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Review

Review

Towards an expanded neurocognitive account of ketamine's rapid antidepressant effects

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Abstract

Ketamine is an N-methyl-D-aspartate receptor antagonist that has shown effectiveness as a rapidly acting treatment for depression. Although advances have been made in understanding ketamine's antidepressant pharmacological and molecular mechanisms of action, the large-scale neurocognitive mechanisms driving its therapeutic effects are less clearly understood. To help provide such a framework, we provide a synthesis of current evidence linking ketamine treatment to the modulation of brain systems supporting reward processing, interoception, and self-related cognition. We suggest that ketamine's antidepressant effects are, at least in part, driven by dynamic multi-level influences across these key functional domains.

Keywords: neurocognitive, ketamine; depression; antidepressant; neurobiology

INTRODUCTION

Major depressive disorder (MDD) is a debilitating mental disorder that causes significant physical and psychological impairment, with conventional monoamine-based antidepressants proving ineffective in about 40% of cases.[1-3] Treatment-resistant depression (TRD), which is defined by failed response to 2 or more first-line antidepressant treatments,[4] has illness remission rates below 15%, underscoring the need to develop novel and more effective interventions.[3,5]

Ketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist which was initially synthesized and applied in clinical practice as an anesthetic agent.[5,6] In the 2000s, the first randomized control trials (RCTs) established the effectiveness of single low-dose intravenous racemic ketamine (0.5 mg/kg) in reducing depressive symptoms in MDD patients.[5,7] Ketamine has been increasingly used as a rapid-acting treatment for TRD since a 2006 double-blind RCT established its effect in treating TRD with a response rate of 35%.[8-11] The antidepressant effects of ketamine are observed as early as 4 hours post-administration, and its persistence can vary considerably between patients.[7] Following the 2019 Food and Drug Administration and European Medicines Agency approval for an intranasal formulation of the s-isomer of ketamine (esketamine or *Spravato*), its use for the treatment of TRD has become even more widespread.[3] While ketamine commonly refers to R/S-ketamine, the racemic mixture of the 2 enantiomers, some recent studies suggest that the rapid and potent antidepressant effects of ketamine might mainly be attributed to esketamine.[12,13] R-ketamine, or arketamine, is also demonstrated in animal studies to provide antidepressant effects in TRD, but NMDAR affinity for arketamine is around 4 times lower than esketamine.[13-15] Likewise, the effective dosage of esketamine is found to be lower than racemic ketamine in treating depression, whereas the side effects and overall response rates of intranasal esketamine compared to intravenous racemic ketamine remain to be further evaluated.[5]

KETAMINE'S MECHANISMS OF ACTION

Ketamine has direct antagonist effects on NMDA receptors. At low doses, it preferentially binds to NMDA receptors on GABAergic neurons, which rapidly blocks the burst firing of interneurons and results in an upstream glutamate surge.[16-18] By disinhibiting pyramidal cells and enhancing excitatory glutamatergic neurotransmission, ketamine administration leads to increased extracellular cortical glutamate levels.[19,20] The glutamate surge resulting from NMDAR antagonism could activate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and could lead to increased brain-derived neurotrophic factor (BDNF) and synaptogenesis.[21-24] Other animal studies also reported arketamine's ameliorative effect on reduced BDNF-TrkB signaling, potentially enhancing the antidepressant effects of racemic ketamine through BDNF-TrkB activation.[14] One brain region that has been implicated in driving ketamine's antidepressant effects is the lateral habenula (LHb), which is made up of predominantly glutamate neurons, interspersed with gamma-aminobutyric acid (GABA) neurons.[16]

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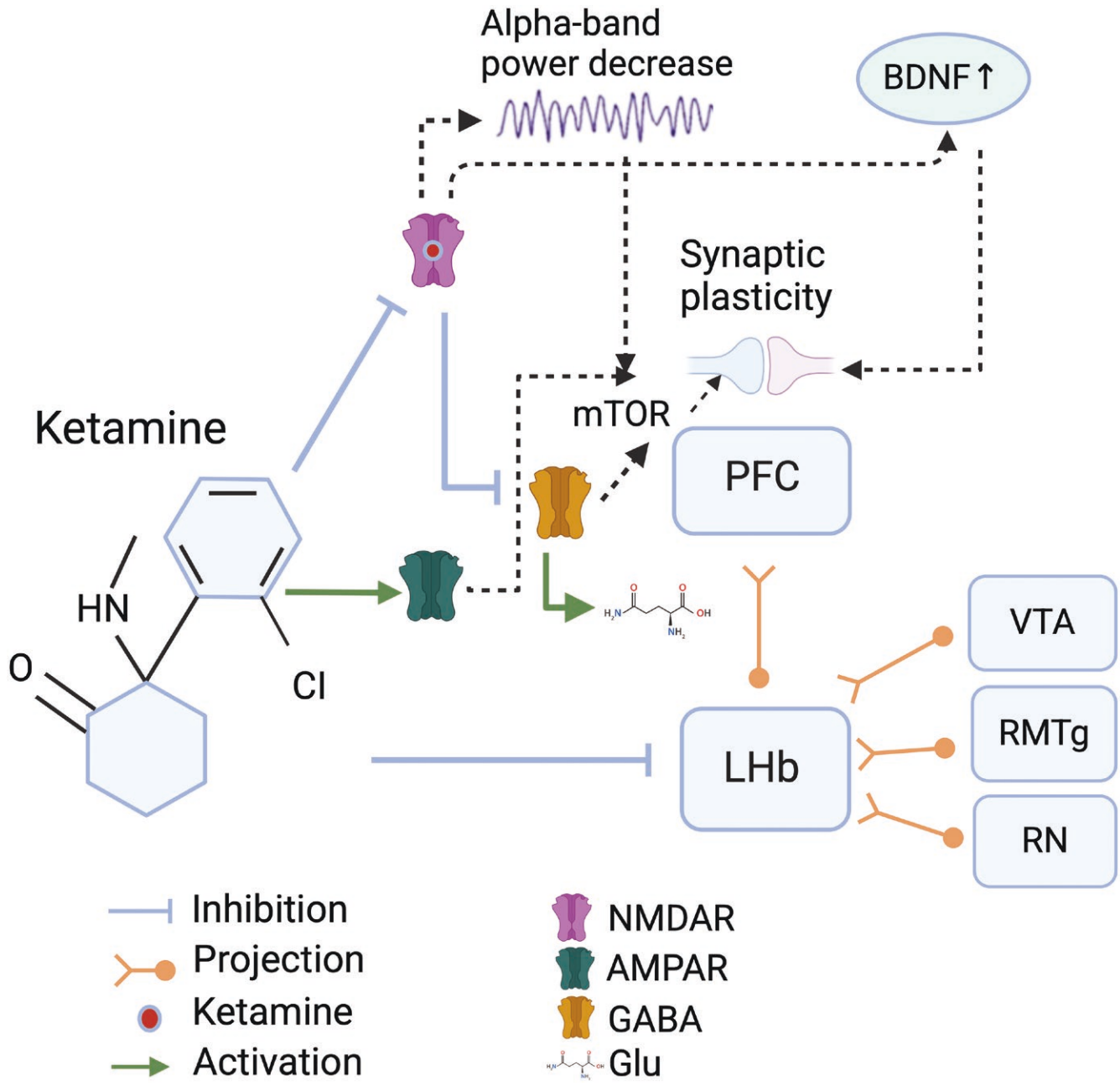

Figure 1. Direct mechanisms of ketamine. Ketamine's direct antidepressant mechanism is through activation of AMPAR and NMDAR antagonism. NMDAR antagonists target GABAergic neurons, rapidly blocking burst firing of interneurons and creating a glutamate surge. By disinhibiting pyramidal cells and enhancing excitatory glutamatergic neurotransmission, extracellular PFC glutamate levels increase. Blockage of NMDARs by ketamine increases brain-derived neurotrophic factor (BDNF) and synaptogenesis, while alpha-band power decreases. By directly blocking burst firing of LHb neurons, ketamine affects other subcortical regions through LHb projection to GABAergic, serotonergic, and DAergic neurons in RMTg, median and dorsal RN, and VTA. Ketamine also modulates PFC projection to LHb. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; LHb, lateral habenula; NMDAR, N-methyl-D-aspartate receptor; PFC, prefrontal cortex; RMTg, rostromedial tegmental nucleus; RN, raphe nucleus; VTA, ventral tegmental area. This figure was created using BioRender (https://biorender.com/).

Rodent models of depression have found that ketamine rapidly blocks the abnormal burst firing activity of LHb neurons.[25] (Figure 1). In turn, ketamine is thought to exert a strong modulatory influence on dopaminergic (DA) and serotonergic neurotransmission in the rostromedial tegmental nucleus (RMTg), raphe nucleus, and ventral tegmental area (VTA) by reducing LHb's inhibitory effect on DA cells in LHb-VTA pathway and through blocking glutamatergic NMDA receptors.[26-28] The blockage stimulates serotonin release in the raphe nucleus, potentially contributing to ketamine's antidepressant effects.[29-31] Other NMDAR targeting agents, such as memantine and lanicemine, have not demonstrated similar antidepressant effects as ketamine.[13,32] Ketamine enhances BNDF expression compared to memantine and demonstrates greater NMDA receptor trapping than lanicemine.[33] On a broader level, phencyclidine as an NMDA antagonist was found to have increased psychotomimetic effects compared to ketamine.[34] While subanesthetic doses of ketamine induce altered state of consciousness during administration, this altered state of consciousness is hypothesized to have implications on ketamine's therapeutic effects.[35,36] The safety of

repeated dosing of ketamine has been validated in some clinical trials, indicating its efficacy as an antidepressant.[34,37]

KETAMINE AND NEUROPLASTICITY

Ketamine has been demonstrated to enhance neuroplasticity in depression by increasing glutamate release via antagonizing NMDA receptors on inhibitory GABAergic interneurons and activating AMPA receptors.[38,39] Ketamine potentially encourages neuroplasticity by triggering BDNF and mammalian target of rapamycin-mediated signaling, principally in the mesocorticolimbic DA system.[40-42] Rodent studies, for instance, have identified increased BDNF expression after ketamine administration in regions such as the medial prefrontal cortex (MPFC) and hippocampus.[43] The AMPAR activation facilitates structural plasticity enhancement of DA neurons and allows ketamine to enhance DA-induced motivation to pursue rewards.[44-46] Ketamine is also thought to increase the expression of synaptic proteins by targeting glutamate and serotonin receptors, which improves neural microstructure stability.[40] Ketamine was found to dampen hyperactivation in the subgenual ACC (sgACC) during feedback valence processing, potentially through rapidly reversing glutamatergic overactivation.[47] Given the direct relationship between sgACC hyperactivation and anticipatory anhedonia, ketamine's effect on sgACC holds special clinical relevance, indicating its anti-anhedonic mechanisms and its influence on reward sensitivity.[47-49]

Clinical trials revealed ketamine's anti-suicidal effects in people with depression, and these effects are also believed to be related to improved neuroplasticity and attenuation of anhedonia.[44] By enhancing DA signaling and connectivity, ketamine is thought to ameliorate cognitive rigidity and anhedonic despair, which is specifically linked to suicidality in depression.[50-52] Enhanced neuroplasticity could further facilitate positive feedback detection and encourage optimistic expectations.[53] Research has also pointed to a specific kynurenine neuroinflammatory mechanism in suicidal individuals with depression,[52,53] which causes impaired plasticity and neurogenesis in animal models.[46] Via its NMDA antagonistic properties, ketamine is capable of decreasing elevated cytokine levels within the kynurenine pathway[52] and potentially reducing depression-related suicide risk.

KETAMINE AND REWARD

Ketamine's direct influence on LHb connectivity has been primarily linked to restored reward functioning in both animals and humans.[16,54,55] The LHb is a key "anti-reward center" involved in signaling unexpected aversive outcomes or negative reward prediction errors (RPEs), such as loss of reward or punishment. RPEs serve as a central mechanism in reward processing and are generated to update or correct prior information when environmental input signals defy expectations.[56-58] Whereas healthy individuals tend to more readily incorporate and respond to reward or positive RPEs,[59-61] people with depression demonstrate greater propensity to respond to negative RPEs.[58,62-65] This "pessimism bias" has also been observed in animal models, which is linked to the overactivation of LHb neurons,[66-68] leading to a reduced ability to identify rewards.

Depressive symptoms, such as avoidance, are associated with negatively biased LHb projections to the raphe nucleus and VTA, and ketamine's broad impact on reward processing is believed to result from its inhibition of LHb burst firing.[16,25,66,69,70] For example, animal work has found that negative external stimuli, such as social defeat, result in dysregulation of DA neurotransmission within the VTA-nucleus accumbens circuit[71] and ensuing loss of interest and sensitivity to positive external stimuli.[72,73] While DA neurons normally switch from baseline firing to phasic firing when unexpected reward is present, reduced VTA DA neuron firing has been observed in depression-susceptible mice.[74] The LHb is integral for encoding the valence of negative external stimuli by inhibiting DA-positive RPE processing systems, further disrupting reward processing. Likewise, LHb-raphe nucleus inhibition is normally attenuated during unexpected reward outcomes,[75] whereas, in the context of depression, aberrant LHb firing over-inhibits serotonergic neurons, which is associated with reduced sensitivity to reward and maintenance of depressed mood.[74]

KETAMINE AND INTEROCEPTION

Adaptive interoceptive processing involves matching sensations with expectations and minimizing RPEs to improve efficiency.[76] In depression, negative affect is hypothesized to arise from the misclassification and feedforwarding of inaccurate bodily signals for cognitive interpretation.[77] Neurobiologically, interoceptive sensory signals are initially processed via the thalamus, amygdala, and hippocampus to reach downstream primary sensory cortices.[62,78] The insula, in particular, serves as a core hub for perceiving, relaying, and integrating these signals while directing attention and shaping mood.[79-82] Dysfunction in the insula and ACC interoceptive pathways has been associated with pervasive pessimism, especially the maintenance of depressed mood-congruent expectations.[80]

The anterior insula has been found to be modulated by ketamine in healthy individuals and is postulated to be associated with detachment from pervasive negative interoceptive states and increased positive emotions.[35,83] (Figure 2A) Ketamine's effect on the insula might be partly achieved through its modulation of pregenual ACC (pgACC)-right insula connectivity,[84] as studies have demonstrated acute increased insula connectivity post-ketamine administration in responsive patients with depression.[85] Similarly, decreased insula activation and insula-ACC response to negative emotional stimuli 7-days post-ketamine administration in TRD patients further supports ketamine's potential effect on insula interoceptive processing.[86]

By modulating ACC activation and connectivity, ketamine may exert an influence on shaping emotional experiences and bodily feelings.[87,88] In addition to the sgACC, ketamine has been shown to acutely attenuate the activation of pgACC and dorsal ACC (dACC) in healthy individuals.[88] While ketamine-related decreases in sgACC activity have been directly associated with reduced negative emotionality scores, decreased pgACC activity has been implicated with improved hedonic value processing.[46,52,89] Ketamine's attenuation of dACC activity, in contrast, might be indicative of its dissociative effects, creating a channel for an altered sense of self.[88] In terms of connectivity, resting-state functional connectivity from ventral ACC subregions to the MPFC and hippocampus has also been found to be modulated by ketamine.[39,87] Decreased ACC-hippocampus functional connectivity in TRD populations following ketamine administration may be indicative of improved regulation of downstream emotional processing regions like the amygdala.[87] Ketamine's potential role in increasing MPFC-amygdala inhibitory effects and decreasing amygdala hyperactivity in individuals with depression has previously been found to facilitate more adaptive emotional experience.[85,90]

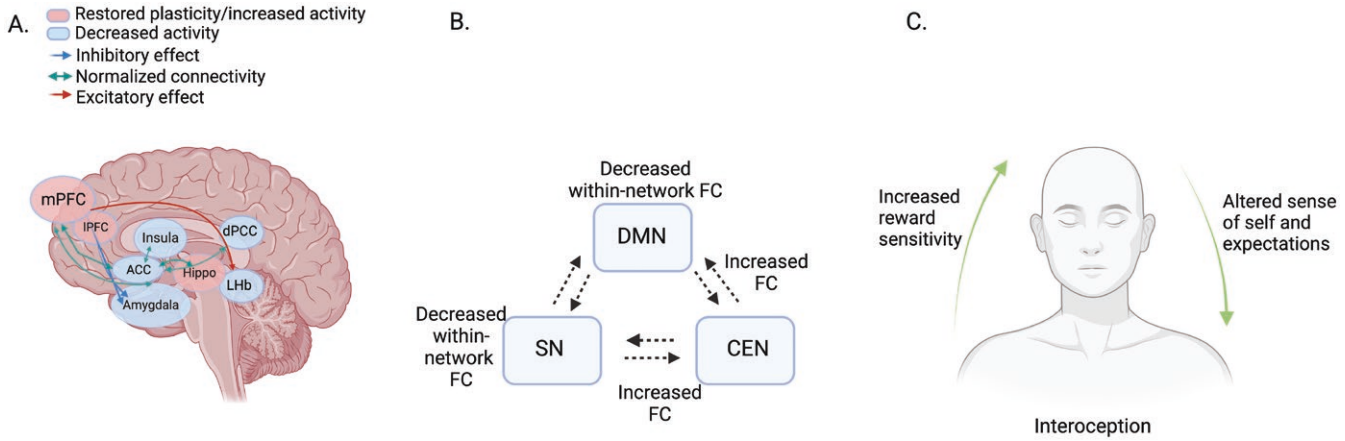

Figure 2. Potential neurocognitive mechanisms of ketamine. (A) Ketamine enhances neuroplasticity of the PFC and increases global brain functional connectivity in the lateral PFC in patients with depression. Glutamatergic overactivation in the ventral ACC is found to be reversed by ketamine, attenuating ACC hyperactivity and normalizing ACC-hippocampus and ACC-right insula functional connectivity. This is accompanied by decreased amygdala hyperactivity and increased inhibitory signaling from the medial PFC to the amygdala. Anterior insula activity is reduced by ketamine in healthy individuals and those with depression. Dampened connectivity between dPCC and pgACC and reductions in PCC resting-state functional connectivity are observed post ketamine. (B) In the resting state, a significant decrease in within-network FC in DMN, CEN, and SN was reported after ketamine treatment in both healthy controls and clinical participants with depression. Between-network FC of CEN with DMN and SN was reported to be increased. (C) Ketamine's comprehensive neurocognitive effect. Ketamine alters exteroceptive input signaling and RPE processing which improves sensitivity toward reward. Neuroplasticity enhancement by ketamine might further facilitate optimistic expectations. Ketamine influences the interoceptive process, normalizing the affective experience. Ketamine potentially reduces self-focus and increases flexibility in self representation. ACC, anterior cingulate cortex; CEN, central executive network; dPCC, dorsal posterior cingulate cortex; DMN, default mode network; PFC, prefrontal cortex; SN, salience network. This figure was created using BioRender (https://biorender.com/).

KETAMINE AND SELF-SCHEMAS

In the context of depression, maladaptive self-schemas are proposed to perpetuate enduring negative self-related expectations and beliefs, which result in a persistent cycle of depressive feelings and behaviors.[91,92] With pervasive negative interoceptive feedforward information being reinforced as self-schemas, self-related beliefs, past experiences, and current perceptions can become distorted.[93,94] Relatedly, cognitive inflexibility in depression can become entrenched by reappraising disconfirming information in a way that further solidifies the original negative beliefs. When inflexible and maladaptive self-schemas encounter the complexity of the external environment, RPEs naturally occur more often and accumulate. This uncertainty facilitates avoidance behaviors and despair as coping mechanisms, and the appearance of protective self-schemas that prioritize internal stability by resisting belief updating.[45,95-99] (Figure 3).

Heightened connectivity within the default mode network (DMN), which is associated with sustaining self-referential cognitions including autobiographical memory and introspection, has been consistently observed in depression and is hypothesized to indicate a ruminative focus on negative self-schemas.[100-102] The MPFC is a central node within the DMN that underpins the constructs of the self, while also providing feedback signals to the ACC, PCC, and subcortical reward regions.[93,103] Beyond the DMN, lateral PFC (lPFC), as part of the central executive network (CEN) and frontostriatal circuits, is also associated with rigid negative self-schemas.[104,105]

Ketamine's top-down antidepressant effects may act by helping to dislodge rigid self-perceptions and representations, as it has multiple effects on DMN self-processing and representation subregions.[106,107] In healthy individuals, connectivity between dorsal PCC and pgACC has been found to be dampened by ketamine and to be associated with decreased rumination.[100] In addition, research has pointed to ketamine-induced disruption in DMN intra-network connectivity in healthy individuals,[107,108] which is frequently associated with reductions in internally focused cognition. Other imaging studies have reported decreased negative self-reflection and reductions in PCC resting-state functional connectivity following ketamine administration.[85] Ketamine's observed modulatory effect on the MPFC could potentially promote the flexibility of self-related information integration, while its effect on the posterior DMN may be implicated in changes in forming self-representations. As ketamine enables more dynamic emotional experiences and valenced information processing, rigid negative self-schemas may become more malleable.[100] Ketamine has also been found to increase global brain functional connectivity in the lPFC in patients with depression, which could also facilitate improvements in biased processing of negatively valenced information and improve cognitive reappraisal implementation.[109-112]

Ego dissolution—the blurring of self-other boundaries and a sense of transcendence—is a frequently reported acute effect of ketamine. This phenomenon is associated with promoting a positive mood and an internal sense of unity.[113] Low-dose ketamine can induce differing states of dissociation in healthy individuals: the state of depersonalization, which is detachment from one's body and negative affect, and amnesia, which promotes negative affective states.[35] This difference has been postulated to mediate ketamine-induced insula reactivity and to serve as a marker of treatment response, with depersonalization mediating lowered insula activity, and amnesia mediating increased insula activity.[35,114,115] Other studies examining ketamine and ego dissolution have proposed that the experience of transcendence and positive emotional arousal could be indicative of treatment response.[116] Ketamine's ability to provoke ego dissolution can be conceptualized neurobiologically using the triple-network model perspective of depression, which is a unified framework incorporating the DMN, CEN, and SN.[117,118] Resting-state studies have found that ketamine induces significant decreases in within-network functional connectivity in the DMN, CEN, and SN in both healthy controls and clinical participants.[35,86] In contrast, ketamine increases between-network functional connectivity between the CEN, DMN,

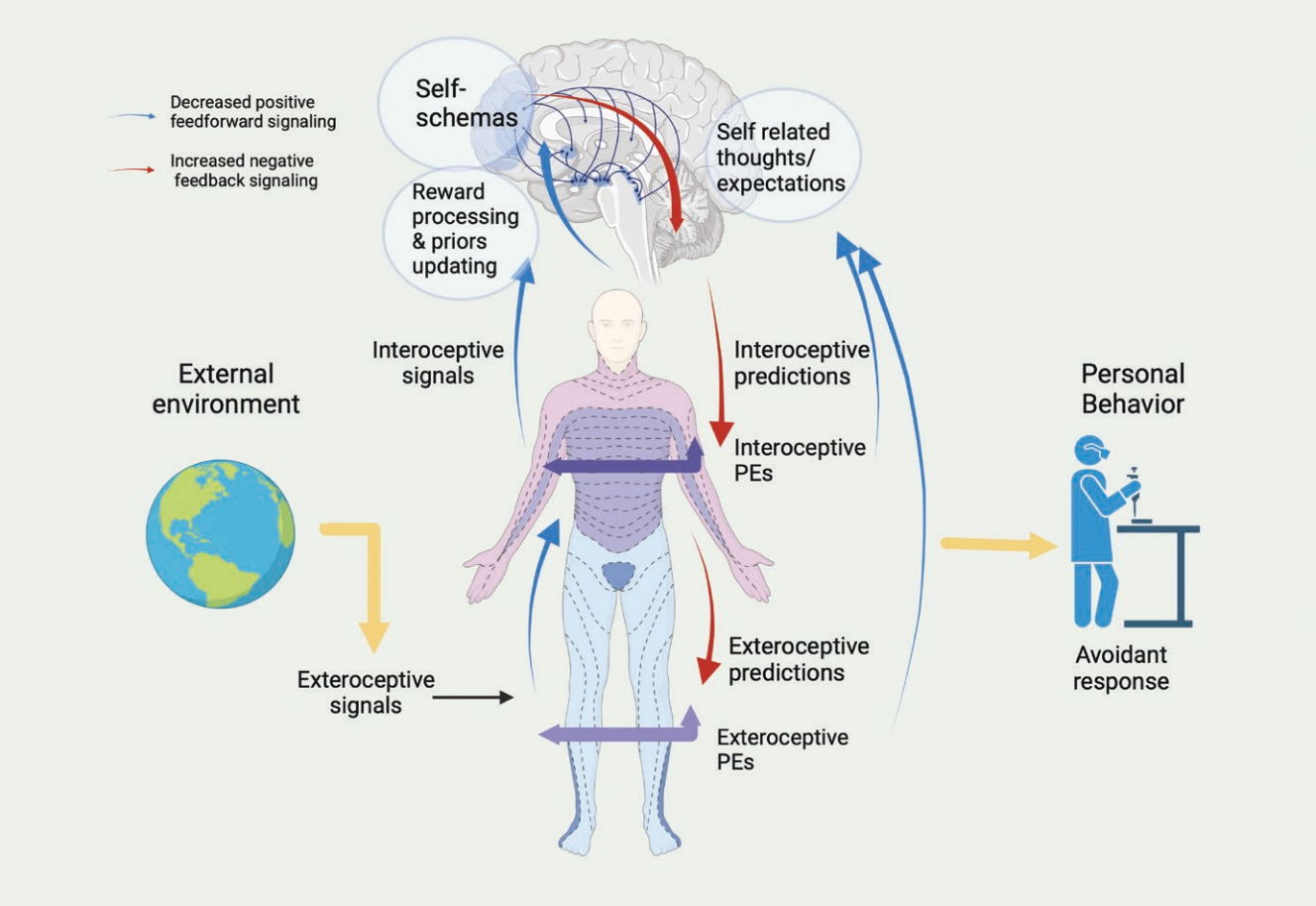

Figure 3. Neurocognitive model of depression. When bottom-up exteroceptive sensory inputs (smell, warmth, etc.) encounter top-down expectations, RPEs are created, signaled, and processed in reward pathways. Interoceptive processing, as the "interpretation" of sensations or emotions, concurrently occurs. To minimize RPEs, incoming RPEs would either update priors (ie, preexisting beliefs) or be selectively neglected. It is observed that in depression, negative RPEs are over-represented, and the interoceptive expectations are negatively biased. The state of self, especially core self-schemas, is the "control station" and is at the top of the model hierarchy. Depressive negative self-schemas are rigid and inflexible, and negative self-related thoughts/expectations are usually maintained, producing increased negative feedback signals. When inflexible self-schemas are maintained, exteroceptive RPEs might accumulate, resulting in increased stress. RPEs, reward prediction errors. This figure was created using BioRender (https://biorender.com/).

and SN.[107] Ketamine's reduction of SN connectivity and enhancement of CEN-DMN connectivity, potentially through its glutaminergic mechanisms modifying oscillatory activity in alpha-band power, is thought to induce the dissociative states that are akin to those found with serotonergic psychedelics.[117] Despite having similar anesthetic effects at high doses, ketamine demonstrates differential effects from other anesthetic agents, such as propofol, through distinct brain dynamics at low doses.[119] Ketamine was found to reduce high-frequency oscillatory activity at low doses, which had a distinct effect of dissociation, instead of ablating consciousness. Propofol, on the other hand, increases alpha spectral band power, which leads to amnestic, sedated, and atonic states at low doses.[120] On a brain level, the reorganization of resting-state intra-DMN and SN-DMN connectivity, and the preservation of sensory and sensorimotor networks by ketamine at low doses is unique in anesthetic agents, inducing a less connected consciousness state instead of switching off consciousness.[121]

UNRESOLVED QUESTIONS AND AVENUES FOR FUTURE RESEARCH

At present, research exploring ketamine's direct psychological mechanisms using task-based fMRI is limited.[122] Our synthesized evidence for ketamine's antidepressive neurocognitive mechanisms requires validation via paradigms that directly test unique human higher-order cognitive processes. It is also worth highlighting that depression is a highly heterogeneous disorder.[123,124] For example, while some studies have reported intra-network hyperconnectivity in DMN in depression, other studies have found differential alterations in posterior and anterior DMN connectivity.[124] Specifically, hypoconnectivity between the anterior and posterior DMN was found in patients with depression that did not respond to serotonergic antidepressants,[125] and some literature has shown functional connectivity increases only in anterior regions of the DMN associated with improvements in depression, while other studies have only identified increased connectivity in the posterior DMN.[124,126]

Results regarding the impact of ketamine's dissociative properties on treatment response are mixed, as the effect of dissociation is dosage and time-dependent.[35] While some studies found ego dissolution and transcendence experience to be potentially therapeutic in healthy individuals, recent clinical trials in TRD patients reported esketamine induced dissociation as a negative side effect unassociated with depressive symptom improvement.[127,128] In terms of ketamine's dose-dependent effects, animal studies reported potential cognitive impairment following anesthetic

doses of ketamine. Relatively, anesthetic doses do not elicit similar improvement in depressive symptoms as the subanesthetic doses in clinical trials.[129-131] In an animal study, subanesthetic doses of ketamine were found to induce antidepressant-like effects such as reduced immobility, while anesthetic doses induce anxiety-like behaviors.[131] In humans, ketamine's brain mechanisms are also dose-dependent, with deeper sedation being correlated with decreased DMN and increased CEN connectivity.[121] Even at subanesthetic doses, ketamine has differential effects in patients with depression and in healthy individuals.[132-135] Ketamine has been reported to induce negative symptoms of schizophrenia at low doses in some healthy participants, such as emotional withdrawal, blunt or negative affect, and psychomotor retardation.[133] In clinical trials comparing ketamine's effects in patients with TRD and healthy participants, ketamine can give rise to depressive symptoms including anhedonia and anxiety in healthy participants, while alleviating depressive symptoms in those with TRD.[134] These differential effects are hypothesized to be related to individualized baseline gamma power level and ketamine's AMPAR properties.[134] The response rate to ketamine in clinical trials on average is only over 50%, with the reasons for non-response remaining unclear. Therefore, effective dosage, predictive factors of treatment response, and evaluation of ketamine's dissociative effect in different populations need to be further explored in a careful manner. Model-driven approaches, such as Bayesian computational models, could be effective in establishing the multifactorial determinants of positive response to ketamine treatment and would allow for causal inferences to be made on how ketamine-driven shifts in neural circuitry are associated with behavior.

Few neuroimaging paradigms in the existing literature elicit activity associated with self-schemas.[113,116] However, research in belief updating using computational and Bayesian decision theory has grown in recent years[126,136] and has been applied to study reward processing and cognitive regulation in psychosis and mood disorders.[137-139] fMRI tasks that specifically test ketamine's role in belief updating as it pertains to self-schemas are warranted as it would permit the identification of the neural circuitry mediating ketamine's positive impact on higher-order cognitive processes—an undertaking that is not possible with animal models.

CONCLUSION

We propose that the neurobiological effects of ketamine in TRD are best understood through a neurocognitive model integrating reward processing, interoception, and self-schemas. We posit that ketamine's anti-anhedonic effects are attributable to its multi-level influence across highly integrated neural systems for reward-motivational processing, interoception, and self-oriented higher cognition. Concurrently, ketamine may act to influence interoceptive pathways by normalizing affective experiences and reducing overly rigid bodily feedback signals. By modulating PFC connectivity and plasticity while disrupting DMN intranetwork connectivity, ketamine may facilitate shifts away from overly active self-directed cognition and boost flexibility in self-representations. Ketamine-induced reductions of within-network connectivity and increases in between-network connectivity may also be a catalyst for dissociative states in which a more dynamic sense of self can be experienced. Taken together, we propose that ketamine's antidepressant effect extends beyond reward processing, and that the full extent of ketamine's neurocognitive impact warrants continued exploration.

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None.

Author contributions

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Conflicts of interest

The authors declare that there is no conflict of interest that might inappropriately influence the judgment. All authors declare no financial interest that could be relevant in this context.

Data availability

None.

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