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Synaptic priming: a framework for pharmacotherapy in depression

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SUMMARY

Recent antidepressant drug development focusses on a next generation of drugs to rapidly relieve symptoms. Yet, how ketamine, the prototype rapid-acting antidepressant, maintains symptom relief days after drug elimination, and how repeated doses sustain longer-lasting therapeutic effects, remains unclear. Derived from elements of metaplasticity (synaptic priming), this review discusses a framework in which rapid-acting antidepressants prime synapses such that subsequent doses evoke stronger plasticity. Within this framework, we describe how the indirect relationship between ketamine's pharmacokinetics and sustained antidepressant pharmacodynamics reveals a dosing model (primer pharmacology) that can be harnessed to fine-tune therapeutic outcomes. This review also explores how plasticity machinery engaged by antidepressant pharmacotherapies overlaps with priming induced by contextual conditions relevant to depression (e.g., stress, psychotherapy), suggesting innovative opportunities for treatment strategies with emerging primers (e.g., psilocybin). The integration of synaptic priming with primer pharmacology reveals a model to guide clinical and translational work in psychiatry.

IN BRIEF BLURB

Through the perspective of metaplasticity, Brown *et al.* examine therapeutic effects of intermittent ketamine infusions and explore how targeting spatiotemporal features of antidepressant dosing and environmental conditions may improve effectiveness of treatments for depression.

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AUTHOR CONTRIBUTION

KAB wrote the manuscript. All authors critically reviewed and revised the work.

All other authors report no conflict of interest.

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Keywords

ketamine; depression; neuroplasticity; metaplasticity; long-term potentiation; synaptic priming; plastogen; psychoplastogen; neuroplastogen; metaplastogen; synaptic psychiatry; Bienenstock-Cooper-Munro; BCM

Introduction

(*R,S*)-ketamine (ketamine) and (*S*)-ketamine (esketamine; Spravato®) can produce rapid relief from depressive symptoms[1–5] . If effective, therapeutic effects can be exerted within hours of a single dose and typically persist after the drug is eliminated from the body. This provides an opportunity to rapidly treat a condition that affects hundreds of millions globally[6] and continues to be a tremendous global health burden[7] that deprives the world economy of hundreds of billions of USD annually[8]. Emerging evidence indicates that ketamine may be an efficacious therapy for not only treatment-resistant depression (TRD; i.e., someone who did not respond to at least two appropriate trials of antidepressant treatments) but also bipolar depression[9–11] and other psychiatric conditions such as anxiety disorders[12], obsessive-compulsive disorder[13], and post-traumatic stress disorder[14]. However, ketamine's psychopharmacology remains unclear[15,16].

The contrast between ketamine's short half-life and sustained pharmacodynamic actions remains underappreciated and unexplained. This is most readily highlighted by two clinical phenomena (Fig. 1): i) a single intravenous (IV) ketamine infusion produces antidepressant effects that persist long after ketamine and metabolites are no longer detectable in the body[17], and ii) ketamine exerts accumulative, longer-lasting symptom relief following repeated infusions in an intermittent schedule (commonly six total infusions over several weeks, followed by weekly then monthly doses)[3,9,18–23]. In this review, we expand on the framework established by us[24] and others[25,26] that integrates fundamental principles of metaplasticity (also called synaptic priming herein) with ketamine's psychopharmacology to interpret these phenomena through a synaptic priming hypothesis: ketamine activates synaptic priming mechanisms that are active long after drug elimination, and brain synapses are more sensitive to the action of subsequent doses. Examining ketamine's antidepressant pharmacology through the lens of synaptic priming reveals how elements of intermittent ketamine dosage regimens (e.g., the dose interval) can be exploited to improve symptom relief in those who exhibit limited response to ketamine/esketamine, which, while better than prior antidepressant pharmacotherapies, still ranges from 30–60% in TRD[27–30]. For instance, foundational studies demonstrate the critical influence of the interval between plasticity stimuli on the ability to sustain changes in synaptic strength, suggesting that incorporating these principles into intermittent ketamine dosing schedules can augment the antidepressant and plastogenic effects of ketamine. This review also critically considers how contextual conditions relevant to psychiatric disorders (e.g., stressful or supportive environments) influences synaptic priming mechanisms to reveal how convergent synaptic actions of contextual primers and antidepressant pharmacological primers (e.g., ketamine and potentially psilocybin[31,32]) could be harnessed to refine treatment outcomes. While pharmacological primers discussed in the present review will be confined to ketamine

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and psilocybin, the synaptic plasticity exerted by other antidepressants fits within the synaptic priming framework[24,26,33]. Synaptic priming presents a framework for augmenting treatment regimens with available therapies and identifying novel therapeutic processes that can be applied in drug discovery and development.

Synaptic plasticity and synaptic priming

Proper brain function, including optimal regulation of affect, requires precise integration of a mosaic of diverse stimuli and, accordingly, the capacity for changes in synaptic strength (e.g., plasticity). Sensory features of novel, regular, or repeated experiences trigger adaptive synaptic machinery to pair input stimuli with an output behavioral response[34,35]. Decades of research have revealed that altered inputs can lead to changes in output to produce behavioral changes associated with the potentiation or reduction of synaptic efficacy[36]. Mammalian neurophysiology has also shown an incredible ability to consolidate spatiotemporal features of inputs (e.g., timing, frequency, magnitude) to activate metaplastic machinery that primes subsequent changes in synaptic efficacy[37]. To facilitate discussion of pharmacological and contextual priming of synaptic plasticity in depression, we present a brief overview of the fundamental components of *N*-methyl-D-aspartate receptor (NMDAR) activation-dependent i) long-term synaptic plasticity and ii) synaptic priming mechanisms.

Synaptic plasticity

The NMDAR is one of the most well-studied initiators of changes in synaptic efficacy as Ca^{2+} influx through this receptor facilitates activation of signaling cascades that can persistently potentiate (e.g., long-term potentiation (LTP)) or reduce (e.g., long-term depression (LTD)) the strength of synaptic transmission and influence behavior[38–40]. Positioned to sense activity-dependent changes in synaptic signaling and respond via Ca^{2+} conduction, the NMDAR is a closely regulated, ionotropic, ligand- and voltage-sensitive receptor[41]. There are two prerequisites for NMDAR Ca^{2+} conduction: i) bound glycine and glutamate at its GluN1 and GluN2 subunits, respectively, and ii) membrane depolarization that allows for the removal of a voltage-dependent Mg^{2+} block[42]. The quantity of activity-driven Ca^{2+} entering the cell through the NMDAR directs intracellular signaling toward the induction phase of either LTP or LTD, followed by two respective phases: expression and maintenance[43]. High-frequency activity (e.g., theta-burst or tetanic stimuli) facilitates substantial Ca^{2+} conduction through the NMDAR. This promotes LTP expression by activation of Ca^{2+}/calmodulin and intracellular kinases (e.g., Ca^{2+} /calmodulin-dependent protein kinase II, protein kinase C) that potentiate synaptic efficacy via phosphorylation-dependent events, including enhancement of glutamatergic receptor conduction, trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) to the cell surface, and dendritic spine enlargement[44,45]. The LTP maintenance phase begins hours later and sustains potentiation for additional hours to days[46].

Conversely, low-frequency stimulation facilitates moderate NMDAR Ca^{2+} conduction to induce LTD[43]. Whereas kinase signaling is critical for LTP expression, activated phosphatases instigate LTD expression via endocytosis of surface-bound AMPARs and dephosphorylation of glutamatergic receptors[47]. Structural alterations, such as decreased

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dendritic spine density, perpetuate the reduction of synaptic efficacy during the protein synthesis-dependent LTD maintenance phase[48,49]. Thus, the NMDAR acts as a sensitive fulcrum of plasticity in a dynamic environment to enable long-lasting changes in synaptic activity and, ultimately, behavior.

Synaptic priming

The spatiotemporal pattern of an input stimulus critically influences the corresponding output response. Synaptic physiologists have shown that the timing, intensity, and/or frequency of an activity event can be manipulated to persistently prime synapses to respond in a quantitatively or qualitatively different way upon subsequent exposure to the same, or a different, event (Fig. 2)[37]. Consequently, the priming induced by diverse forms of stimuli (e.g., stress, environment, medicine, drugs of abuse, etc.) dynamically shifts the capacity for synaptic plasticity toward states that favor potentiation or reduction of synaptic efficacy[50]. This bidirectional change in the propensity for plasticity can last for hours to days after baseline transmission is reestablished following removal of the primer[51,52].

The NMDAR functions as a principal regulator of cellular mechanisms engaged by primers that can alter the ability for plasticity. For instance, shortly after the delivery of electrical stimulation that failed to reach the threshold for LTP induction in the CA1 subfield of the hippocampus, the threshold for forming high-frequency stimulation-elicited, NMDAR-dependent LTP is increased[53]. Priming of NMDARs may alter the ability for plasticity at the synapse directly activated (i.e., homosynaptic priming[54]) or indirectly at other synapses (i.e., heterosynaptic priming[51]). The physiological mechanisms activated by synaptic primers shape incredibly diverse functions, ranging from homeostatic protection against aberrant excitability to fine-tuning cognition[55,56]. Thus, the spatiotemporal features of priming stimuli must be carefully considered when used in the treatment of conditions associated with plasticity deficits.

A synaptic priming hypothesis

Depression as a disorder of synaptic rigidity

An impaired capacity for plasticity (synaptic rigidity) at synapses involved in the regulation of affect (e.g., prefrontal cortex [PFC], hippocampus, etc.) has long been hypothesized as a key neurobiological contributor to mood disorders (Fig. 2)[57,58]. Directly associating synaptic rigidity with clinical symptoms of depression has been historically challenging due to limitations inherent to measuring stimulation-evoked changes in synaptic efficacy in the human brain. Yet, over time, a body of physiology research has strengthened the neuroplasticity hypothesis of depression[59,60], particularly due to the emergence of non-invasive neuromodulatory techniques such as transcranial magnetic stimulation (TMS). Approaches employing TMS can selectively stimulate brain regions to record plasticity-sensitive motor-evoked potentials (MEP) in the human cortex[61]. Other strategies use visual stimuli to robustly evoke plasticity that can be measured by electroencephalogram (EEG) in regions integrating sensory stimulation[62]. Importantly, the physiological mechanisms underlying these forms of plasticity appear to overlap with well-studied forms of canonical

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NMDAR activation-dependent plasticity. Specifically, a human study found that the NMDAR antagonist dextromethorphan blocked LTP-like plasticity evoked by TMS[63].

Numerous clinical studies have used these paradigms to reveal plasticity deficits in individuals with depression[64–70]. Normann *et al.*[68] provided an important demonstration of this, finding that the ability for sensory-evoked, long-term plasticity in the visual cortex was impaired in patients diagnosed with major depressive disorder (MDD) compared to healthy subjects. Reports have directly linked symptoms of depression to impaired plasticity, such as one study that measured LTP-like plasticity in the motor cortex by monitoring the MEP before and after plasticity induction via paired stimulation of the peripheral median nerve and a single TMS pulse to the contralateral motor cortex[65]. This investigation found an impaired capacity for LTP-like plasticity of the MEP in individuals with MDD who were experiencing symptoms compared to healthy controls, but this synaptic rigidity was no longer present when individuals who previously had depression were in symptom remission. Thus, conceptualizing therapeutic target(s) for the treatment of depression as mechanisms that underlie synaptic rigidity provides a unifying framework in the pursuit of next-generation therapeutics, including those that putatively instigate their actions at distinct sites (e.g., NMDAR, μ-opioid receptors, 5HT2A receptor, or undiscovered targets)[24,71–74].

Hypotheses interpreting the antidepressant actions of a single ketamine dose

The antidepressant effects rapidly (i.e., minutes to hours) observed after a single dose of ketamine are proposed to be initiated by an alteration in glutamatergic transmission within the PFC[75–77] or other brain regions with weakened synaptic strength that regulate affect (e.g., ventral hippocampus[78] or lateral habenula[79]). Numerous theories presuppose ketamine's well-established pharmacological action as an open-channel NMDAR antagonist necessary for this action, which is followed by long-term symptom relief. Briefly, these hypotheses include, i) preferential inhibition of NMDARs expressed on interneurons that rapidly disinhibit glutamatergic transmission to promote sustained activity-dependent plasticity[80]; ii) acute blockade of spontaneously active NMDARs expressed on postsynaptic pyramidal cells facilitates homeostatic plasticity[81]; or iii) preferential antagonism of NMDARs on hyperactive neurons localized to the lateral habenula, whose activity is then persistently attenuated to balance excessive excitatory activity[82].

Deficiencies remain in these hypotheses[15,83,84]. First is the contradiction of ketamine's pharmacology as an NMDAR open channel blocker with the well-described role of NMDAR activation in mediating plasticity events believed to be associated with the antidepressant effects of ketamine (Reviewed in[24]). Second, other NMDAR antagonists lack the robust, rapid, and/or sustained antidepressant effectiveness produced by ketamine in humans[85–92], including the recently approved dextromethorphan/bupropion combination (Auvelity) marketed as an NMDAR antagonist. While effective as an adjunct treatment for depression[93–95], Auvelity is neither rapid-acting[94,95] nor effective for TRD[96].

These clinical results suggest that relief from depression symptoms produced by a ketamine infusion occurs independent of NMDAR antagonism, but such a mechanism remains unclear. Ketamine metabolites, most notably (*2R,6R*)-hydroxynorketamine (2R6R), rapidly induce AMPAR-dependent antidepressant-relevant actions[97] that then promote

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NMDAR activity-dependent plasticity for sustained effects[98,99]. These rapid/sustained outcomes occurred independently of NMDAR inhibition[97,98,100,101], indicating that ketamine metabolites may engage an unknown antidepressant target to rapidly potentiate synaptic strength that persistently primes plasticity[24,98]. Yet, while safe and well-tolerated in humans[102], clinical trials assessing 2R6R antidepressant efficacy for TRD remain ongoing (Clinicaltrials.gov ID: NCT06511908).

Synaptic priming: linking the actions of a single ketamine infusion with those observed after repeated doses

Clinical evidence demonstrates that one ketamine administration can produce transient symptom relief (i.e., hours to days), whereas repeated doses of ketamine[3,9,18–23] or esketamine[4,103–105] can relieve symptoms for weeks to months (Figs. 1–2). This distinction suggests that the antidepressant pharmacodynamic profile of ketamine contains two distinct phases: one phase that is directly associated with the presence of the drug (e.g., dissociation that matches the time course of the ketamine's pharmacokinetics) and another phase that occurs independent of ketamine's presence (e.g., hours to days later when antidepressant effects are observed). Further, repeated, intermittent dosing does not appear to meaningfully affect the initial phase, but can increase the cumulative effect and duration of the latter phase. Hence, ketamine's dual-phased pharmacokinetic/pharmacodynamic relationship diverges from the profile of other antidepressants that are commonly used (e.g., monoamine-targeting pharmacotherapies that necessitate daily dosing to facilitate a sustained drug presence that is necessary for initiation of antidepressant pharmacodynamic action[106,107]).

Improved outcomes following repeated doses are consistent with ketamine acting as a primer to facilitate a shift from synaptic rigidity to plasticity, in which the initial doses prime synaptic machinery such that subsequent exposures evoke stronger antidepressant plasticity (Figs. 1–2). That is, rather than repeated doses directly and persistently potentiating weak excitatory synapses, the first dose of ketamine elicits long-lasting, activity-dependent priming that is leveraged by a subsequent dose to evoke augmented and sustained synaptic strengthening. Due to practical limitations in resolving longitudinal, synapse-specific changes in humans, preclinical studies have provided the strongest evidence to support this hypothesis. For instance, evoked excitatory responses measured at the hippocampal SC-CA1 synapse in slices collected from mice treated with ketamine seven days earlier responded stronger to *in vitro* ketamine exposure compared to slices derived from mice administered vehicle, even though basal synaptic strength was comparable between slices from vehicle- and ketamine-injected mice[108]. This finding suggests that *in vivo* ketamine administration persistently primed synaptic machinery to facilitate a greater capacity for plasticity evoked by the subsequent, *in vitro* ketamine exposure. Following ketamine-evoked synaptic plasticity that occurs minutes to hours after administration, functional changes in neurophysiology are proposed to facilitate the onset of structural plasticity that promotes long-lasting rectification of neuronal morphology (e.g., beginning in the prefrontal cortex of mice approximately 12 hours post-injection and lasting up to a week[109,110]). Results from preclinical investigations of ketamine-evoked structural plasticity are consistent with one dose of ketamine priming structural plasticity evoked by subsequent doses. For instance, longitudinal studies employing two-photon microscopy found that, while a single dose

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of ketamine induced plasticity that prompted sustained increases in the density and size of neuronal dendritic spines, subsequent ketamine doses augmented such action in the mouse PFC[111] and somatosensory cortex[112]. Ketamine-induced priming of functional and structural plasticity is also in line with preclinical findings indicative of a single ketamine administration priming behavioral changes induced by successive doses. This is highlighted by ketamine-elicited alterations in behavior predictive of antidepressant efficacy persisting for days to weeks longer in rodents that received repeated administrations compared to those that received only one administration[113,114].

Evidence of ketamine's ability to prime the therapeutic action of a successive dose raises additional critical questions, including: does ketamine only prime subsequent ketamine-evoked plasticity, or plasticity induction in general? The answer to this question is critical as ketamine is sometimes delivered with other therapeutic, plasticity-evoking treatment modalities (e.g., neuromodulation[115] or psychotherapy[116]). Clinical and preclinical results support ketamine's ability to prime numerous forms of plasticity in healthy conditions and the context of depression. For instance, current evidence indicates ketamine primes plasticity in patients diagnosed with MDD to promote the propensity for LTP-like synaptic strengthening hours later. This was shown by a double-blind, active-placebo-controlled crossover study in which individuals diagnosed with MDD had an enhanced capacity for visually-evoked LTP-like plasticity three to four hours after one ketamine infusion[117]. Consistent with this clinical result, the administration of ketamine promoted a sensory stimulation-mediated measurement of synaptic priming *in vivo*, NMDAR activation-dependent ocular dominance plasticity[118], in the visual cortex of adult mice two days after treatment[119,120]. Similarly, a dose of ketamine enhanced LTP magnitude measured in rodents i) *ex vivo*[99,121–124] and *in vivo*[125] at SC-CA1, ii) *in vivo* at the ventral hippocampal-infralimbic cortex pathway[119], and iii) *in vivo* at the ventral hippocampal-accumbens pathway[126]. LTP recorded *ex vivo* in the nucleus accumbens core was less readily formed for up to a week after a dose[127], suggesting ketamine priming may evoke distinct shifts in plasticity between cell types of different nuclei.

While few studies have rigorously assessed the mechanisms by which ketamine exerts antidepressant priming, the ability to shape NMDAR-dependent plasticity processes at synapses in numerous brain regions of humans and rodents strongly implicates the necessity of NMDAR activity. Indeed, preclinical results support the requirement of NMDAR activity at the time of ketamine administration for persistent priming of electrically-evoked plasticity. This is highlighted by a study showing that treatment with the NMDAR antagonist MK801 before ketamine prevented increased SC-CA1 LTP measured *ex vivo* 24 hours later[99]. Sustained structural plasticity (e.g., increased AMPAR subunit protein levels in the hippocampus) and behavior indicative of antidepressant efficacy were similarly blocked when mice were pretreated with MK801. Consistent with a distinct contribution of NMDAR subtypes to synaptic priming[128], a single dose of ketamine facilitated a GluN2B-mediated increase in electrically-induced, SC-CA1 LTP recorded 24 hours after treatment[124]; however, additional studies are needed to address the involvement of other GluN subunits in ketamine's antidepressant-relevant synaptic priming.

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Signaling regulated by monoaminergic receptors also contributes to synaptic priming mechanisms, particularly noradrenergic and dopaminergic receptors[129,130]. Such signaling has been implicated in the unique plasticity exerted by repeated doses of ketamine. Specifically, Iro et al.[131] reported no change in spontaneous activity recorded *in vivo* from noradrenergic and dopaminergic neurons in the rat locus coeruleus and ventral tegmental area, respectively, 24 hours after a single dose of ketamine. Following six intermittent doses, the authors then observed enhanced spontaneous noradrenergic and dopaminergic activity that persisted three and seven days after the last treatment, respectively.

Prominent hypotheses propose that numerous signaling cascades mediate the sustained antidepressant actions evoked by a single ketamine dose, but critical mediators of these molecular sequences also converge with synaptic priming mechanisms. For instance, Kim *et al.*[108] implicated a postsynaptic transcriptional regulator, methyl-CpG-binding protein 2 (MeCP2), in persisting antidepressant-like behavior and SC-CA1 synaptic priming elicited by a single ketamine dose in mice. In this study, a delayed, brain-derived neurotrophic factor (BDNF)-dependent phosphorylation of hippocampal MeCP2 was necessary for antidepressant-relevant priming and behavior. The necessity of such BDNF-dependent signaling for long-lasting synaptic priming is consistent with a series of studies conducted by the Castrén laboratory. In their work, ketamine and emerging rapid-acting antidepressants (e.g., 2R6R and the psilocybin metabolite, psilocin) exert pharmacological actions that putatively prime tropomyosin receptor kinase B (TrkB) for BDNF binding, promoting long-lasting antidepressant-relevant plasticity and behavior[132–134]. BDNF/TrkB-dependent antidepressant priming may then converge on targets linked to rapid-acting antidepressant functional and structural plasticity, such as intracellular 5HT2A receptors[135,136] or extracellular matrix transcriptional regulators[137]. Other possible contributors include convergent opioidergic-related mechanisms given that pharmacological actions on opioid receptors can exert long-lasting shifts in synaptic plasticity[138] and ketamine's antidepressant effects have been linked to the μ-opioid receptor[139–141].

Much work is still needed to strengthen the synaptic priming hypothesis of ketamine's antidepressant actions, the most pressing of which is the completion of more studies that directly associate the priming of LTP/LTD-like plasticity with clinical response, or remission, after ketamine administration. A negative result from such a study may indicate alternative mechanisms, such as those involved in hysteresis models[142]. Separately, establishing the minimally effective dose for ketamine-initiated synaptic priming, and its longitudinal durability, could facilitate the refined use of ketamine in the treatment of depression. Critical examination of phenomena inherent to ketamine's psychopharmacology may provide clues to answer these questions, particularly the divergence of its rapid drug elimination (i.e., <24 hours) from its longer-lasting pharmacodynamic actions (i.e., days to weeks). Thus, we will next interpret clinical outcomes of ketamine's priming actions in depression to reveal how a here-to-fore underrecognized dosing model (primer pharmacology) can be used to reframe fundamental elements of clinical practice (e.g., dose selection, dose interval) around synaptic priming and improve treatment outcomes.

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Primer pharmacology

Balancing the benefits and risks of clinical pharmacology may be summarized in Paracelsus' prominent adage, "the dose makes the poison"[143]. Dose selection, count, and interval are among the many considerations inherent to pharmacology and must be carefully weighed to maximize efficacy while minimizing adverse responses. Decades of experience with monoamine-targeting and other psychiatric pharmacotherapies have informed an expectation of the most effective approaches to dosing. This experience led to standard dosage regimens that consist of a maximally tolerable daily dose of a monoamine-targeting antidepressant that alleviates debilitating symptoms, but with limitations, including numerous side effects associated with the requirement of the drug to be regularly engaged with the protein target (e.g., monoamine transporters, receptors, etc.) for sustained efficacy[144]. Such dosage regimens are in line with a receptor occupancy pharmacology framework. In this model, symptom relief is associated with a direct relationship between levels of drug exposure and pharmacodynamics. Hence, the rapid relief from symptoms of TRD that persist after clearance of ketamine stands in notable contrast to the therapeutic profile of drugs that fit within the receptor occupancy model, necessitating a reconceptualization of drug dosing and dose interval. We describe a model derived from ketamine's primer pharmacology and suggest that careful reinterpretation of ketamine's antidepressant primer profile can help promote antidepressant efficacy in patients who were formerly unresponsive or to increase duration of symptom relief in responders.

Dose-dependent antidepressant actions of ketamine

The establishment of subanesthetic, IV ketamine doses as a model for the induction of schizophrenic psychosis symptoms[145] led to the fortuitous discovery that a 40-min infusion of 0.5 mg/kg ketamine produced rapid and sustained antidepressant effects in patients diagnosed with MDD[5]. Nearly all subsequent studies utilizing ketamine for treating depression delivered a 0.5 mg/kg dose[146]. Based upon i) the historical tradition set by the pharmacology of monoamine-targeting antidepressants in which the maximally tolerable dose was administered[147], and ii) hypotheses positing the necessity of NMDAR blockade for ketamine's antidepressant effects[148], it followed that larger subanesthetic ketamine doses (0.5–1.0 mg/kg) could be even more efficacious.

However, clinical outcomes diverged with ketamine's NMDAR antagonism-focused antidepressant hypotheses, highlighted by the lack of a robust correlation between outcomes indicative of dissociation and antidepressant effects following ketamine administration in dose-response studies[149]. Specifically, results suggested that larger ketamine doses (>0.5 mg/kg) elicited greater signals of dissociation, but antidepressant effects were largely unchanged[150,151]. For instance, a double-blind, placebo-controlled study reported a dose-dependent increase in dissociation as measured by the Clinician-Administered Dissociative States Scale (CADSS) after ketamine infusion (0.1, 0.2, 0.5, or 1 mg/kg), but not in antidepressant response. There was no correlation between CADSS scores and antidepressant efficacy in this study[2] nor any consistent correlation in a meta-analysis[152]. Other reports obtained consistent results, demonstrating no additional enhancement of antidepressant response at doses beyond 0.5 mg/kg[146].

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Preclinical assessments of ketamine's antidepressant profile have found an inverted-U-shaped dose-response relationship where antidepressant-relevant behavioral, electrophysiological, and molecular effects were detected at subanesthetic doses, but not at high doses or concentrations[99,153–155]. Notably, a subanesthetic ketamine dose increased LTP magnitude at SC-CA1 3–24 hours after rodents were injected[99,121–125], but no change in the ability to generate LTP was measured at this synapse when mice were treated with an anesthetic dose 24 hours earlier[156]. Coupled with preclinical reports suggesting the requirement of NMDAR activity at the time of ketamine treatment for antidepressant-relevant synaptic priming[99,154], these human and rodent studies indicate that surplus NMDAR blockade by high levels of ketamine may impede antidepressant synaptic priming while eliciting dose-dependent side effects.

Dose interval-dependent antidepressant actions of ketamine

Similar to ketamine's inverted-U-shaped dose-antidepressant response curve, conclusions from decades of research by synaptic physiologists suggest an inverted U-shaped dose-response relationship between the quantity (dose) of high-frequency stimulation bursts and synaptic potentiation (Fig. 3A). Abraham and Huggett[157] provided critical evidence to support this, finding that an insufficient number of theta-burst stimulation trains delivered to the SC-CA1 synapse in rat hippocampal slices failed to reach the threshold for LTP, and a surplus number of trains reversed LTP via depotentiation. Separate studies found that the capacity for homosynaptic depotentiation *in vitro* was transient, only persisting for 1–2 hours after plasticity induction[157,158]. Similarly, CA1 LTP measured *in vivo* after homosynaptic, high-frequency stimulation can be reversed up to just 30 min after LTP induction[159]. Yet *in vivo*, heterosynaptic, high-frequency stimulation before sufficient decay of potentiation induced by an event hours to days earlier can reverse LTP[160]. Importantly, adjusting the plasticity induction interval can facilitate synaptic priming. Kramar *et al.*[158] and Cao and Harris[161] provided crucial evidence of this, finding that increasing the interval between two theta-burst stimulation events administered at SC-CA1 *in vitro* could double the magnitude of LTP induced by the second event. This is consistent with plasticity machinery requiring sufficient time to be available for subsequent LTP induction[162,163].

These basic science findings demonstrate that too frequent delivery of stimuli that rapidly induce heterosynaptic, high-frequency stimulation-like plasticity limits subsequent potentiation. This suggests that antidepressant plastogens (i.e., ketamine) may operate by similar dosing and dose interval principles (Fig. 3B). Hence, too frequent ketamine dosing may be unnecessary, and potentially preclusive, of therapeutic action. Optimized intermittent dosing can, therefore, be interpreted as maximizing an inverted U-shaped response, which requires careful consideration of ketamine's primer pharmacology, and, thus, an evaluation of ketamine dosing intervals and their associated antidepressant outcomes.

Current clinical ketamine serial infusion paradigms often begin caring for patients diagnosed with TRD by delivering six total administrations in a treatment induction phase (Fig. 1)[150]. In this phase, a dose interval of twice- or thrice-weekly has been shown to produce comparable levels of antidepressant outcomes to one another[150,164]. Thus, twice- or thrice-weekly ketamine infusions over two weeks (e.g., Tuesday/Thursday or Monday/

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Wednesday/Friday, respectively) have become common[151]. Following the induction phase, responders enter a maintenance phase in which doses are delivered at longer intervals to sustain symptom relief[21]. In contrast to the induction phase, the maintenance phase of ketamine treatment generally requires only a single dose to facilitate sustained symptom relief putatively instigated by the totality of the induction regimen[20,165]. Indeed, a single, weekly ketamine dose over four total weeks was found to maintain antidepressant effects in patients diagnosed with TRD following the induction of response[21]. Other studies showed that only a single dose every few weeks to months maintains the antidepressant action of ketamine after initial dosing[165]. Such results are consistent with clinical trial results demonstrating weekly doses of intranasal esketamine maintain TRD symptom relief following the induction phase, a dose frequency the US FDA recommends in clinical care for TRD[166]. Outcomes from preclinical literature are in line with these clinical data as a single dose of ketamine produced antidepressant-relevant actions lasting a week in mice[108,114,167,168]. These results suggest that less frequent ketamine doses could also be used to induce symptom relief, underscoring the urgent need for biomarkers that indicate the likelihood of responding to ketamine[28,29]. Still, randomized, placebo-controlled clinical studies are needed to directly compare whether longer dosing intervals (e.g., weekly) can induce and maintain antidepressant outcomes to levels currently reported by intervals of twice/thrice weekly.

In the receptor occupancy dosing model, drugs are administered as frequently as tolerable[106], yet clinical evidence supports longer-lasting therapeutic effects following repeated intermittent doses of ketamine[3,9,18–23]. These results suggest that ketamine dosage strategies derived from the receptor occupancy model may evoke unnecessary side effects, misuse liability, and preclude antidepressant actions. The framework of synaptic priming and primer pharmacology can be used to guide therapeutic, intermittent dosage schedules for plastogenic antidepressants.

Synaptic psychiatry: Integrating the BCM framework with primer pharmacology

Evidence supports the spatiotemporal characteristics of ketamine dosage regimens influencing antidepressant outcomes, and results from numerous preclinical studies suggest that the priming action of ketamine can persistently shift the baseline ability for LTP/LTD at glutamatergic synapses. Thus, ketamine's primer plasticity appears consistent with the framework of the Bienenstock-Cooper-Munro (BCM) model[169]. The BCM model was established in 1982 to interpret how priming stimuli can persistently shift the ability for plasticity[50]. Within such a paradigm, plasticity is conceived as a function comparable to a nonlinear, dynamic, bidirectional threshold. Application of the BCM theory has revealed the ability for synaptic depression/potentiation shifts as a sliding scale in healthy conditions[170,171] and in disorders affecting the nervous system[50,172,173]. For instance, investigations of synaptic plasticity changes in animal models of amblyopia (a condition induced by aberrant visual experience that impairs visual cortex development and vision) have provided results that support a crucial functional role of synaptic priming *in vivo*. This is highlighted by findings of visual deprivation reducing the threshold for NMDAR-dependent thalamocortical synaptic potentiation in adult rats, which then promotes an increased ability for ocular dominance plasticity[172]. As the BCM framework has been

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applied to delineate physiological mechanisms that contribute to aberrant conditions, it has also been used to improve therapeutic outcomes in numerous diseases[55,174].

In psychiatry, clinicians have translated the physiological principles underlying the inverted-U-shaped curve between the quantity/interval of plasticity-inducing stimuli and the capacity for altered synaptic efficacy to advance the use of antidepressant neuromodulation paradigms (Fig. 3)[61,175]. Specifically, the interval between repetitive TMS pulses delivered as theta-burst stimulation trains is now recognized to crucially shape the onset, persistence, and magnitude of weakened or strengthened synaptic efficacy in healthy humans[176–179]. The translation of these plasticity principles has reconceptualized how noninvasive brain stimulation can be delivered to more rapidly and effectively treat depression[180,181].

While such a conceptualization has not yet been widely integrated in the clinical use of rapid-acting antidepressant pharmacotherapies, the evidence presented here indicates that features of serial pharmacological primer dosage regimens (e.g., dose level and dose interval) can shift the sliding scale for antidepressant plasticity. Within such a BCM-like framework, a theoretical dosage paradigm that exerts optimal antidepressant priming can, therefore, be depicted as dosing regimens that increase the threshold for persistent weakening of synaptic efficacy (i.e., LTD-like) while lowering the threshold for long-lasting synaptic strengthening (i.e., LTP-like) at rigid synapses weakened in depression (e.g., in brain regions such as the PFC or hippocampus; Fig. 4). Contrarily, surplus antidepressant priming (e.g., excessively high dosage or dose frequency) may raise the threshold for synaptic potentiation at these synapses. This interpretation reveals a guide that can be broadly applied to innovate interventions within psychiatry. For instance, it provides a practical approach for designing treatment regimens that intermittently deliver ketamine with selective, noninvasive stimulation of circuits implicated in patient-specific depression symptoms[182]. This is supported by results from a clinical study that relieved depression symptoms in patients diagnosed with MDD by carefully considering dose and dose interval when combining a pharmacological NMDAR activator with neuromodulation (i.e., D-cycloserine combined with TMS)[183].

Overall, the integration of synaptic plasticity principles with primer pharmacology presents a framework for guiding studies of antidepressant plasticity, customized dosage regimens, and the development of novel therapies.

Synaptic priming initiated by contextual conditions

The results of studies indicate that a single dose of ketamine activates synaptic priming mechanisms that are leveraged by subsequent doses to produce stronger antidepressant effects in the absence of other forms of inputs. In practice, synapses experience a flux of stimuli that requires an adaptive capacity. Contextual features of experience necessitating adaptive behavior (e.g., stress or environmental enrichment) prime plasticity[184]. For instance, clinical studies have found that exposure to acute stress, or brief treatment with cortisol, primes cortical LTP-like plasticity in healthy subjects[185,186]. Thus, mechanisms underlying the adaptive plasticity evoked by contextual and pharmacological primers appear convergent, suggesting a double-edge: on one hand, untapped therapeutic opportunities

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(e.g., pharmacologically mimicking the adaptive plasticity elicited by context). On the other hand, potential confounds for interpreting the efficacy of pharmacological primers (e.g., psychotherapy paired with psychedelics). Next, we expand on the interaction of pharmacological and contextual primers in the context of depression.

A role for stressful or supportive environments in antidepressant actions

Chronic stress, but not acute stress, is associated with the likelihood of developing depression[187,188]. Preclinical studies have explored the circuit-level machinery mediating the transition from the fine-tuning, adaptive plasticity elicited by acute stress compared to the deleterious effects arising from chronic exposure. Work by Maggio and Segal made critical advancements in delineating the unique plasticity evoked by acute stress[189]. After revealing that the SC-CA1 synapse in the hippocampal region engaged by affective stimuli (ventral) exhibits a lower baseline capacity for synaptic potentiation relative to that of the portion associated with higher-order cognitive function (dorsal), they demonstrated that priming the ventral SC-CA1 with acute stress increased the ability for LTP[190]. Contrarily, acute stress impaired the capacity for LTP at dorsal SC-CA1. These findings suggested that acute stress evokes an adaptive plasticity that preferentially alters affective circuitry, which was supported by behavioral outcomes[189,191] and shown to be modulated by pharmacological primers[130]. Importantly, manipulating the duration of stress exposure qualitatively alters subsequent plasticity. This is supported by results showing that daily stress for weeks reduced the ability for LTP in the ventral CA1 subfield of the hippocampus[192]. Others report that chronic stress also diminishes the capacity for synaptic potentiation at dorsal SC-CA1[193,194].

Beyond stress, adaptive plasticity elicited by contextual conditions relevant to depression appears to evoke contextual priming, the most well-studied being a supportive environment. This is reinforced by clinical results showing that patients diagnosed with MDD achieved symptom remission faster, and in a plasticity-dependent manner, when they rated the contextual conditions contributing to their quality of life favorably, indicating an important interaction between the ability for changes in synaptic strength and life environment[195]. Similarly, numerous investigations have demonstrated that the spatiotemporal features of a preclinical equivalent of a socially supportive environment (i.e., environmental enrichment) shift the capacity for synaptic plasticity[196]. For example, environmental enrichment (2 to 6 weeks) facilitates SC-CA1 LTP recorded *in vivo* in the rodent dorsal hippocampus[52], an effect likely related to the enriched environment enhancing CA1 pyramidal cell excitability[197].

As rapid-acting pharmacotherapy exogenously evokes a plasticity resembling the adaptive plasticity induced by acute stress or a supportive environment, exploiting the convergent synaptic actions of contextual and pharmacological primers may improve treatment outcomes in psychiatric conditions (Fig. 5). Clinical results support this interpretation. For instance, a randomized, controlled trial found that the antidepressant effects of repeated ketamine infusions in individuals diagnosed with TRD were prolonged by subsequent cognitive behavioral therapy compared to those who received treatment-as-usual after infusions[116]. Study designs may also inadvertently confound or impede the action of

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ketamine due to contextual priming. Most readily apparent of these are preclinical investigations employing various stress paradigms that intend to recapitulate biological mechanisms associated with symptoms of depression[198–200], very few of which critically consider the convergence of pharmacological and contextual primer mechanisms. This is underscored by evidence indicating corticotropin-releasing factor (CRF)-induced synaptic priming is necessary for antidepressant-relevant effects of ketamine[201]. Specifically, the scent of a biologically male experimenter, but not a female experimenter, elicited a CRF-mediated stress response in rodents, and this was required for ketamine to produce antidepressant-like synaptic effects *in vivo*. This finding suggests that adaptive plasticity evoked by acute stress shortly before ketamine administration may promote antidepressant action in some conditions, though it remains unclear how repeated acute stress, chronic stress, or a combination of acute/chronic stress may influence ketamine's therapeutic effect in patients diagnosed with depression. Still, this result underscores how the framework of synaptic priming can be used to refine experimental design and approach the development of customized therapeutic interventions.

The role of context in psychedelic actions

The scope of pharmacological primers that act within the framework of synaptic priming does not appear limited to ketamine. This is highlighted by a single dose of psilocybin inducing dramatic, rapid plasticity in the hippocampus of healthy subjects, and the ability for plasticity remains altered for weeks after[202]. Although study designs were inconsistent, current clinical results indicate that a single psilocybin dose primes a subsequent dose to produce an antidepressant effect when delivered to individuals diagnosed with depression[31], even in treatment-resistant cases[32]. The detailed mechanisms of this priming effect are unclear, but are consistent with psilocybin putatively inducing rapid therapeutic effects via serotonergic receptor-dependent signaling[203] that then converge, like ketamine, on plasticity mechanisms in glutamatergic cells to produce prolonged antidepressant effects[204,205].

Unlike in most clinical studies assessing ketamine efficacy in the treatment of depression, psilocybin administration in controlled clinical trials is nearly always coincident with psychological support (e.g., psychotherapy)[206]. The integral role of priming psilocybin treatment with psychological support is reinforced by the traditional view that context critically contributes to the likelihood of psilocybin yielding therapeutic outcomes[207–209]. This is underscored by a clinical study finding that healthy subjects who received high levels of social support for months before delivery of a double-blinded, large dose of psilocybin exhibited longer-lasting improvements in affect (e.g., mood, sociability) compared to those treated with the same dosage but with less social support[210]. Similarly, hours to days of psychological support before psilocybin treatment has been reported to improve therapeutic response in subjects diagnosed with an affective disorder[211]. This context-specific outcome may be linked to the unique sensitivity of psilocybin's putative therapeutic target (i.e., the 5HT2A receptor), and subsequent short-term changes in serotonergic signaling, to the environment[212–214]. This is consistent with a study finding that substantial changes in functional connectivity of brain-wide activity during the acute psychedelic phase of psilocybin treatment could be readily disrupted by requiring subjects to engage in a simple auditory-visual matching task[202]. This evidence of contextual priming impacting

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antidepressant response to psilocybin, and a lack of rigorous studies assessing the efficacy of psilocybin without psychological support, prompts the question: is the pharmacological action of psilocybin, or the context leading up to its administration, predominantly responsible for subsequent therapeutic outcomes?

A particular obstacle in disentangling the priming action of context that precedes psilocybin treatment is the heterogeneity in the duration, intensity, and interval of psychological support preceding the administration of the drug[215]. Obvious ethical limitations also prevent rigorous investigation of the synaptic mechanisms engaged by manipulating controlled clinical settings' negative/positive contextual valence. Published preclinical studies underscore the challenge of delineating the contribution of contextual priming from psilocybin-induced priming on synaptic indicators of antidepressant efficacy. One such study used an innovative approach to assess brain region-specific alterations in neural activity at a cellular level in mice that were treated with psilocybin and placed in an environmentally enriched context, finding only additive, rather than synergistic, brain-wide indicators of activity (i.e., c-fos, immediate early gene expression) compared to mice that experienced the acute effects of psilocybin in their familiar homecage[216]. Contextual priming must be carefully considered in clinical study design as regulatory agencies attempt to resolve the antidepressant actions of psychedelic therapies alone versus the environment experienced by study subjects.

Future directions

Preclinical and clinical results indicate that synaptic rigidity contributes to the pathophysiology of depression. A single subanesthetic ketamine infusion can rapidly induce antidepressant effects and, in those who respond, can become more pronounced and long-lasting following repeated intermittent administrations. These antidepressant actions, and their equivalent effects in preclinical depression models, coincide with an increased ability for synaptic plasticity, suggesting amelioration of synaptic rigidity. The capacity for plasticity appears to be further increased by serial ketamine administrations, suggesting that initial ketamine doses prime the plasticity evoked by subsequent doses.

The acute side effects (e.g., increases in blood pressure, dissociation, respiratory depression), the possibility of tachyphylaxis and other adverse effects with continued use[165,217,218], and misuse potential of ketamine necessitated a break from dosing traditions established by the receptor occupancy model (e.g., daily delivery of a maximally tolerable dose of drugs such as monoamine-targeting antidepressants). This change serendipitously revealed an opportunity to reconceptualize the delivery of rapid-acting antidepressants around a new dosing model, primer pharmacology (e.g., intermittent administration at a submaximal dose). The ability for synaptic priming mechanisms to remain activated after ketamine elimination differentiates this new dosing model from prior frameworks. Targeting priming machinery presents many therapeutic avenues that can address some of ketamine’s notable shortcomings[219,220], such as promotion of an antidepressant response in formerly unresponsive individuals (e.g., 30–60% of patients diagnosed with treatment-resistant depression respond insufficiently to ketamine/esketamine[27–29]), or limiting misuse

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potential by decreasing the total number of ketamine doses, or dose frequency, to induce/sustain antidepressant outcomes.

In the antidepressant synaptic priming framework, the pharmacological profiles of ketamine/psilocybin are consistent with those of a psychoplastogen (i.e., an exogenous agent that evokes neuroplasticity and acutely alters subjective mental state) and a primer/metaplastogen (i.e., an exogenous agent that evokes long-lasting changes in the ability for plasticity). Still, not all primers that act as psychoplastogens are effective antidepressants (e.g., cocaine[130]). Notably, some emerging rapid-acting antidepressants exhibit a primer profile, but do not exert psychoactive effects (e.g., 2R6R, a neuroplastogen with an antidepressant primer profile). Neuroplastogens that do not prime plasticity or exert psychoactive effects can elicit antidepressant effects (e.g., fluoxetine), whereas many other purely neuroplastogenic drugs are unknown to be effective monotherapies for TRD. Hence, carefully designed experiments are needed to determine what individual or combinatorial forms of plastogenic action are necessary for sustained antidepressant-relevant actions.

The framework of primer pharmacology reveals avenues in clinical care for depression and creates opportunities to increase the efficacy of a wide variety of therapeutic interventions, from psychotherapy to neuromodulation. For instance, leveraging persistently active priming mechanisms in regimens that combine treatment modalities (e.g., TMS and pharmacotherapy) offers potential opportunities for the enhanced treatment of depression. While here we have focused on weakened synapses associated with depression symptomology, emerging technology may permit the identification of circuit-specific subtypes of depression[182] that could present with symptomology associated with excessive synaptic strength in select brain regions (e.g., lateral habenula[79]). Hence, the integration of the BCM model of synaptic plasticity with primer pharmacology can be used to guide the design of customized primer dosage regimens that promote long-lasting synaptic weakening in hyperactive regions linked to depressive and comorbid symptoms. Further, electrophysiological approaches that quantify antidepressant-induced synaptic priming[61] can be used as a physiological biomarker to predict therapeutic response. The assessment of translational, electrophysiology-measured synaptic priming metrics (e.g., LTP/LTD) can also fill the void left by increasing scrutiny of preclinical behavioral assays previously accepted to have predictive validity of antidepressant outcomes[221].

Ketamine continues to be investigated in clinical trials assessing its efficacy in the treatment of affective symptoms presented in other psychiatric disorders (e.g., substance use disorder, obsessive-compulsive disorder, etc.)[83]. The evaluation of ketamine’s therapeutic actions in such diverse physiological conditions underscores the urgent need to elucidate its psychopharmacology, which will likely require new dosage strategies to be effective. In the context of primer pharmacology, optimizing dose frequency is equally important to optimizing dose level. In short, the integration of synaptic priming principles with primer pharmacology reveals a future in which the fields of biological, synaptic, and molecular psychiatry can advance customized therapies to treat depression symptoms faster, safer, and more effectively.

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Box 1. Glossary of key terms.

Term	Definition	Example
Synaptic plasticity terms		
Synaptic rigidity	A state of limited capacity for synaptic plasticity, which is present in some neuropsychiatric disorders	Cognitive and other learning deficits associated with major depressive disorder
Synaptic plasticity	Synaptic efficacy changes in response to stimuli. These changes can be short-term or long-term.	Long-term potentiation (LTP, which is the long-term strengthening of synaptic efficacy) or long-term depression (LTD, which is the long-term weakening of synaptic efficacy)
Synaptic primer	A plasticity event that activates priming mechanisms that persistently change the magnitude, direction, or duration of plasticity evoked by a later event	A prior stimulation event that is unable to induce LTP on its own decreases the threshold for later LTP formation
Pharmacology terms		
Receptor occupancy pharmacology	A pharmacology model for the treatment of psychiatric conditions that presupposes the requirement of continuous engagement of a drug with a protein target(s) for symptom relief	Daily dosing with a selective monoamine reuptake inhibitor for the treatment of depression
Primer pharmacology	A pharmacology model for the treatment of psychiatric disorders that studies how the direct and indirect relationship between a drug's pharmacokinetics-pharmacodynamics exerts symptom relief through metaplasticity processes	Intermittent ketamine dosing exerts pharmacodynamic effects directly (dissociation) and indirectly (antidepressant response) associated with the presence of the drug
Pharmacological primer/ metaplastogen	An exogenous agent that evokes long-lasting changes in the ability for subsequent plasticity (e.g., priming/ metaplasticity)	Ketamine, psilocybin, (*2R,6R*)-hydroxynorketamine
Contextual primer	An environmental event that elicits a sustained shift in the capacity for later plasticity	Stress, psychotherapy

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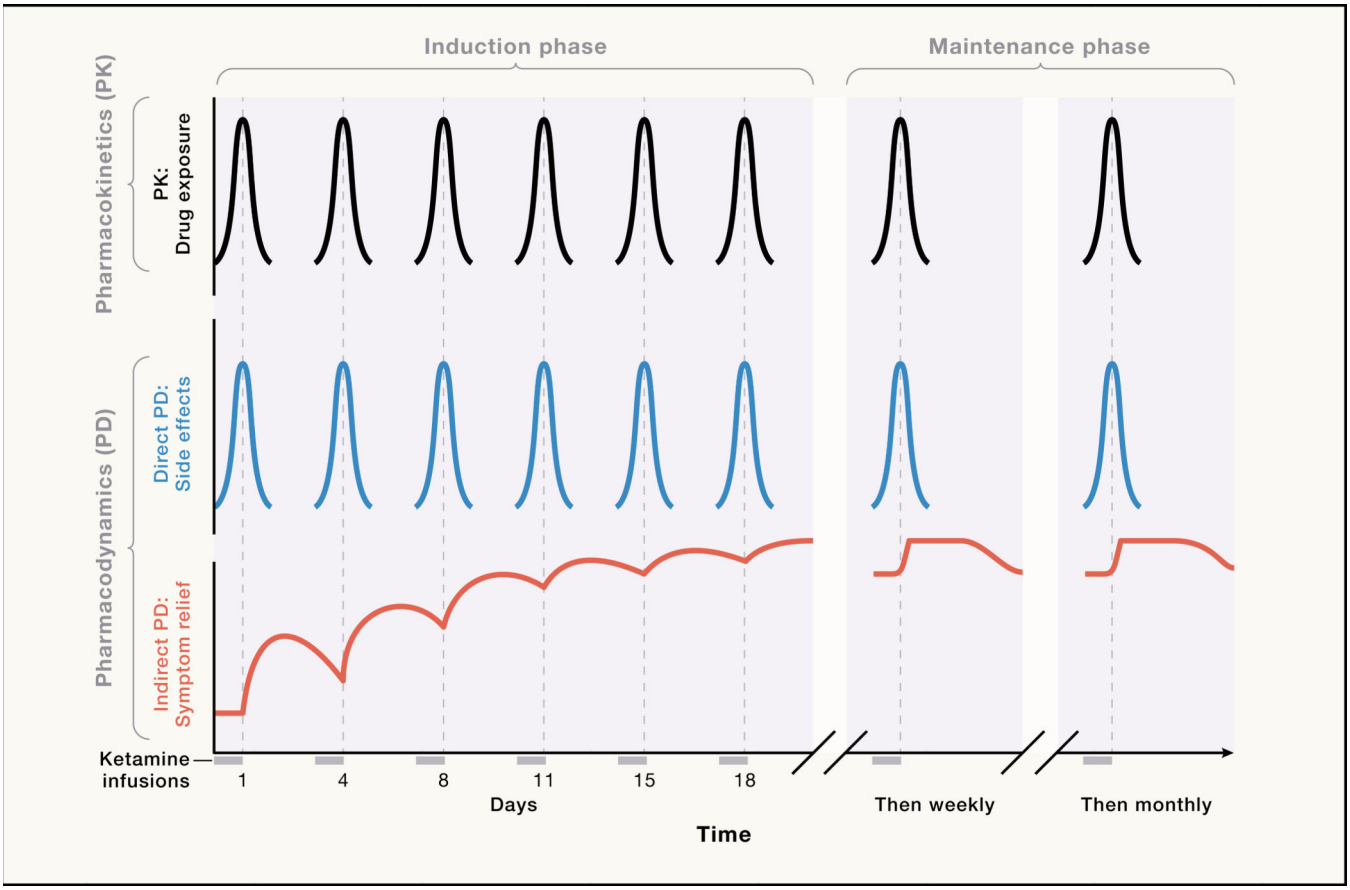


Figure 1. Clinical observations consistent with synaptic priming following repeated antidepressant doses of ketamine.

(**Upper**) Ketamine has a short half-life following administration, as noted by its pharmacokinetic (PK) profile.

(**Middle**) Direct pharmacodynamic (PD) effects (e.g., dissociation) are associated with the presence of ketamine and match the time course of the drug's PK.

(**Lower**) Long after the elimination of ketamine, antidepressant effects are still observed, consistent with an indirect PD action. Intermittent infusions of ketamine enhance the duration and/or cumulative action of these indirect PD effects. These clinical results suggest initial ketamine dose(s) prime physiological processes such that subsequent doses evoke longer-lasting therapeutic action.

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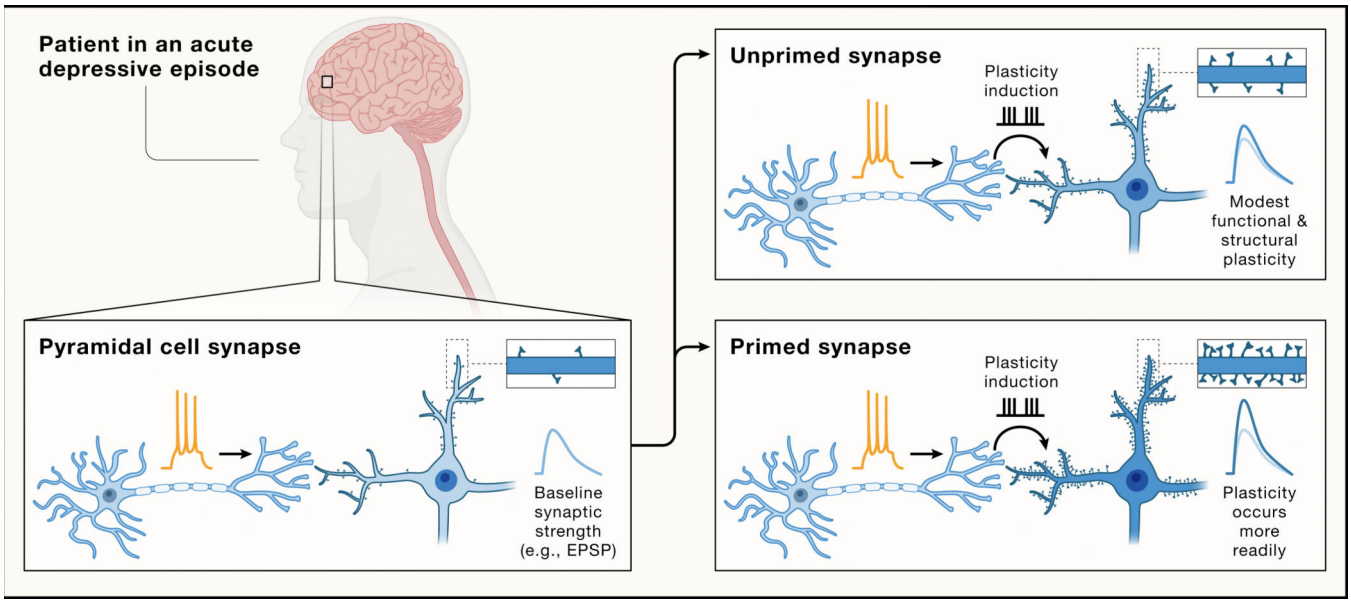


Figure 2. A limited ability for synaptic strength is improved by antidepressant synaptic priming (metaplasticity).

(**Upper**) Patients experiencing an acute depressive episode demonstrate a limited ability for synaptic plasticity[64–70] (i.e., synaptic rigidity).

(**Lower left**) In such a patient, plasticity induction (e.g., theta burst stimulation [TBS]) results in a restricted ability for long-term potentiation-like enhancement of synaptic strength (depicted as an excitatory postsynaptic potential [EPSP]; lighter shade: baseline EPSP, darker shade: post-TBS EPSP). Functional plasticity facilitates structural plasticity, as illustrated by a modest increase in pyramidal cell dendritic spines.

(**Lower right**) A metaplastic/priming stimulus (e.g., ketamine) shifts the threshold for later plasticity without persistently altering baseline synaptic strength and/or neuronal morphology. Here, priming lowers the threshold for synaptic potentiation, allowing for the same TBS event to elicit a greater increase in the EPSP and subsequent structural plasticity.

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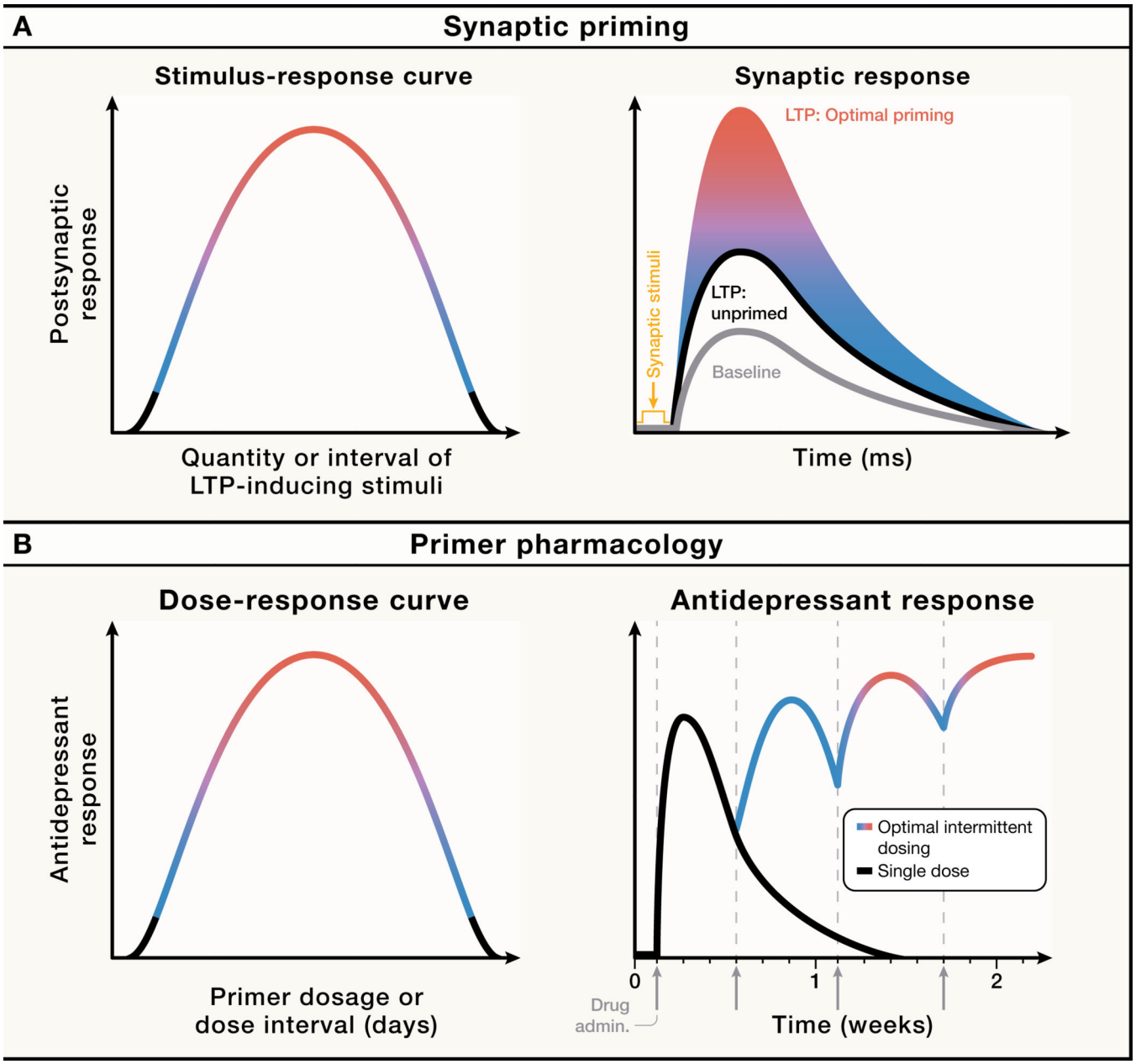


Figure 3. Synaptic plasticity principles regulate primer pharmacology.

(**A**) Depiction of the inverted-U-shaped stimulus-response relationship between long-term potentiation (LTP)-inducing stimuli (e.g., trains of high-frequency or theta-burst stimulation) and the magnitude of LTP. The corresponding excitatory postsynaptic potential (EPSP) waveform is depicted to the right. Gray arrow denotes low-frequency stimulation to evoke EPSP.

A low quantity of stimuli is insufficient to prime LTP (gray EPSP, baseline response; black EPSP, unprimed LTP). Priming occurs as the number of stimuli delivered reaches a threshold amount, resulting in greater potentiation upon subsequent plasticity induction (red gradient of EPSP). A surplus quantity of stimuli precludes/reverses priming (blue gradient of EPSP).

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LTP-inducing stimuli separated by excessively brief intervals preclude/reverse priming (blue gradient of EPSP). Optimized intervals between LTP induction stimuli allow for the priming of subsequent plasticity events (red gradient of EPSP). Excessively long intervals are insufficient to prime subsequent plasticity-inducing events (blue gradient of EPSP).
(**B**) (**Left**) Similarly, rapid-acting antidepressant primers are proposed to elicit an inverted-U-shaped dose-response curve. Specifically, no antidepressant-relevant response is observed until reaching a threshold dose. A surplus dose precludes antidepressant outcomes.
The dosing interval of rapid-acting antidepressant primers is also proposed to follow an inverted-U-shaped curve. Excessively brief or prolonged intervals are unable to leverage the plasticity-dependent antidepressant actions evoked by the initial dose(s).
(**Right**) Depiction of the relationship between primer-induced antidepressant response and dosing interval is depicted. A single dose rapidly evokes antidepressant response, but this commonly diminishes within a week (black curve). An optimal intermittent dosing interval can leverage priming elicited by a prior dose (blue/red curve, gradient matches colors in left panel). Black arrows depict doses.

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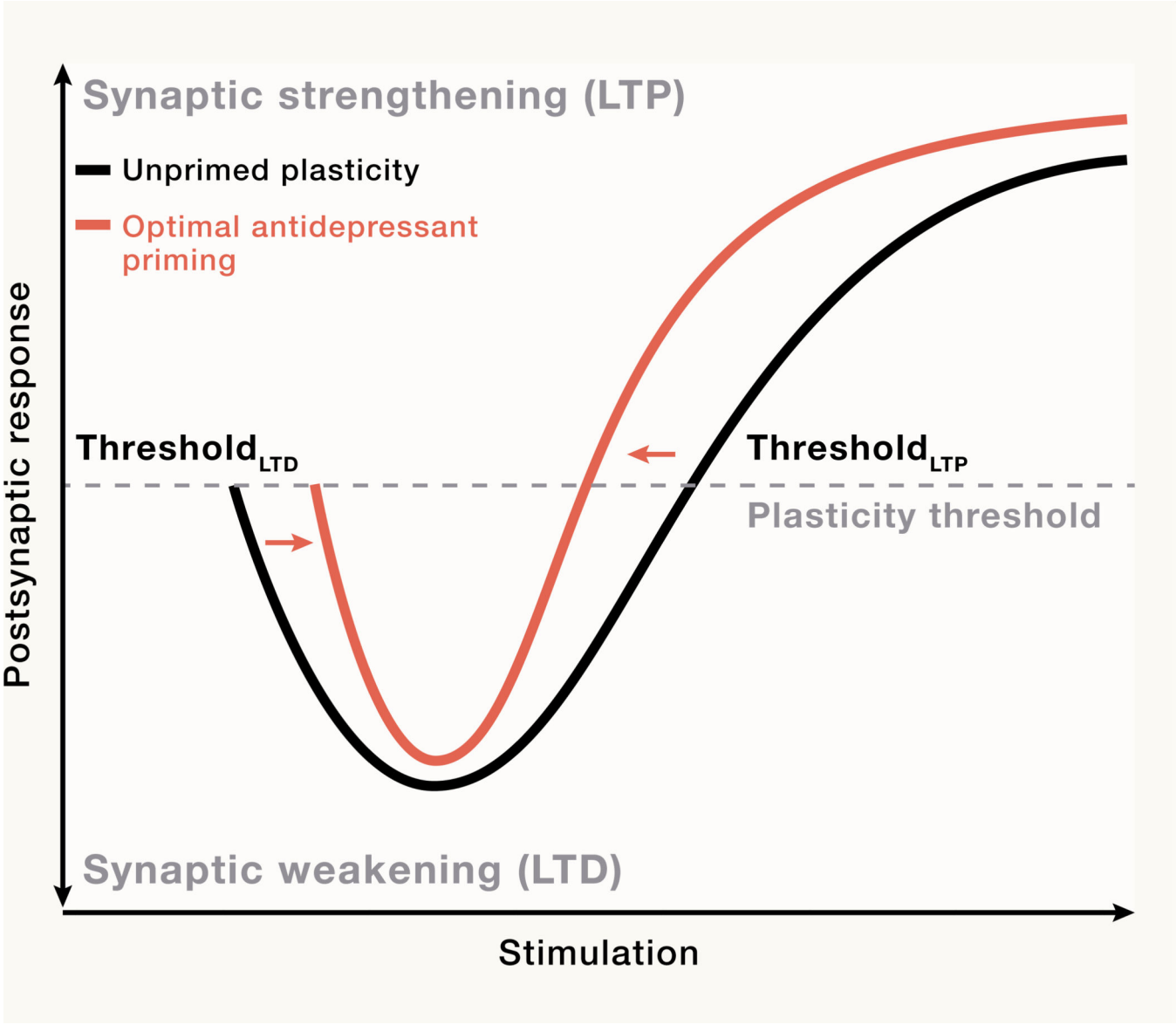


Figure 4. A Bienenstock–Cooper–Munro (BCM) framework for integrating primer pharmacology and antidepressant synaptic priming.

Similar to high-frequency stimulation protocols used to induce plasticity, features of antidepressant dosage regimens (e.g., dose and dose interval) critically influence the sliding scale for plasticity. Specifically, the baseline threshold for long-term depression-like activity (Threshold$_{LTD}$) and long-term potentiation-like activity (Threshold$_{LTP}$) of synaptic activity (black curve) can be shifted by antidepressants days to weeks after treatment in a manner consistent with BCM theory[50]. Thus, when targeting brain regions associated with depression symptomology that also exhibit weakened synaptic strength and synaptic rigidity (e.g., prefrontal cortex, hippocampus), synaptic priming principles and primer pharmacology can be integrated to design a dosage regimen that increases the threshold for LTD-like activity and decreases the threshold for LTP-like activity (red curve and arrows).

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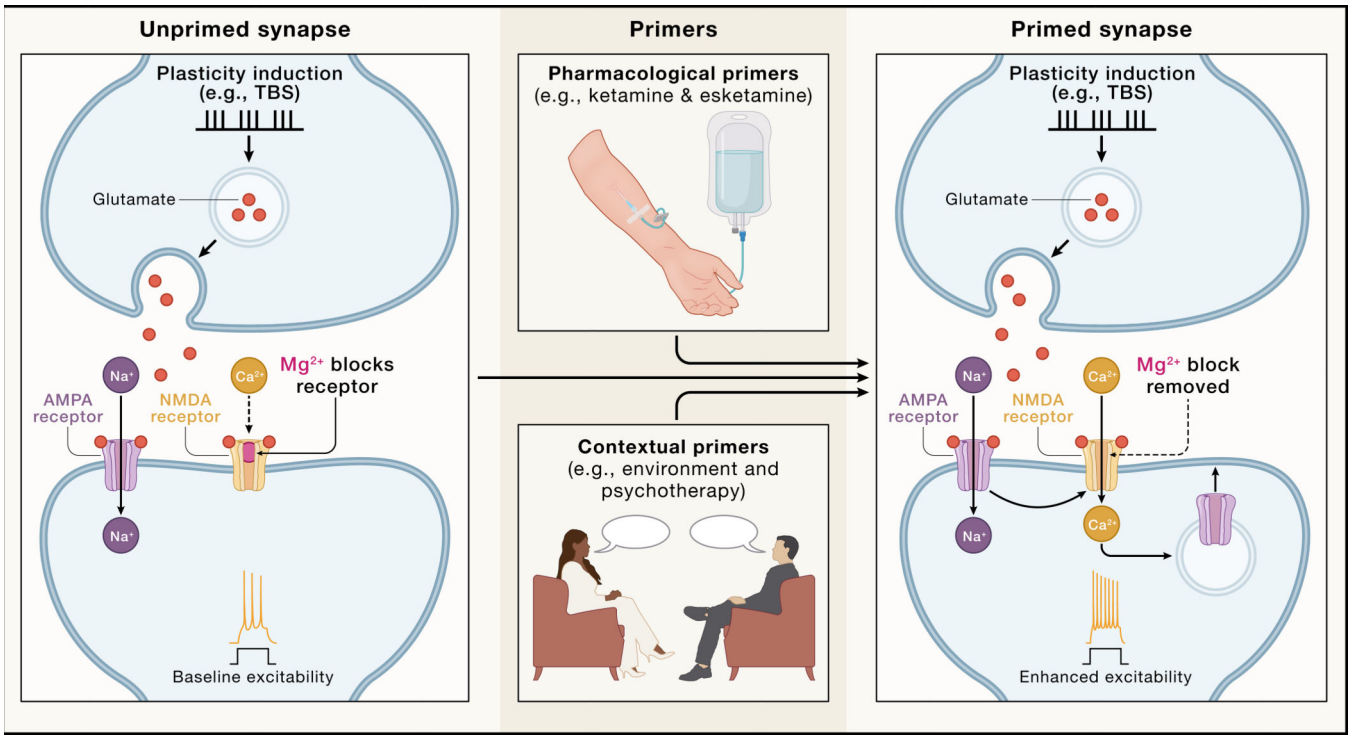


Figure 5. Harnessing the convergent synaptic actions of pharmacological and contextual primers.

The antidepressant effects of ketamine and esketamine stimulate NMDAR-dependent priming mechanisms to persistently change the capacity for plasticity. Contextual conditions (e.g., environment or psychotherapy) also activate these priming mechanisms. Carefully considered approaches that leverage the convergent action of pharmacological and contextual primers can promote priming to facilitate long-lasting changes in synaptic strength and relief from symptoms of depression. This is depicted in the following synapse, in which synaptic potentiation is only induced after combined treatment with pharmacological and contextual primers.

(**Left**) The unprimed synapse does not respond to plasticity induction (theta-burst stimulation [TBS]) due to a greater threshold for plasticity.

(**Right**) Exposure to pharmacological and contextual primers increases postsynaptic cellular excitability. This lowers the threshold for plasticity such that the same plasticity event is capable of inducing, expressing, and maintaining synaptic potentiation.