted in subjects that had previously used MDMA in a recreational context; however, when this group received MDMA in a psychotherapeutic context, they showed equal reductions in PTSD symptoms compared to participants who were drug naive prior to the study (US Food and Drug Administration 2024). The mechanisms underlying the context dependence of therapeutic effects of psychedelics are unclear, but recent advances described below offer important clues.

3. CRITICAL PERIODS

Konrad Lorenz (1935) coined the term "critical period" to describe the narrow temporal window during which imprinting behavior in Greylag geese is shaped by experience-dependent learning and memory. Critical periods exist because there are not enough genes in the genome to encode every possible behavior; instead, what is encoded is the ability to learn in a manner that is flexibly

responsive to the environment. This arrangement is thought to dramatically expand the repertoire and complexity of animal behavior (Yoon et al. 2023). To date, dozens of critical periods have been described, and these are thought to underwrite almost all learned behavior, including language, sensory perception, and motor movements, as well as personality traits and emotional responses (Chen & Hartshorne 2021, Dahl et al. 2018, Dromerick et al. 2021, Pedrosa et al. 2022). For example, building on decades of human development research (Blakemore & Mills 2014), the Dölen lab (Nardou et al. 2019) has described a social reward learning critical period, which is thought to underlie the formation of stable social hierarchies (Pedersen 2004), as well as explain the heightened susceptibility to peer pressure during adolescence (Leung et al. 2014) and the enduring impact of social injury incurred during childhood (Li et al. 2025, Sebalo et al. 2023, Zheng et al. 2025). The closure of critical periods marks the end of this energetically costly stage of development, which brings with it both efficiency and stability in adulthood (Gopnik 2020). Nevertheless, because the nervous system is no longer malleable for learning, the closure of critical periods limits the ability to effectively treat neuropsychiatric disease, even when the underlying problem is corrected (Dromerick et al. 2021, Hensch & Quinlan 2018). Unsurprisingly, thousands of mechanistic studies have sought to understand the rules governing critical periods, with the ultimate goal of discovering methods for reopening them for therapeutic benefit (Beretta et al. 2025, Brandt & Ackerman 2025, Carulli et al. 2021, Gibel-Russo et al. 2022, Nabel & Morishita 2013, Nelson et al. 2025, Uchigashima & Mikuni 2024).

The first evidence that psychedelics may be the long-sought master keys for unlocking critical periods came from research in the Dölen lab (Nardou et al. 2019) demonstrating that MDMA, but not the psychostimulant cocaine, reopens the critical period for social reward learning. Shortly thereafter, three other labs demonstrated that ketamine is able to reopen the critical period for ocular dominance plasticity (Grieco et al. 2020, Venturino et al. 2021) and orientation selectivity (Ouelhazi et al. 2019). Subsequent studies extended these findings across psychedelics, including ketamine, psilocybin, LSD, and ibogaine, for the social reward learning critical period (Nardou et al. 2023), as well as LSD (Moliner et al. 2023) and ibogaine (Acuña et al. 2026) for the ocular dominance plasticity critical period. Importantly, the ability to reopen critical periods is a neurobiological effect that is shared across psychedelics, though not universally dependent on 5-HTR_{2A} binding (Moliner et al. 2023, Nardou et al. 2023).

As shown in **Figure 2**, psychedelics vary dramatically in the duration of the acute subjective effects they produce in humans, ranging from minutes (ketamine) to days (ibogaine) (Kolbrich et al. 2008, Maciulaitis et al. 2008, Madsen et al. 2019, Niesters et al. 2014, Schmid et al. 2015), and these effects are proportional to the duration of the critical period open state they induce in mice (Nardou et al. 2023). Although the mechanisms underlying this proportionality are not known (but see below for further discussion), these results suggest that the acute subjective experience (the "trip") initiates critical period reopening, and what it feels like to be in an altered state of consciousness is just what it feels like to reopen critical periods.

Supporting this view, previous studies have shown that sensory deprivation also reopens critical periods (Murase et al. 2017) and produces altered states of consciousness (mystical states and hallucinations) that are phenomenologically similar to those produced by psychedelics (Merabet & Pascual-Leone 2010, Merabet et al. 2004, Pitskel et al. 2007). Indeed, it may be that religious traditions that use deprivation techniques to induce altered states (including, for example, beginner's mind in the Zen Buddhist tradition) do so in order to achieve the same mystical state that other cultures have used psychedelics to produce (Griffiths et al. 2019, Suzuki 2020, Winkelman 1990). Importantly, the proportionality between the duration of the psychedelic trip and the duration of the critical period open state is another neurobiological property shared across psychedelics that is not restricted to the subset of these compounds that bind 5-HTR_{2A}

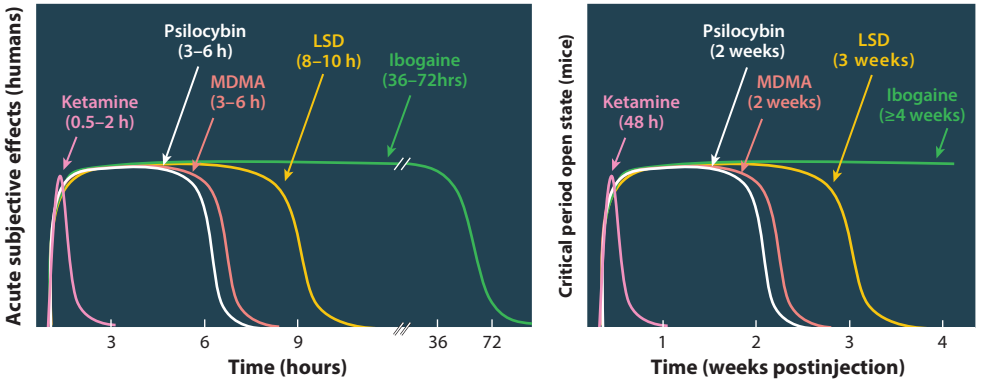

Figure 2

The duration of the subjective experience for various psychedelics in humans is proportional to the duration of the critical period open state induced by psychedelics in mice (as measured by social conditioned place preference learning in adulthood). Figure adapted from Nardou et al. (2023) (CC BY 4.0).

(Nardou et al. 2023). Moreover, 5-HTR_{2A}-mediated mechanisms are not thought to govern deprivation-induced reopening of critical periods (Murase et al. 2017). Taken together, these observations underscore the need to take a neurobiological, rather than a purely pharmacological, approach to understanding the phenomenology of psychedelics.

Psychedelic-mediated critical period reopening offers a mechanistic explanation for a number of clinical observations (described above) that are not easily reconciled with a purely pharmacological account. First, psychedelics show transdiagnostic efficacy for a diverse array of neuropsychiatric conditions (**Figure 1**) that might be unified by their shared etiology [e.g., adverse childhood experiences or trauma (Li et al. 2025, Sebalo et al. 2023, Zheng et al. 2025)] or pathogenesis (maladaptive or no-longer-adaptive learned habits of emotion and thought) (Brady et al. 2000, D'Andrea et al. 2012, Ford et al. 2010); in either case, understanding psychedelics' therapeutic effects through the critical period framework suggests that these medicines work by restoring the ability to unlearn unwanted behavioral patterns and replace them with new habits. For example, psychedelic-mediated reopening of the social reward learning critical period (Nardou et al. 2019, 2023) could support learning of new patterns of social behavior (for example, learning to trust others after trauma, building the therapeutic alliance, or adherence to social mores around drug use). However, the learning model need not be restricted to therapeutic effects that can easily be traced to social injury or peer pressure (e.g., PTSD and addiction), and the therapeutic promise of psychedelics for the treatment of major depression, anxiety, and traumatic brain injury may be better explained by psychedelic-mediated reopening of cortical critical periods (some of which are yet to be described) that enable rewiring of sensory, motor, cognitive processing, and decision-making circuits of the brain (Grieco et al. 2020, Hsiao et al. 2025, Jiang et al. 2026, Moliner et al. 2023, Ouelhazi et al. 2019, Venturino et al. 2021). As discussed below, it is tempting to speculate that the context under which psychedelics are delivered determines which critical period gets reopened (e.g., social context reopens a social critical period, visual context reopens a visual critical period).

Second, the duration of the critical period open state circumscribes the window of opportunity for this learning and memory to take place. Importantly, in this conceptualization, the durability of the therapeutic response is only *indirectly* related to the duration of the critical period open state, such that recalcitrant or entrenched memories (e.g., heroin addiction) benefit from a longer open

state (e.g., ibogaine) to reconfigure a larger network of interconnected patterns of thought. This mechanistic insight suggests that the open state of the critical period explains the importance of the integration phase (see clinical description above) and that clinical outcomes could be improved by making better use of this learning window that persists in the days to weeks after the acute subjective effects have worn off (**Figure 2**). Furthermore, these observations suggest that novel psychedelic derivatives that shorten or eliminate the trip would likely attenuate or eliminate the therapeutic efficacy of these compounds. Although not conclusive evidence that the trip is required for the therapeutic effects of psychedelics, these results strongly suggest that there is a mechanistic relationship between the acute subjective effects and the duration of the open state of the critical period they induce.

Third, as discussed above (see also **Figure 1**), therapeutic and acute subjective effects of psychedelics are context dependent, and this feature is recapitulated by psychedelic-induced critical period reopening. Specifically, if MDMA is given in a social context, it reopens the social reward learning critical period, but if it is given in an isolation context, it does not (Nardou et al. 2019). Similarly, while psychedelic doses of ketamine reopen the social reward learning critical period, anesthetic doses do not, possibly because the relevant social context is not experienced during unconsciousness (Nardou et al. 2023). Methodological differences notwithstanding, a recent study found that pairing psilocybin with 3 days of isolation failed to reopen the social reward learning critical period (Lu et al. 2025), suggesting that, like MDMA and ketamine, psilocybin's effects are also context dependent. Likewise, following a period of chronic stress, psilocybin delivered in an unstressed context is able to attenuate the depression-like behavioral responses (Hesselgrave et al. 2021) but fails to alter these behaviors in the absence of the traumatic stress (Lu et al. 2025). Taken together, these studies provide a mechanistic basis for the importance of the therapeutic context in reopening critical periods and, consistent with the learning model, challenge the view that psychedelics' therapeutic effects would persist in the absence of the psychotherapeutic context.

4. METAPLASTICITY

Over a hundred years ago, before the discovery of the synapse, William James (1890) coined the term plasticity as "the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once... the change of structure here spoken of need not involve the outward shape; it may be invisible and molecular" (p. 105). Although James primarily wrote of plasticity as a mechanism of habit learning, including addiction, he also implicates it in the development of the nervous system: "Man is born with a tendency to do more things than he has ready-made arrangements for in his nerve-centres... Could the young but realize how soon they will become mere walking bundles of habits, they would give more heed to their conduct during the plastic state" (James 1890, pp. 113, 127). Today, plasticity is defined as a long-lasting form of synaptic modification (strengthening or weakening) that manifests as both morphological and molecular changes and provides the basis for most models of learning and memory, as well as the development of response selectivity and cortical maps. There are several fundamental types of plasticity. For example, while homosynaptic plasticity is input specific (typically glutamatergic or GABAergic), heterosynaptic plasticity can affect the strength of neighboring synapses (typically neuromodulatory or peptidergic) (Bliss & Lomo 1973, Castellucci et al. 1978, Levy & Steward 1979). Hebbian plasticity (also called associative plasticity) depends on correlations between pre- and postsynaptic firing that lead to activity-dependent changes in synaptic strength, whereas homeostatic plasticity is a feedback mechanism that prevents runaway excitation or inhibition in neural circuits (Nicoll et al. 1988, Turrigiano & Nelson 2000). Finally, metaplasticity refers to the plasticity of plasticity, a change (downregulation or upregulation) in the ability to induce plasticity

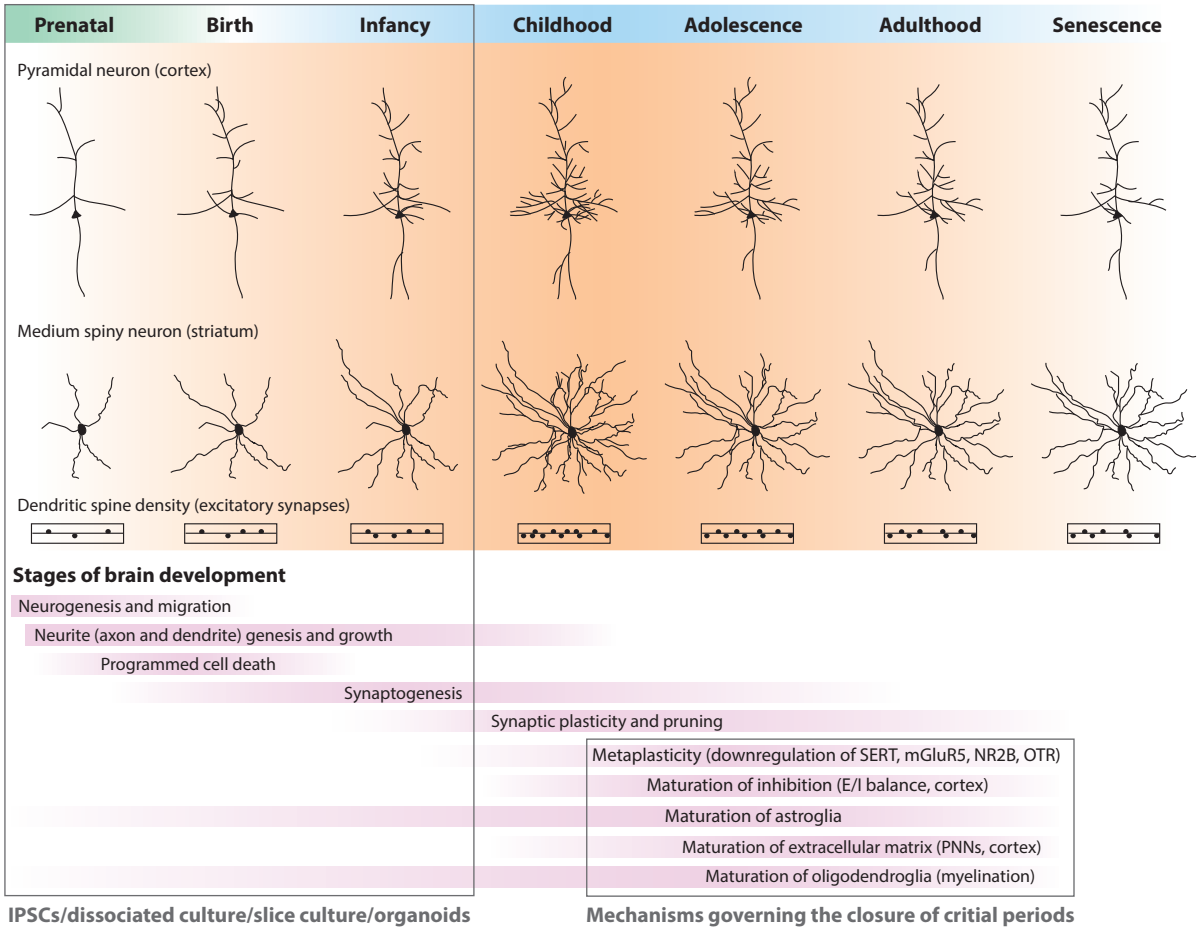

Figure 3

Developmental trajectory of a pyramidal neuron and medium spiny neuron showing increased dendritic spine density and arborization through childhood, followed by stabilization and pruning in adolescence, and gradual decline in function and structure with aging. As shown, early stages of brain development precede the maturation of mechanisms that constrain plasticity. For this reason, in vitro tissue culture models (IPSCs, dissociated neuronal culture, organotypic slice culture, and organoids) are not suitable for studying psychedelic mechanisms, since neurogenesis, neuritogenesis, and spinogenesis are not mechanistically constrained by the normal developmental, cellular, synaptic, and circuit mechanisms in these immature systems. Abbreviations: E/I, excitatory/inhibitory; IPSC, induced pluripotent stem cell; mGluR5, metabotropic glutamate receptor 5; NR2B, *N*-methyl-D-aspartate receptor subunit 2B; OTR, oxytocin receptor; PNN, perineuronal net; SERT, serotonin transporter.

(Abraham & Bear 1996). Importantly, metaplasticity may be either homosynaptic or heterosynaptic, and while it is one of the mechanisms implicated in homeostatic plasticity (Clothiaux et al. 1991), it can also describe Hebbian plasticity, especially as a mechanism underlying the closure of critical periods (**Figure 3**).

Metaplasticity has been implicated in the regulation of critical periods by studies identifying temporal and regional correlations between critical periods and the developmental expression patterns of plasticity proteins. For example, the downregulation of metabotropic glutamate receptor 5 (mGluR5) expression in the primary visual cortex coincides with the closure of the ocular dominance plasticity critical period (Dudek & Bear 1989, Reid et al. 1997, Romano et al. 1996).

Furthermore, activation of mGluR5 induces long-term depression (LTD) (Huber et al. 2000), and genetic ablation of mGluR5 blocks ocular dominance plasticity (Dölen et al. 2007). Similarly, the glutamatergic NMDAR is required for ocular dominance plasticity (Kleinschmidt et al. 1987). This heteromeric receptor is made up of the *N*-methyl-D-aspartate receptor 2A and 2B subunits (NR2A and NR2B, respectively) that confer distinct gating and plasticity properties (Bellone & Nicoll 2007, Liu et al. 2004), and the developmental switch from NR2B to NR2A subunit–dominant NMDARs corresponds to the closure of the ocular dominance plasticity critical period (Cho et al. 2009). In the somatosensory cortex, SERT is highly and selectively expressed in the regions mapping the whisker barrels, and this expression pattern is temporally restricted to the somatosensory critical period (Lebrand et al. 1998). Moreover, overexpression of SERT in adult brains restores the ability of serotonin-releasing drugs to induce morphological plasticity (Vargas et al. 2023). Finally, the expression pattern of the oxytocin receptor (OTR) is differentially regulated across brain regions and development; in the nucleus accumbens (NAc), OTR expression peaks during adolescence (Shapiro & Insel 1989). This regional pattern parallels the expression of oxytocin-induced plasticity (OT-LTD) in the NAc (Dölen et al. 2013), and the developmental downregulation of both OTR expression and OT-LTD coincides with the closure of the social reward learning critical period (Nardou et al. 2019). Each of these metaplastic changes alters the rules of Hebbian plasticity, effectively constraining associative learning as the critical period closes.

The first evidence to suggest that psychedelics induce metaplasticity came from the Monteggia lab (Crawford et al. 2017, Kim et al. 2021, Piazza et al. 2025). These investigators showed that repeated dosing of ketamine induces metaplasticity by upregulating hippocampal brain-derived nerve growth factor (BDNF) and tyrosine receptor kinase B (Trk-B) receptors. Similarly, in the prefrontal cortex, other studies have shown that ketamine pretreatment enhances the ability of glutamate to induce morphological plasticity, perhaps indirectly by modifying dopaminergic signaling (Wu et al. 2021). Studies in the Dölen lab (Nardou et al. 2019) have shown that MDMA induces metaplasticity in adulthood, whereby pretreatment with MDMA restores the ability to induce OT-LTD in acute slices prepared 48 h later. Since OT-LTD is presynaptically expressed, it can also be measured indirectly by quantifying the decrease in the frequency, but not the amplitude, of miniature excitatory postsynaptic currents following application of OT (Dölen et al. 2013); pretreatment with ketamine, MDMA, LSD, or ibogaine, but not cocaine, restores the ability to induce OTergic plasticity in slices prepared from adult animals (Nardou et al. 2023). Moreover, the time course of this metaplasticity correlates with the duration of the critical period open state induced by psychedelics since, at 2 weeks postinjection, OT induces plasticity in LSD, but not ketamine, pretreatment conditions (Nardou et al. 2023). Interestingly, although psychedelics do not directly attenuate addiction-like behaviors in mice (Nardou et al. 2023), recent studies have shown that LSD-mediated metaplasticity (restoration of excitatory LTD) in the ventral tegmental area corresponds to the extinction (context-dependent unlearning) of morphine place preference memories (Von Gunten et al. 2025). Since the learning model posits that transdiagnostic efficacy is achieved by pairing psychedelics with different therapeutic contexts, it is tempting to speculate that the engagement of these metaplastic mechanisms is, like the selection of which critical period is opened, supervised by the context under which psychedelics are delivered.

At this time, it is not clear whether psychedelic-mediated metaplasticity is the consequence of a homeostatic or Hebbian mechanism. A homeostatic mechanism could be triggered by prolonged overexcitation of the synapse, for example, following an unusually slow off rate of LSD bound to its receptor (Kim et al. 2020), or durable psychoactive metabolites of ibogaine (Knuijver et al. 2024). Alternatively, a Hebbian mechanism could be triggered by context- and activity-dependent synaptic stimulation that selectively recruits downstream signaling cascades and immediate early genes to coordinate coincidence detection with receptor expression and extracellular matrix

(ECM) remodeling (Jiang et al. 2026, Nardou et al. 2023). In either case, the ability to induce metaplasticity is another property that coheres the category of psychedelics and provides a neurobiological framework for understanding the relationship between psychedelic-mediated critical period reopening and durable, context-dependent, therapeutic learning and memory enabled by the restoration of experience-dependent synaptic plasticity.

As shown in **Figure 3**, brain development is a dynamically regulated process, with the early postnatal period characterized by exuberant neurogenesis, neuritogenesis, and spinogenesis (Elston & Fujita 2014, Lee & Sawatari 2011). Later in development, these processes are curtailed, and a number of mechanisms, including metaplasticity, maturation of inhibition, and the maturation of the ECM, emerge to constrain plasticity and close critical periods in adulthood. Thus, in vitro tissue culture, which is restricted to early postnatal brain development, is not an appropriate method for studying the effects of psychedelics on plasticity and critical periods. Moreover, failure to properly control for these developmental changes could explain reports of neuritogenesis following administration of psychedelics in tissue culture (Cameron et al. 2021, Dunlap et al. 2020, Ly et al. 2018, Tuck et al. 2025, Vargas et al. 2023, Warner-Schmidt et al. 2026) since these effects have not been seen in mature brains.

Nevertheless, a number of studies have reported psychedelic-induced structural plasticity in adult tissues ex vivo and in vivo (Jefferson et al. 2023; Jiang et al. 2026; Li et al. 2010; Moda-Sava et al. 2019; Shao et al. 2021, 2025; Wu et al. 2021). These morphological changes could represent either the product of learning (the excitatory postsynaptic representation of a highly memorable event, e.g., "a mouse seeing god") or the process of learning (a metaplastic change that restores the ability to learn, as described above). The former interpretation is favored by the magnitude and duration of spine density changes (15–20%, 2 months) induced by psilocybin doses roughly three times as high (Shao et al. 2025) as those required for reopening the social reward learning critical period (Nardou et al. 2023), and are markedly larger than what would be predicted for normal memory engrams that are sparsely and dynamically encoded across distributed networks of cells and synapses (Josselyn et al. 2015, Sweis et al. 2021). The latter interpretation is supported by glutamate uncaging experiments showing that ketamine pretreatment enhances the ability of glutamate to induce spines (Wu et al. 2021). Moreover, ketamine-induced spine changes appear to be context dependent (occurring only at spines that were recently modified by a stress-inducing manipulation) and are formed with a time course that indicates they occur after the induction of the acute behavioral effects (Moda-Sava et al. 2019). Ultimately it is likely that the products and process of learning emerge in tandem and are mechanistically related, particularly in light of the evidence described above suggesting that the duration of the acute subjective effects of psychedelics is proportional to the duration of the critical period open state they induce (Nardou et al. 2019, 2023) (**Figure 2**). Future studies parsing these mechanistic relationships and relating them to behavior and electrophysiologically defined synaptic plasticity and metaplasticity will be informative.

Finally, an alternative to the learning model presented above is the "psychoplastogen" framework, which represents a new iteration of the biochemical imbalance model of neuropsychiatric disease, frames depression as a loss or deficiency of dendritic spines, and proposes that psychedelics' therapeutic effects are the consequence of correcting this imbalance by generating dendritic spines (Ly et al. 2018). Unfortunately, this approach strives to develop novel compounds selected for their ability to induce plasticity, apparently without regard for the decades of research showing that this type of hyperplasticity is a hallmark effect of drugs of abuse such as cocaine (Spiga et al. 2014). Moreover, the "psychoplastogen" model would predict that since psychedelics induce dendritic spines, they would exacerbate diseases characterized by spine overgrowth such as addiction. Instead, clinical evidence indicates that psychedelic drugs show minimal abuse liability

(Heal et al. 2018, Schlag et al. 2022) and indeed, as discussed above, demonstrate significant therapeutic potential for the treatment of addiction (Bogenschutz et al. 2022, Dakwar et al. 2017, Davis et al. 2017, Krupitsky et al. 2002, Savage & McCabe 1973). Taken together, these observations challenge the utility of the "psychoplastogen" framework for explaining the therapeutic effects of psychedelics.

5. EXTRACELLULAR MATRIX REMODELING

The recognition that the fundamental forms of plasticity described above depend not only on neurons but also on the local environment marked a major shift in how neuroscientists conceptualized the synapse. Originally defined by pre- and postsynaptic elements alone, the framework was first expanded to include glia (Araque et al. 1999), then the ECM; thus, the so-called tetrapartite synapse is composed of presynaptic, postsynaptic, glial, and ECM components (Dityatev et al. 2006). The ECM primarily functions as the scaffold that surrounds and stabilizes all synapses in the brain, which in some neurons (e.g., parvalbumin-positive interneurons) accumulates in a densely packed specialization called the perineuronal net (Wilbrecht & Davidow 2024). Neuronal ECMs are composed of long sugar chains [primarily the glycosaminoglycan hyaluronic acid (HA)] that form a backbone for chondroitin sulfate proteoglycans (CSPGs) and their binding partners [glycoproteins fibronectin (FN), tenascin (TN), etc.] to create a sturdy lattice (Dankovich & Rizzoli 2022). Different ECM receptors such as integrins tether the ECM to the pre- and postsynaptic neuron, while mechanosensitive ion channels such as transient receptor potential vanilloid 4 (TRPV4) detect changes in ECM tension (Frantz et al. 2010).

As the brain matures, ECM components (HA, CSPGs, FN, TN) become remarkably stable and long-lasting, restricting reorganization and preventing structural changes by holding synapses in place (Frantz et al. 2010). This mature ECM restricts synaptogenesis and the wiring of neural networks and coincides with a reduction of receptor exchange, an inhibition of axonal sprouting, and a decrease in the ability to induce experience-dependent plasticity (Frischknecht & Gundelfinger 2012) (**Figure 3**). In the adult brain, some degree of learning and memory persists, which is enabled by local remodeling of the ECM by enzymatic degradation [e.g., matrix metalloproteinases (MMPs)] that cleaves the glycoproteins (e.g., FN) holding the lattice together; adult ECM remodeling is modest and dynamically regulated (Dankovich & Rizzoli 2022). Moreover, manipulations that prolong the open state of critical periods such as sensory deprivation have been shown to delay maturation of the ECM (Gibel-Russo et al. 2022, Sigal et al. 2019). Similarly, chondroitinase, which enzymatically degrades ECM components, promotes poststroke sensorimotor recovery, perhaps by reopening the motor learning critical period (Dromerick et al. 2021, Wiersma et al. 2017). ECM remodeling has also been observed following visual deprivation–induced critical period reopening, and pharmacological inhibition and genetic ablation of MMP-9 block both ECM remodeling and critical period reopening (Murase et al. 2017). Interestingly, sensory deprivation–induced ECM remodeling and critical period reopening appear to be context dependent, since MMP-mediated degradation of the ECM is triggered by and requires a specific visual context (light reintroduction) (Murase et al. 2017).

The first evidence to suggest that psychedelics induce reorganization of the ECM came from studies demonstrating that ketamine induces microglia-dependent degradation of the ECM in the visual cortex and reopens the ocular dominance critical period (Venturino et al. 2021). Subsequently, the Dölen lab (Nardou et al. 2023) used bulk RNA sequencing to identify genes differentially expressed in the NAc between the psychedelic-induced critical period open versus closed state; a significant subset of these genes (roughly 20%) encode either ECM components or regulators, including the glycoproteins *Fn1* and tubulointerstitial nephritis antigen-like

1 (*Tinagl1*), enzymatic regulator *Mmp16*, and *Trpv4*, among others (Nardou et al. 2023). Importantly, these results recapitulate the time course of the critical period open state and metaplasticity induced by psychedelics (but not cocaine) (Nardou et al. 2023). More recently, pretreatment with DOI has also been shown to induce breakdown of the ECM in the prefrontal cortex (Hsiao et al. 2025). Taken together, these results demonstrate that ECM remodeling is a common downstream mechanism observed in many brain regions and shared across psychedelics. Although it is not currently known how ECM remodeling, metaplasticity, and context dependence mechanistically converge, our working model posits that ECM degradation is the permissive event that enables metaplasticity, and that the context dependence of ECM degradation specifies the synapses where metaplastic mechanisms are engaged (Nardou et al. 2023).

As mentioned above, in the cortex, ECM accumulates in a densely packed specialization called the perineuronal net that surrounds parvalbumin-expressing interneurons (PV cells) (Wilbrecht & Davidow 2024). These inhibitory interneurons are thought to serve as functional brakes on excitatory signaling in the cortex. A handful of studies have implicated PV cells in the functional response underlying psychedelic-mediated critical period reopening in the visual cortex (Grieco et al. 2020, Venturino et al. 2021) or psychedelic-induced changes to the intrinsic physiology of the prefrontal cortex (Hsiao et al. 2025). In the NAc, most inhibitory synapses onto the principal cells, medium spiny neurons (MSNs), are recurrent collaterals from other MSNs (Shi & Rayport 1994). Moreover, in the NAc, PV cells make up only 1–2% of cells (Kita et al. 1990), and these neurons are not thought to play a significant role in the regulation of social reward learning behavior (Dölen et al. 2013). Thus, it remains to be seen whether these mechanisms will generalize to psychedelic-mediated reopening of the social reward learning critical period in the NAc.

6. CONCLUSIONS

Here we have argued that the biochemical imbalance model of neuropsychiatric disease should be updated with a learning model, which better accounts for the remarkable diversity of neuropsychiatric diseases for which psychedelics show therapeutic promise, as well as the durability and context dependence of these effects. Furthermore, we propose that psychedelic-mediated critical period reopening and the concomitant restoration of the ability to induce plasticity (metaplasticity) and the reorganization of the ECM provide a unifying mechanistic explanation for the therapeutic and acute subjective effects of psychedelics. Moreover, these results suggest that psychedelics may be the long-sought master keys for unlocking critical periods across the brain. If so, psychedelics' therapeutic applications could be broadened to any number of other clinical and nonclinical contexts (e.g., stroke, allergy, language learning), perhaps by simply altering the context (e.g., occupational therapy, allergen exposure therapy, language immersion).

Learning following critical period reopening is unlikely to account for all of psychedelics' therapeutic promise, since some clinical effects (e.g., curing cluster headaches) appear to be direct and context independent (see also **Figure 1**) (Schindler et al. 2024). While there is considerable enthusiasm for psychedelics' therapeutic potential, these mechanistic insights also reveal important opportunities to mitigate their potential risks. For example, just as bedrest is recommended to avoid reperfusion injury following open heart surgery, psychedelic therapies might be best understood as open mind surgery, which requires safeguarding and supportive care during the extended integration period during which patients are in a vulnerable state (similar to childhood). Although a number of important mechanistic questions remain (as described above), viewing psychedelics' translational properties through a neurobiological lens clarifies that these medications are not merely next-generation SSRIs, but rather adjunct therapies that restore the learning potential of the brain.

DISCLOSURE STATEMENT

G.D. is an inventor on patents that are related to this manuscript (patent application numbers WO 2022/120289 A1; Patent Cooperation Treaty (PCT) Canada 3,203,642, pending; PCT United States 18/255,518, pending).

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