

Opinion

A Dendrite-Focused Framework for Understanding the Actions of Ketamine and Psychedelics

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Pilot studies have hinted that serotonergic psychedelics such as psilocybin may relieve depression, and could possibly do so by promoting neural plasticity. Intriguingly, another psychotomimetic compound, ketamine, is a fast-acting antidepressant and induces synapse formation. The similarities in behavioral and neural effects have been puzzling because the compounds target distinct molecular receptors in the brain. In this opinion article, we develop a conceptual framework that suggests the actions of ketamine and serotonergic psychedelics may converge at the dendrites, to both enhance and suppress membrane excitability. We speculate that mismatches in the opposing actions on dendritic excitability may relate to these compounds' cell-type and region selectivity, their moderate range of effects and toxicity, and their plasticity-promoting capacities.

Towards a Shared Basis for Rapid-Acting Antidepressants

Psychedelics are compounds that produce an atypical state of consciousness characterized by altered perception, cognition, and mood [1]. Drugs with these properties include serotonergic psychedelics, such as psilocybin and lysergic acid diethylamide (LSD), and dissociatives, such as ketamine. Research interest in these compounds has grown due to their therapeutic potential. At subanesthetic dose, ketamine relieves depression with a rapid onset (within 4 h) and sustained positive effects (for at least a week) [2,3]. The antidepressant effect of ketamine is supported by two decades of studies, culminating in successful clinical trials and the approval of esketamine nasal spray [3–5]. For serotonergic psychedelics, their potential as a treatment for mood disorders has long been recognized but historically less studied [6,7]. Clinical trials examining psilocybin, for example, are still underway, although a few studies with small sample sizes have suggested that the compound relieves symptoms of depression and anxiety with rapid onset and perhaps longer duration (weeks if not months) [8,9].

Many psychedelics are broken down in the body rapidly (plasma half-life after intravenous injection in humans is 79 min for ketamine [10], and 74 min for psilocybin [11]), yet behavioral improvements are reported to last for weeks. A current theory for how the short half-life can translate into enduring benefits is that the drugs engage neurotrophic factors to promote neural plasticity [12,13]. Supporting this idea, in rodents, a single dose of ketamine elevates the expression of synaptic proteins [14] and increases the formation rate of new dendritic spines in the medial frontal cortex [15,16]. Likewise, serotonergic psychedelics and related agonists enhance the expression of neurotrophic factors and genes associated with synaptic plasticity [17,18], as well as induce remodeling of dendritic arbors [19].

We are not the first to note the comparable effects of serotonergic psychedelics and ketamine in terms of neural and behavioral consequences [20,21]. However, ketamine is an N-methyl-D-

Highlights

Ketamine can relieve symptoms of depression and anxiety, therefore filling a critically unmet psychiatric need. A few small-scale clinical studies suggest serotonergic psychedelics may have similar therapeutic effects.

Ketamine may both enhance and suppress dendritic excitability, through microcircuit interactions involving disinhibition.

Serotonergic psychedelics may both enhance and suppress excitability, through targeting coexpressed receptors.

Spatial mismatch in the opposing drug actions on dendritic excitability is predicted to steer plasticity actions towards certain synapses and cell types.

We present a dendrite-focused framework as a novel lens to view the actions of ketamine and serotonergic psychedelics on cortical circuits.

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aspartate glutamate receptor (NMDAR) antagonist, whereas serotonergic psychedelics act primarily on serotonergic receptors. The mechanisms for how the disparate molecular targets converge to drive similar plasticity and behavioral effects remain unknown. In this opinion article, we propose that these drugs share a common ability to both enhance and suppress the excitability of dendrites. What is the consequence of a drug that can drive opposing actions on dendritic excitability? We hypothesize that spatial mismatches in the opposing actions may account for the plasticity-promoting capacities of the drugs as well as their cell-type and brain-region specificity. In other words, competition at the dendrites might steer which synapses, neurons, and brain regions undergo plasticity and are modified, thereby positioning dendrites as an important substrate for understanding the actions of ketamine and serotonergic psychedelics (Figure 1A, Key Figure).

Key Figure

Dendritic Excitability as a Plausible Shared Substrate of Compounds with Fast-Acting Antidepressant Properties

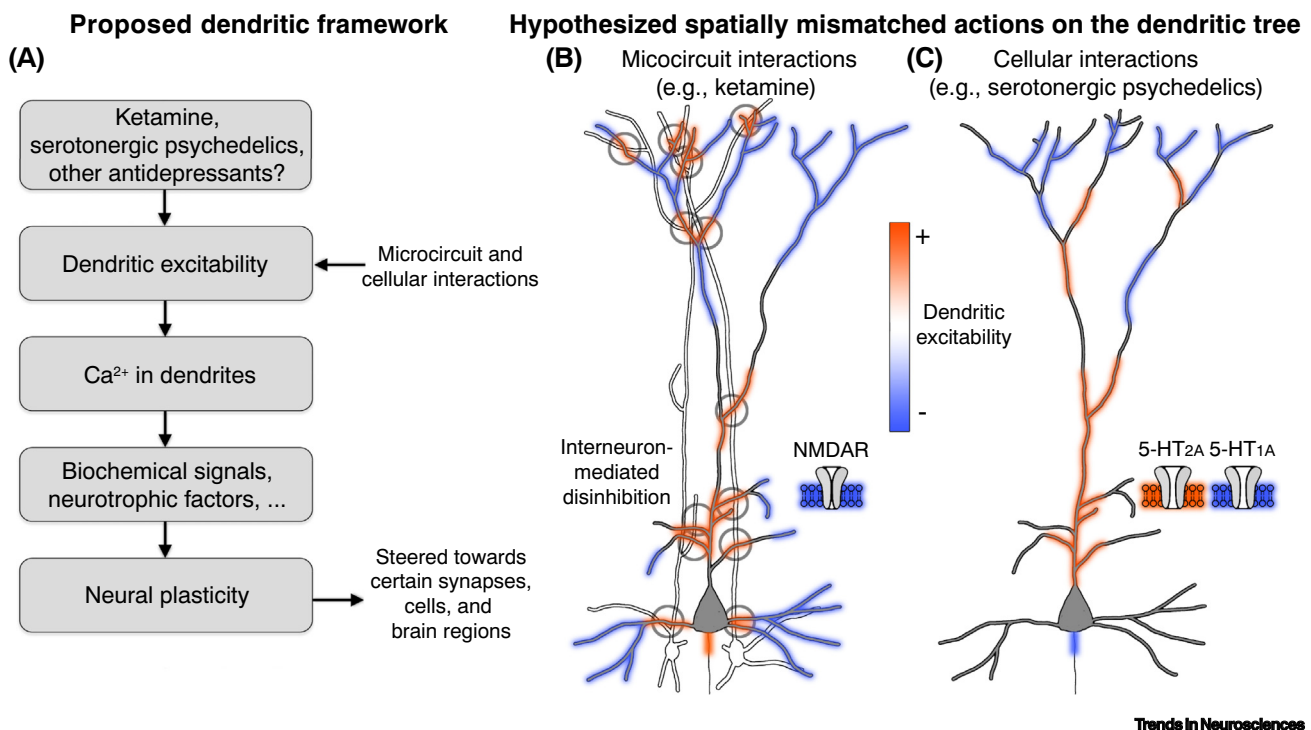


Figure 1. (A) A flowchart outlining the intuition behind a dendrite-focused framework of antidepressant drug actions: ketamine, serotonergic psychedelics, and potentially other drugs with rapid-acting antidepressant effects could acutely modulate dendritic excitability through idiosyncratic ligand–receptor interactions, inducing local gradients of Ca²⁺ influx that drive neurotrophic factors [e.g., brain-derived neurotrophic factor (BDNF)] and biochemical cascades [e.g., mammalian target of rapamycin (mTOR)] to bias certain synapses for the favorable effects of long-term neural plasticity. Based on this view, schematic illustrations show how (B) ketamine is hypothesized to leverage the microcircuit architecture to drive competing actions on pyramidal cell dendrites: inhibition from N-methyl-D-aspartate glutamate receptor (NMDAR) antagonism directly on pyramidal cells (blue shading) and excitation from interneuron-mediated disinhibition (red shading). (C) By contrast, serotonergic psychedelics may take advantage of compartmentalized distributions of serotonin (5-HT) receptor subtypes to drive competing actions on dendritic excitability: agonism of 5-HT_{1A} receptors, likely along the axonal initial segment or in somatodendritic distribution, decreases excitability (blue shading), while agonism of 5-HT_{2A} receptors, primarily along the proximal apical dendritic trunk, leads to increased excitability (red shading). The hypothesized spatially mismatched actions illustrated in (B) and (C) are supported by some evidence on interneuron connectivity [62,63] and receptor localization [41–43,46,47], but the scheme remains to be validated.

Ketamine – Competition for Dendritic Excitability through Microcircuit Interactions

Ketamine is a noncompetitive NMDAR antagonist with complex pharmacology [22]. One notable characteristic is that both the induction and reversal of NMDAR blockade are use dependent. That is, ketamine binds only when the receptor is in its agonist-bound form, but the compound also becomes trapped in a closed channel and cannot unbind until the receptor is reopened by an agonist [23]. Accordingly, although ketamine exhibits similar micromolar affinities for NMDARs of various subunit compositions [24], it may favor receptor subtypes with slower deactivation times [25]. Because blockade decreases the open time and frequency of NMDARs, the anticipated effect of ketamine on dendrites of pyramidal neurons is to reduce membrane excitability (Figure 1B, blue shading).

However, in cortical microcircuits, ketamine antagonizes not only NMDARs on pyramidal neurons, but also NMDARs on GABAergic inhibitory neurons. From the perspective of pyramidal neurons, the consequence is a loss of inhibition, which is the basis of the disinhibition framework of NMDAR antagonism [26]. The disinhibition framework is in agreement with the elevated glutamate efflux [27] and heightened firing rates of pyramidal neurons [28] observed in medial frontal cortex *in vivo* following the systemic administration of NMDAR antagonists. The heightened spike rates, in particular, suggest decreased inhibition on the cell body. Indeed, NMDAR antagonists have been shown to attenuate the activity of soma-targeting, parvalbumin-expressing (PV) GABAergic neurons [29–31]. A recent study showed that knockdown of NMDARs in PV interneurons can block ketamine's antidepressant-like effects in mice [32], although the behavioral effects of interneuron manipulation can be complicated [33]. Nonetheless, this finding and other lines of evidence [32,34] indicate PV interneurons may be involved in ketamine's antidepressant action.

Extending the disinhibition framework, a recent study demonstrated that ketamine has a substantial impact on inhibition mediated by the dendrite-targeting, somatostatin-expressing (SST) GABAergic interneurons [35]. Using subcellular-resolution two-photon imaging to monitor cellular and synaptic Ca^{2+} signals, it was shown that the activity of frontal cortical SST interneurons was markedly reduced in awake mice within an hour of ketamine administration. The diminished dendritic inhibition was accompanied by elevated Ca^{2+} influx in apical dendritic spines, indicative of increased synaptic excitability. Blocking ketamine's actions on prefrontal SST interneurons prevented drug-induced behavioral outcomes. Therefore, an indirect effect of ketamine on dendrites of pyramidal neurons, through disinhibition, is an increase of membrane excitability (Figure 1B, red shading). Of note, disinhibition by PV interneurons may also contribute to elevating dendritic excitability, as the PV interneurons may influence the proximal portion of the dendritic tree. Taken together, these findings suggest that the direct and indirect effects of ketamine produce opposing actions on the dendritic excitability of pyramidal neurons.

Serotonergic Psychedelics – Competition for Dendritic Excitability through Coexpressing Receptors

Serotonergic psychedelics, also referred to as serotonergic hallucinogens (e.g., psilocybin, LSD, and mescaline), have high affinity for serotonin (5-HT) receptors. Take for example psilocybin: after entering the body, it is rapidly converted in the liver into multiple metabolites including psilocin [36]. Psilocin, a structural analog of 5-HT, has affinity for many 5-HT receptor subtypes and select adrenergic, dopaminergic, and histaminergic receptors (Table 1). The listed 5-HT receptors are G-protein-coupled receptors that engage a wide range of intracellular signal transduction pathways that can influence neuronal excitability. Here, we focus mainly on 5-HT_{2A} and 5-HT_{1A} receptors because these subtypes have been most heavily characterized in the cortex for their potential roles in mediating the actions of serotonergic psychedelics.

Table 1. Binding Affinities of Ketamine and Psilocin for Various Receptor Types^a

K _i values, binding affinity (nM)			
	Ketamine	Psilocin	Radioligand
5-HT _{1A}	Low affinity	567	[3H]-8-OH-DPAT
5-HT _{1B}	Low affinity	220	[3H]-GR-125743
5-HT _{1D}	Low affinity	36	[3H]-GR-125743
5-HT _{1E}	Low affinity	52	[3H]-5HT
5-HT _{2A}	Low affinity	107	[3H]-Ketanserin
5-HT _{2B}	Low affinity	5	[3H]-LSD
5-HT _{2C}	Low affinity	97 ^b	[3H]-Mesulergine
5-HT ₃	Low affinity	Low affinity	[3H]-LY 278584
5-HT ₅	Low affinity	84	[3H]-LSD
5-HT ₆	Low affinity	57	[3H]-LSD
5-HT ₇	Low affinity	4	[3H]-LSD
5-HT transporter	Not available (N.A.)	3801	[3H]-Citalopram
NMDA	661 ^p	N.A.	[3H]-MK-801
Adrenergic α _{2A}	Low affinity	1379	Ketamine: [3H]-rauwolscine; Psilocin: [125I]-clonidine
Adrenergic α _{2B}	Low affinity	1894	Ketamine: [3H]-rauwolscine; Psilocin: [125I]-clonidine
Dopamine D ₃	Low affinity	2645 ^a	Ketamine: [3H]-N-methylspiperone; Psilocin: [3H]-NMSP
Histamine H ₁	Low affinity	305	[3H]-Pyrilamine

^aSource: NIMH Psychoactive Drug Screen Program (PDSP) [129]. K_i values are PDSP certified values (human data except where ^b indicates value from rats when human data were unavailable). Note that values for ketamine are for the racemic mixture, which consists of (S)- and (R)-ketamine that are converted into multiple metabolites. The enantiomers and metabolites have varying affinities to NMDAR and other receptors [22]. Low affinity means K_i >10 000 nM.

As expected from their respective coupling to G_q and G_{i/o} protein pathways, activation of 5-HT_{2A} and 5-HT_{1A} receptors has contrasting effects on neuronal excitability. For 5-HT_{2A} receptors, electrophysiological recordings from layer 5 pyramidal neurons in the rat frontal cortex *in vitro* indicate that activation leads acutely to membrane depolarization [37], and facilitates spiking activity by reducing afterhyperpolarization and decreasing spike frequency accommodation [38]. By contrast, activation of 5-HT_{1A} receptors is associated with membrane hyperpolarization [37,38]. Similar opponent actions have been reported for human neocortical neurons [39].

Where are these receptors located in the frontal cortex? In one early study, it was estimated that about 60% of frontal cortical neurons in the rat have detectable levels of *Htr1a* or *Htr2a* transcripts and, among these cells, about 80% showed coexpression in the same cell [40]. The coexpression is in line with electrophysiological observations of within-neuron competition: some pyramidal neurons have a biphasic firing response to 5-HT, where the addition of a 5-HT_{2A} or 5-HT_{1A} receptor-specific antagonist could diminish the excitatory or suppressive component respectively [38].

Although 5-HT_{2A} and 5-HT_{1A} receptors can be present in the same pyramidal neurons, their subcellular localization appears to differ. Immunohistochemical stains revealed a strikingly high density of 5-HT_{2A} receptors in the proximal apical dendritic trunk of pyramidal neurons in rat and macaque frontal cortex [41,42]. The postsynaptic localization to dendritic shafts and dendritic spines was confirmed by an ultrastructural characterization [43], as well as identification

of molecular partners that drive the preferential sorting of 5-HT_{2A} receptors [44]. In a study using microiontophoresis to target different dendritic locations, it was shown that adding 5-HT locally at the apical dendrite was sufficient to elevate the frequency and amplitude of spontaneous excitatory postsynaptic currents; an effect that was notably absent when the same manipulation was performed on basilar dendrites [45]. Converging evidence therefore indicates that 5-HT_{2A} agonism leads to increased membrane excitability, most strongly in the proximal apical dendrite (Figure 1C, red shading).

There is less consensus on the subcellular localization of 5-HT_{1A} receptors. An immunohistochemical study indicated a somatodendritic distribution for 5-HT_{1A} receptors on pyramidal neurons in the rat hippocampus [46]. However, subsequent work, which relied on an antibody recognizing a different epitope, reported a concentration of 5-HT_{1A} receptors on the axon initial segment of cortical pyramidal cells [47]. Despite uncertainty in the subcellular localization, what is clear is that the effect of 5-HT_{1A} agonism is a decrease in membrane excitability (Figure 1C, blue shading).

Putting it all together, multiple lines of evidence suggest ketamine and serotonergic psychedelics exert competing actions on dendritic excitability. Although the principal mechanisms – microcircuit interactions for ketamine and receptor coexpression for serotonergic psychedelics – may differ, we reason that the ability of the compounds to drive opposing effects on dendritic function in the same cell is similar. In the following sections, we will explore five ways in which the proposed opposing actions could account for some of the neural and behavioral features of ketamine and serotonergic psychedelics.

Opposing Actions as a Mechanism to Promote Long-Term Neural Plasticity

An increase of membrane excitability boosts Ca²⁺ influx through calcium-permeable channels including NMDARs and voltage-gated Ca²⁺ channels. Once in the dendritic compartment, Ca²⁺ acts as a second messenger to initiate signaling cascades and engage neurotrophic factors responsible for spine growth [48]. The essential role of Ca²⁺ in synaptic plasticity has been demonstrated thoroughly by studies involving bidirectional manipulation of postsynaptic Ca²⁺ levels during protocols of synaptic potentiation [49,50]. The relationship is supported by how the peak Ca²⁺ accumulation in dendritic spines tracks the magnitude of long-term changes in synaptic efficacy [51]. Overall, our perspective (Figure 1A) is in line with the prevailing neurotrophic model for stress-related mood disorders and antidepressant actions [12,52], because postsynaptic Ca²⁺ influx is expected to upregulate neurotrophins [53], such as brain-derived neurotrophic factor (BDNF), which acts on tropomyosin receptor kinase B (TrkB) receptors to stimulate mammalian target of rapamycin (mTOR) signaling crucial to synapse formation. The plasticity actions of ketamine [54] and serotonergic psychedelics [19] have been linked to BDNF expression and mTOR activation, suggesting that these cascades underlie the shared capacity to drive sustained antidepressant effects. What differs is that the proposed framework emphasizes the acute drug actions on dendritic excitability and Ca²⁺ influx as leading factors and equally important contributors to the plasticity effects.

Through their actions on dendritic excitability, ketamine and serotonergic psychedelics are expected to initiate plasticity. Plasticity is predicted, by our framework, to occur only for select dendritic branches and spines because the impact of the drugs on the dendritic tree is likely to be heterogeneous, due to spatial mismatches in the opposing actions. In particular, ‘hot spots’ of elevated excitability may be potentiated to enhance synaptic coupling, congruent with the excitatory synapse hypothesis of depression [55,56]. Although the idea seems intuitive, details remain open for experimental confirmation, because precise measurements of the pharmacological effect across the entire dendritic tree are currently lacking (see [Outstanding Questions](#)). For

example, there could be differences in the exact dendritic locations targeted by ketamine and serotonergic psychedelics, which would allow for differences in time course and phenotype of the drugs' antidepressant actions.

Although a full picture of each drug's actions on dendrites is lacking, one can still appreciate the powerful impact of how local control of dendritic excitability can sculpt Ca^{2+} signaling and plasticity, by surveying experiments in which dendritic excitability is perturbed directly using electrical or optical methods. At the dendritic trunk, raising excitability by current injection increases the occurrence of dendritic Ca^{2+} spikes that lead to widespread Ca^{2+} influx in apical dendritic tufts *in vivo* [57]. By contrast, reducing excitability by evoking a unitary inhibitory input is sufficient to short circuit back-propagating regenerative events [58]. These empirical findings are in agreement with computational models showing that inhibition at the dendrites modifies the threshold and amplitude of dendritic electrogenesis [59]. At the dendritic tuft, dendrite-targeting interneurons have a propensity to inhibit cortical apical dendrites in a branch-specific fashion [60,61]. The inhibitory inputs are primarily located on shafts [62,63], and the impact of SST interneuron-mediated inhibition on Ca^{2+} signaling varies greatly across individual dendritic spines [64,65]. The specificity in dendritic inhibitory innervation suggests that ketamine-induced disinhibition may apply to only a subset of dendritic spines. In one study, the impact of individual GABAergic synapses on dendritic Ca^{2+} signals was measured and the attenuation had a narrow spatial window of $\sim 25 \mu\text{m}$ [66]. Collectively, diverse forms of local and widespread dendritic Ca^{2+} signals are associated with a multitude of plasticity mechanisms [67,68], which we suspect are targeted by spatially confined changes in excitability arising from the actions of ketamine and serotonergic psychedelics.

We focused on dendritic locations with increased excitability, but is there also a role for other locations in the same dendritic tree with concomitant reductions in excitability? One possibility is that the balance of excitatory and inhibitory effects serves to stabilize the overall excitability of the neuron, preventing aberrant spiking activity. Intriguingly, higher doses of ketamine, where it acts as an anesthetic, dramatically reduce the propagation of electrical signals from the apical dendritic tuft to the cell body of layer 5 pyramidal neurons, leading to an electrical decoupling of the dendritic tree from the somatic compartment [69].

Opposing Actions as a Mechanism to Acutely Alter Synaptic Integration

A central function of the dendrite is synaptic integration, where thousands of inputs are transformed into a (typically) all-or-none output. The integration process is regulated by a balance of excitatory and inhibitory synapses along dendrites [70], which is tuned by homeostatic mechanisms that can calibrate excitability in a branch-specific manner [71] or even at the level of local GABAergic inputs [72]. Because ketamine and serotonergic psychedelics acutely perturb dendritic excitability, the drugs are expected to impair the ability of dendrites to receive and filter inputs. In the frontal cortex, inputs impinging on dendrites carry behaviorally relevant information including sensory- and reinforcement-related signals [61,73,74].

The behavioral alterations during the short period when ketamine or a serotonergic psychedelic is bioavailable are consistent with altered synaptic integration. For psychedelics, a core symptom is a warped awareness of the surroundings, corresponding to a disruption of sensory input filtering [1]. The dendritic origin of this phenotype is supported by experiments that have knocked out the dendrite-localized 5-HT_{2A} receptors in neocortex [75] and, more specifically, compromised the dendritic targeting of 5-HT_{2A} receptors [44]. These manipulations eliminated head-twitch responses, a drug-induced motor stereotype in rodents that correlates closely with the potency of hallucinogen exposure in humans [76]. Furthermore, a neural signature for diminished input filtering would be an aberrant increase in functional connectivity with the frontal cortex. Combined

electrical microstimulation to excite long-range inputs and two-photon imaging to record from frontal cortical dendrites have demonstrated that ketamine administration in mice elicits hypersensitivity to long-range cortical inputs [35].

Reinforcement-related signals arriving at the apical dendrites could serve as a substrate for forming new associations or calculating credit assignments during reward-guided learning [58,77]. In this instance, it is instructive to consider one of the more carefully designed studies that have characterized effects of subanesthetic ketamine on cognitive flexibility. In this study, the authors instructed participants to play the Wisconsin Card Sorting Task twice, one week apart [78]. Administration of ketamine immediately prior to the first task exposure induced perseverative deficits, whereas the same treatment before the second task exposure had no noticeable effect on performance. These results suggest that cognitive rigidity due to subanesthetic ketamine may be ascribed to a learning deficit, because the effect is absent when subjects merely have to re-implement a learned rule.

Opposing Actions as a Mechanism to Influence Select Cortical Regions

Thus far, we have discussed the actions of ketamine and serotonergic psychedelics with an emphasis on the medial frontal cortex. In part, this is because numerous preclinical studies have implicated neural plasticity in the medial frontal cortex as essential for the antidepressant-like effects of ketamine [14,16]. Another reason is that although the drug would be broadly present in the brain following systemic administration, mapping studies indicated higher metabolic activity in select regions, which included the medial frontal cortex for ketamine in humans [79,80] and rodents [81], and for psilocybin in humans [82]. These results indicate that the drugs act on certain brain regions more than others (see [Box 1](#) for a brief discussion of other targeted brain regions).

For ketamine, we have proposed that the competing actions coalesce at the apical dendrites of pyramidal cells due to interneuron-mediated disinhibition that opposes the direct effects of NMDAR antagonism. Thus, one prediction is that ketamine should have a stronger influence in regions with a high abundance of SST interneurons relative to the overall inhibitory tone (PV interneurons used as a proxy in the following analyses), because of the relative preponderance of sites available for dendritic disinhibition. This interneuron distribution is indeed the case for medial frontal cortex, in terms of transcript expression in humans [83] as well as cell density in mice [84,85]. To reproduce these earlier findings but for transcript expression in mice, we plotted the relative levels of *Sst* and *Pvalb* mRNA from *in situ* hybridization data [86] against neuroimaging-based estimates of cortical hierarchy [85] (Figure 2A–C). As the visualization indicates, prefrontal and anterolateral regions have increased expression of *Sst* relative to *Pvalb*, consistent with recent measures of cell density [84,85]. This pattern, we speculate, may render these brain areas more susceptible to drug-induced dendritic disinhibition relative to, for example, motor regions. Such region specificity for ketamine-induced disinhibition is consistent with recent measurements [35], although will require further testing. We note that, in addition to neocortex, similar dendrite-targeting interneurons and microcircuit motifs exist in the hippocampus, another location that is activated robustly by ketamine [81,87].

Similarly, the relative abundance of 5-HT_{1A} and 5-HT_{2A} receptors might determine the regional selectivity of serotonergic psychedelics. In a study using high-resolution positron emission tomography in humans, it was found that while 5-HT_{1A} and 5-HT_{2A} receptors showed enrichment in the frontal cortex, entorhinal cortex, temporal cortex, and insula, the ratio of expression differs across the regions [88]. Moreover, LSD-induced functional connectivity matches the *HTR2A* gene expression in human neocortex [89]. To investigate the relationship in mice, we mined *in situ* hybridization data for *Htr1a* and *Htr2a* (Figure 2D). Prefrontal regions tend to have

a higher *Htr2a:Htr1a* expression ratio than posterior cortical regions (i.e., medial and visual areas in Figure 2B). The extent to which these differences relate (for instance in mice) to the effect of serotonergic psychedelics on brain-wide activity remains to be measured. It is worth noting that regions important for drug actions are often assumed to have elevated firing or metabolic activity, but this may not be the case for serotonergic psychedelics [90], as plasticity arising from dendritic electrogenesis could occur independent of spiking output [91,92].

Opposing Actions as a Mechanism to Target Subpopulations of Neurons

Within the frontal cortex, there are numerous subtypes of pyramidal neurons, and each subtype's response to ketamine and serotonergic psychedelics may depend on its sensitivity to the hypothesized opposing actions. Take serotonergic psychedelics as an example; subpopulations of pyramidal neurons that have high levels of 5-HT_{2A} relative to 5-HT_{1A} receptors may exhibit pronounced excitation, whereas other cells with favored expression of 5-HT_{1A} receptors display the opposite response.

There are many anatomical and molecular differences that could contribute to differential sensitivity across subtypes of pyramidal neurons. For example, pertaining to ketamine, supragranular pyramidal neurons have more inhibitory inputs near the main dendritic bifurcation, but fewer inhibitory inputs in distal tufts, relative to deep-layer pyramidal neurons [63]. Among layer 5 pyramidal neurons, the thick- and slender-tufted pyramidal neurons [putatively pyramidal tract (PT) and intratelencephalic (IT) subtypes] have different amounts of inhibitory innervations [63]. Similarly, with regard to their sensitivity to 5-HT, most IT neurons exhibit 5-HT_{2A}-receptor-dependent increase in firing, whereas many PT neurons display 5-HT_{1A}-receptor-dependent activity suppression in the mouse frontal cortex [93,94], although differences across cell types may be species specific and developmentally regulated [94].

To seek insight into the cell types likely responsive to serotonergic psychedelics, we took advantage of a public database of single-cell RNA sequencing data from >10 000 cells sampled from the anterolateral motor cortex in mice [95]. Focusing on 5-HT receptor subtypes with high affinity to psilocin (Table 1), this visualization reveals that although most neuronal subclasses have low levels of *Htr1a*, IT neurons have enriched expression of *Htr2a* (Figure 3A). Consistent with prior literature [93,94], we suggest that the high *Htr2a:Htr1a* expression ratio in IT neurons should render these cells susceptible to psychedelic-induced increases in membrane excitability (Figure 3B). Other intriguing observations include: a *Htr1a* bias for SST interneurons suggesting serotonergic psychedelics may also induce dendritic disinhibition, the near absence of coexpression in layer 6 pyramidal neurons and non-SST interneuron subtypes, as well as considerable levels of several other 5-HT receptor subtypes whose cell-type-specific functions are unknown (Figure 3C). Overall, the gradient of receptor composition in different cells should correspond to a spectrum of pharmacological responses (Figure 4A–C), with the implication that through a balance of receptor expression ratios, plasticity is steered towards select subpopulations of neurons.

Opposing Actions as a Mechanism to Mitigate Toxicity

Although transient imbalance in dendritic excitability can promote plasticity, prolonged and excessive dendritic alterations may be deleterious and underpin various neuropsychiatric disorders [96,97]. Confronted with excitotoxicity, dendrites appear to be particularly vulnerable to overactivation [98], perhaps because of their morphology and limited ability to invoke intracellular pathways to counter the excitotoxic challenge [99].

For ketamine and serotonergic psychedelics, the concurrent push-and-pull actions are expected to influence dendritic excitability with a dose–response curve that depends on the precise nature

of excitatory and inhibitory responses to each dose. In an illustrated example (Figure 4D–F), the response is tempered at high dose because both actions are engaged. At a lower dose, depending on the potency (i.e., receptor affinity) and efficacy (i.e., maximum biological response) of the competing actions, the excitatory actions can exceed inhibitory effects to generate maximal increase in dendritic excitability for the compound. An inverted U-shaped dose–response curve safeguards against high-intensity responses associated with drug toxicity [100]. This, in combination with the rapid pharmacokinetics, may be crucial for inducing neural plasticity while avoiding dendritic damage. Consistent with this idea, while low-dose ketamine has fast-acting antidepressant effects, higher doses produce general anesthesia. Likewise, although chronic exposure may be neurotoxic [101], serotonergic psychedelics are typically tolerated at high doses. For example, the therapeutic ratio of LSD in humans is 280 (effective dose = 50 mg; lethal dose = 14 000 mg), making the therapeutic dose remarkably distant from doses carrying any lethality risk [1]. By contrast, the hallucinogen NBOMe, which has higher selectivity for 5-HT_{2A} compared with 5-HT_{1A} receptors, presents negative side effects and has been linked to fatalities [102].

The mitigation of toxicity is a core appeal of nonselective pharmacological therapies. Specifically, ketamine and serotonergic psychedelics may generate a summative therapeutic action, while limiting adverse effects stemming from excessively agonizing or antagonizing a single target. This idea has been championed as the ‘magic shotgun’ [103], in contrast to highly selective agents which would be ‘magic bullets’.

Limitations of the Proposed Framework

It is important to consider features of ketamine and serotonergic psychedelics that may be inconsistent with the dendritic framework. We have proposed that ketamine’s opposing actions on dendritic excitability are due to NMDAR antagonism. However, other NMDAR antagonists (e.g., dizocilpine, phencyclidine, memantine, rapastinel, and lanicemine) have not consistently produced

Box 1. Future Work Informed by the Dendritic Framework

The dendritic framework has a number of gaps and predictions that compel further study. We focused discussion of ketamine on the frontal cortex, but regions such as lateral habenula may respond through mechanisms other than dendritic excitability, and play important roles in the antidepressant effects [130]. Serotonergic psychedelics can inhibit spontaneous activity in subcortical nuclei, for example, through direct actions on dorsal raphe [131] and indirect actions on locus coeruleus [132]. These neuromodulatory effects may underpin reduced sensory drive in primary cortex [133], contributing to the unique subjective effects of these compounds such as visual hallucinations, which are distinct from ketamine’s effect of distorting sensory perception.

Given the myriad target regions, one intriguing hypothesis is that ketamine and serotonergic psychedelics open a critical window of plasticity in the frontal cortex, with concomitant inputs from other regions as necessary ingredients to strengthen specific long-range pathways. If true, this would suggest that purposeful, pathway-specific stimulation during the acute phase of drug administration or within the time window of neurotrophin induction could be beneficial, and may be leveraged to augment plasticity actions. It remains unclear how the direct receptor-level actions of ketamine and serotonergic psychedelics contribute to the acute dissociative or hallucinogenic effects, and whether these psychotomimetic effects are related to the antidepressant action [134,135]. High-fidelity behavioral phenotyping during and following drug administration may help uncover the relations between the on- and off-target behavioral effects. To this end, it may be fruitful to examine whether psychedelics affecting other receptors (e.g., salvinorin A acting on κ -opioid receptors [136]) exhibit similar competing actions on dendritic excitability and rapid antidepressant effect [137].

For serotonergic psychedelics, novel insights might be gained by characterizing the relative expression of 5-HT receptor subtypes, rather than their absolute abundances, in relation to dendritic responses, neural pathways [138], and behavioral outcomes [139]. For ketamine, current evidence suggests that only a subset of dendritic spines are under the influence of inhibitory inputs, and therefore sensitive to ketamine-induced disinhibition. Future experiments that focus on these plastic connections, perhaps to identify the source of their presynaptic inputs [63,140], will be informative. Relatedly, visualizing the acute and sustained drug actions across the entire dendritic tree will help address the nature of the predicted spatial mismatches in dendritic excitability. Current optical methods are limited in terms of relatively small fields of view and poor temporal resolution [141]. New imaging approaches, for instance those relying on remote focusing and Bessel beam technologies [73,142], open the possibility to measure calcium and other biochemical signals over a large fraction of the dendritic field following drug administration.

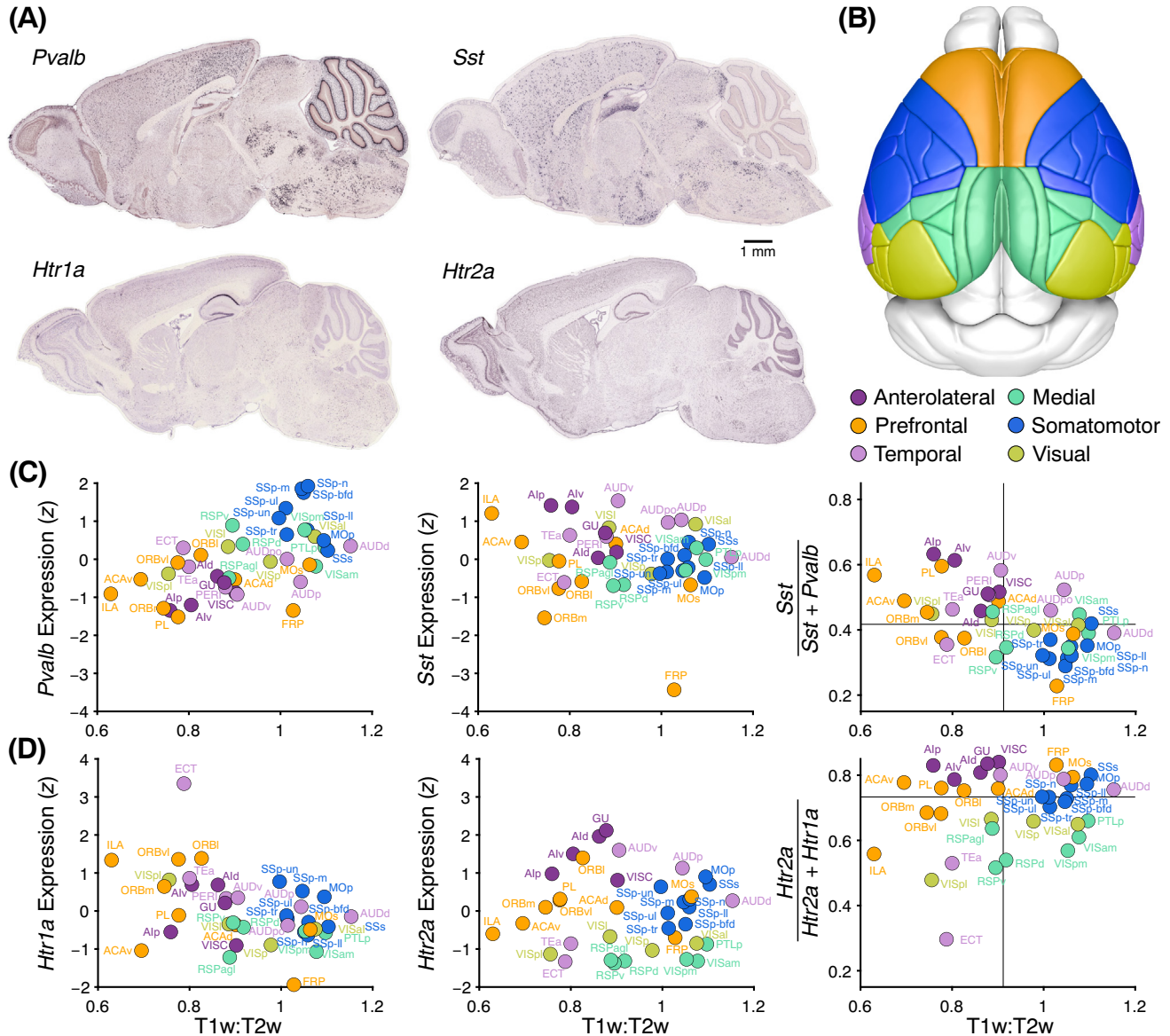


Figure 2. Regional Differences in the Expression of *Sst*, *Pvalb*, *Htr1a*, and *Htr2a* in the Adult Mouse Neocortex. (A) For each gene, an example of the mRNA transcripts detected from *in situ* hybridization in a near-midsagittal section of an adult C57BL/6J mouse, from the Allen Institute for Brain Science database [86]. (B) Cortical regions as demarcated in the Allen Mouse Common Coordinate Framework, and further color-coded based on six groupings. (C) Regional expression of *Pvalb* and *Sst* as well as their ratios, obtained from [86], plotted against the T1w:T2w parameter (inversely related to cortical hierarchy), obtained via [85] from the Scalable Brain Atlas [143] in Waxholm space [144]. Lines, medians. (D) Similar to (C), but for *Htr1a* and *Htr2a*.

antidepressant effects [104]. What sets ketamine apart? A parsimonious explanation is that subanesthetic ketamine may induce just the right amount of delicate balance of suppressive and disinhibitory actions on dendritic excitability, varying from other NMDAR antagonists due to differences in pharmacological properties. Indeed, ketamine differs from other NMDAR antagonists in binding-site affinity [105], NMDAR trapping [106], potency of effect on intracellular cascades [107], and even preference for particular receptor states and subcellular locations [108]. Still, the exact reasons remain unknown.

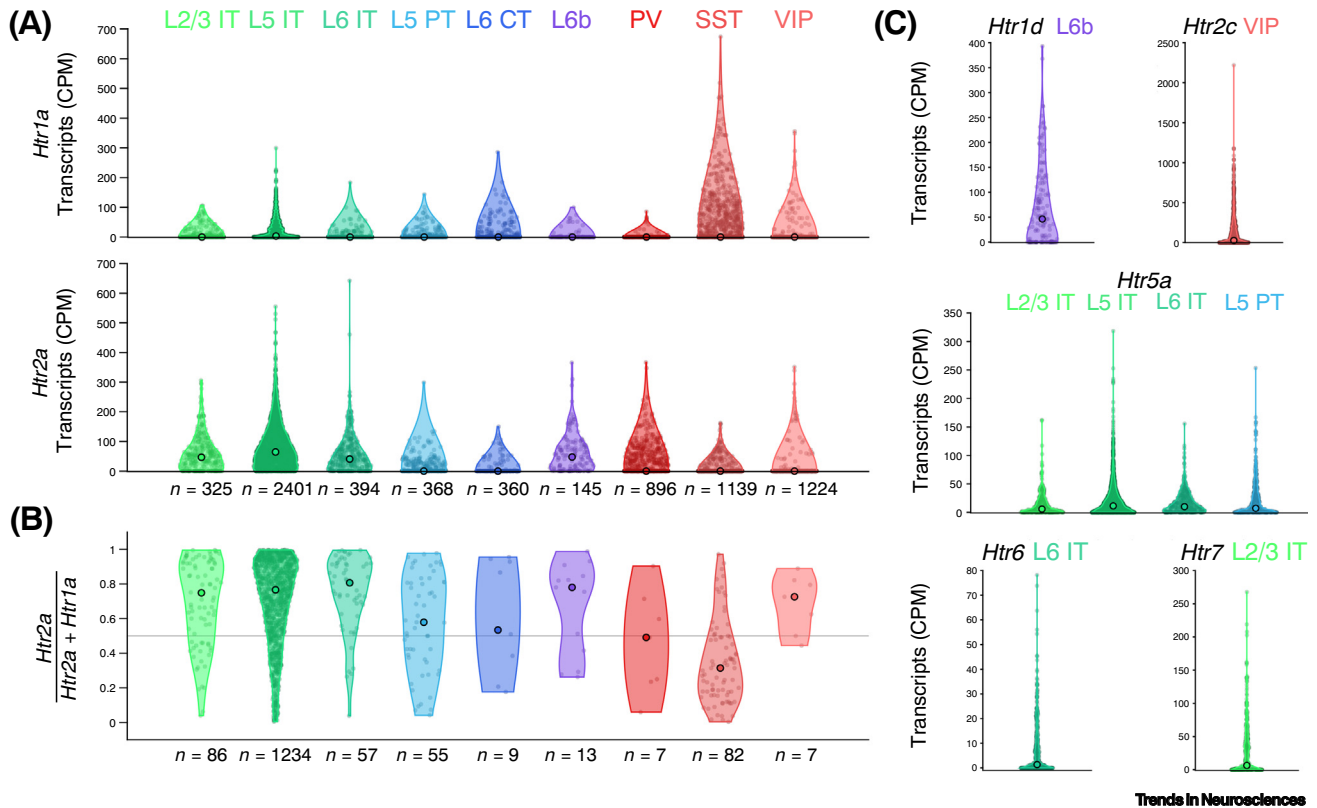


Figure 3. Cell-Type Differences in the Expression of *Htr1a*, *Htr2a*, and Other Serotonin Receptor Genes in the Adult Mouse Frontal Cortex. (A) Expression of *Htr1a* and *Htr2a* transcripts in cortical cell types, based on analyzing single-cell RNA sequencing (SMART-Seq v4) data from 7252 neurons sampled from the anterolateral motor cortex of adult C57BL/6J mice of both sexes by the Allen Institute for Brain Science [95]. Open circle, median value; n, count of the cell subclass. (B) The *Htr2a*:*Htr1a* expression ratio, for neurons with non-zero expression values for both *Htr1a* and *Htr2a*. Open circle, median value; n, count of the cell subclass. (C) Additional serotonin (5-HT) receptor subtypes (among those listed in Table 1) that show enriched expression (median CPM > 0) in select neuronal subclasses. Abbreviations: CPM, counts per million reads; CT, corticothalamic; IT, intratelencephalic; L2/3, layer 2/3; L5, layer 5; L6, layer 6; PT, pyramidal tract; PV, parvalbumin; SST, somatostatin; VIP, vasoactive-intestinal protein.

Ketamine has additional intriguing characteristics and off-target effects, but these features generally align with the hypothesized push and pull on dendritic excitability. For example, at a higher dose, ketamine appears to suppress HCN1-containing channels, which would relieve shunting in dendrites and also enhance excitability [109]. Recent data indicate that (*R*)-ketamine may exert more potent antidepressant effect with fewer adverse effects than (*S*)-ketamine [110,111], although both enantiomers are suspected to antagonize NMDARs albeit with slightly different affinity [22]. Moreover, the metabolite hydroxynorketamine has been shown to mediate rapid antidepressant-like action without antagonizing NMDARs [112,113]. Although the effects of ketamine metabolites on dendritic excitability are not yet known, and therefore cannot be fully explained by the present framework, they appear to drive antidepressant-like effects in mice through similar neurotrophic cascades as ketamine [22].

5-HT receptor signaling is complex, and the pharmacological features distinguishing psychedelics from other 5-HT-related agents are not well understood [6]. On the one hand, although 5-HT can promote neurite growth in cortical neurons, the effect is minimal compared with psychedelics [19]. On the other hand, the selective 5-HT_{2A} agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) may promote neurite growth [19] and anxiolytic action [114] without agonizing 5-HT_{1A} receptors. Moreover, selective serotonin-reuptake inhibitors (SSRIs) exert antidepressant effects on a different

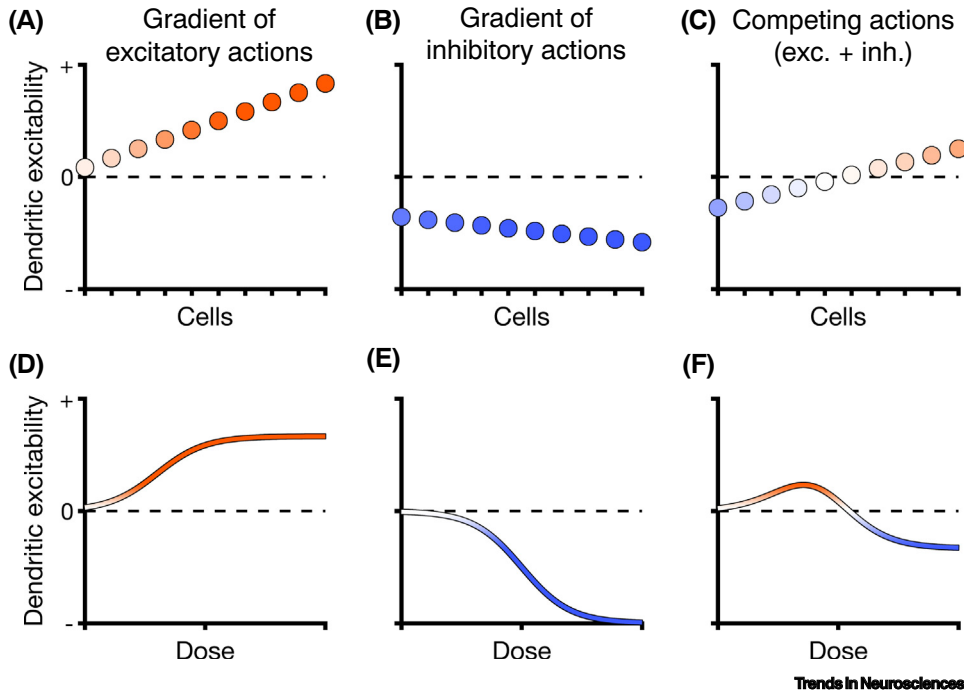


Figure 4. Mismatches in Excitatory and Inhibitory Actions Can Mediate Drug Selectivity: A Schematic Illustration. A drug may exert a gradient of (A) excitatory (exc.) effects (e.g., interneuron-mediated disinhibition for ketamine, serotonin (5-HT)_{2A} receptor agonism for serotonergic psychedelics) and (B) inhibitory (inh.) effects [e.g., N-methyl-D-aspartate glutamate receptor (NMDAR) antagonism, 5-HT_{1A} receptor agonism] on dendritic excitability across cells or brain regions. (C) The summative effect of the competing actions may steer increases in dendritic plasticity towards a subpopulation of cells or select brain regions, while leaving others unaffected or even suppressed. (D–F) Similarly, for dose–response curves, the summative effect of the competing actions could constrain the effects of a drug on dendritic excitability, limiting the positive effects to a restricted dose range and safeguarding against high-intensity responses associated with drug toxicity.

time scale. Some of the complexity may arise because 5-HT_{2A} receptors can form heteromeric complexes (e.g., with metabotropic glutamate 2 receptor; [115]) to recruit additional signal transduction pathways. Furthermore, the effect of 5-HT on its receptors may not fully recapitulate the actions of serotonergic psychedelics, as agonist-directed signaling of the 5-HT_{2A} receptor can involve different intracellular partners and transduction pathways [75,116–118] leading to unique effects on Ca²⁺ mobilization [119]. Beyond the acute drug actions, there is substantial adaptation in the receptors following agonist exposure, including the well-documented desensitization and downregulation in 5-HT_{2A} receptors [120]. A key challenge will be to reconcile how the various effects at the molecular, cellular, and circuit levels contribute to the antidepressant actions of serotonergic psychedelics.

Dysfunctional signaling of monoamines, including glutamate [5] and 5-HT [121], is thought to play a major role in the etiology of depression. Ideally, the actions of an antidepressant should be viewed through the lens of the dysfunction, as the goal of pharmacological treatments is to restore function. In particular, the excitability of dendritic branches and spines may be regulated with homeostatic set points [122]. By nudging excitability in both directions, ketamine and serotonergic psychedelics could act to restore the homeostasis required for proper dendritic function [13]. However, the interaction of dysfunction and pharmacological actions on the dendritic substrate remains poorly understood. In this opinion article, we have focused on discussing how psychedelics may converge to prompt selective plasticity actions, but it will also be important to know why the selected plasticity actions are beneficial.

To develop a comprehensive understanding of the antidepressant effects of ketamine and serotonergic psychedelics, one will need to consider these compounds' actions in various brain regions and their potential off-target effects. Even within the frontal cortex, it should be emphasized that pyramidal neurons are embedded in cortical microcircuits, therefore considering the drugs' actions at the individual cell level leads to an incomplete picture. The reverberation of excitatory activity and influences from other cell types is expected to lead to higher-order, downstream effects that further shape dendritic excitability. Serotonergic psychedelics, for example, while preferentially exciting IT pyramidal neurons [93] (Figure 3B), are likely to have second-order effects on PT pyramidal neurons as well, because of the biased connectivity between the two cell types [123]. Moreover, a minor fraction of 5-HT_{1A} and 5-HT_{2A} receptors reside in interneurons (Figure 3A), which can modify GABAergic signaling [124,125]. There are also possibly 5-HT_{2A} receptors in thalamocortical axons in the frontal cortex [126], although the presynaptic localization is at odds with other evidence [43,75]. In a similar vein, drug actions on other brain regions are expected to regulate the long-range synaptic inputs arriving at the dendrites. In the medial frontal cortex, inputs impinging on the apical dendritic tufts can arise from a variety of sources (e.g., thalamus, amygdala, and other cortical regions) [127], and neuromodulatory inputs such as dopaminergic terminals can play a crucial role [128]. The extent to which these additional layers of micro- and mesoscale circuit interactions relate to the plasticity actions of ketamine and serotonergic psychedelics will be a key question for future research (Box 1).

Concluding Remarks

In summary, ketamine and serotonergic psychedelics have sparked interest as potential groundbreaking neuropsychiatric therapies. Our current understanding of these compounds suggests that the diverse drug actions converge around dendritic signaling. Given that the hypothesized mismatches in opposing actions can have important ramifications for plasticity and selectivity of drug targets, a promising avenue for future exploration will be to clarify the details of the competing mechanisms (see Outstanding Questions). By uncovering the neurobiology for how drug actions translate into sustained symptom improvement, basic science research can reveal critical insights into how to use and innovate on these emerging pharmacological therapies to best serve patients.

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Outstanding Questions

What is the impact of psychedelics on membrane excitability across the entire dendritic tree? The proposed framework predicts that select dendritic locations could be targeted due to spatial mismatches in the microcircuit or cellular interactions, yet measurements across the totality of an individual neuron's dendrites remains technically challenging.

To the extent that exposure to ketamine and serotonergic psychedelics may open a critical window of plasticity in the frontal cortex, can this period be used to steer and augment the long-term plasticity effects towards connections that would yield therapeutic effects?

Ketamine appears to engage at least two forms of disinhibition via PV and SST interneurons. What are the relative contributions of these disinhibitory mechanisms for the psychotomimetic and fast-acting antidepressant effects of ketamine?

A small but notable fraction of 5-HT_{1A} and 5-HT_{2A} receptors are expressed in GABAergic interneurons. Do serotonergic psychedelics also engage microcircuit interactions (e.g., SST neuron-mediated disinhibition) as ketamine does?

Several neuronal subclasses express 5-HT receptor subtypes that are far less understood than 5-HT_{1A} and 5-HT_{2A} receptors, but for which psilocin shows affinity. How do these additional receptor subtypes contribute to the actions of serotonergic psychedelics?

SSRIs also target the serotonergic system and promote antidepressant effects. Do they recruit opposing actions at dendrites? Why do SSRIs not have comparable rapid or durable antidepressant effects?

During acute intoxication, ketamine distorts sensory perception whereas classical psychedelics generate vivid hallucinations. The compounds may also differ in their duration of antidepressant action. What is the neural basis underlying these differences?

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