

## The role of ketamine in major depressive disorders: Effects on parvalbumin-positive interneurons in hippocampus

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### Impact statement

Depression is a common mental disorder that is becoming a public health problem worldwide. In this regard, the search for new treatments becomes highly relevant, and it has been recently described that blockade of *N*-methyl-D-aspartate receptors (NMDARs) in parvalbumin-positive interneurons could be a promising therapeutic approach. Ketamine administered at subanesthetic doses induces blockade of NMDARs which in turn leads to activation of pyramidal cells. Consequently, the release of brain-derived neurotrophic factor (BDNF) is enhanced and acts rapidly to alleviate the symptoms of major depressive disorder (MDD). This review details the mechanisms of action by which ketamine ameliorates MDD, with particular emphasis on the hippocampus.

### Abstract

Major depressive disorder (MDD) is a complex illness that is arising as a growing public health concern. Although several brain areas are related to this type of disorders, at the cellular level, the parvalbumin-positive cells of the hippocampus interplay a very relevant role. They control pyramidal cell bursts, neuronal networks, basic microcircuit functions, and other complex neuronal tasks involved in mood disorders. In resistant depressions, the efficacy of current antidepressant treatments drops dramatically, so the new rapid-acting antidepressants (RAADs) are being postulated as novel treatments. Ketamine at subanesthetic doses and its derivative metabolites have been proposed as RAADs due to their rapid and sustained action by blocking *N*-methyl-D-aspartate (NMDA) receptors, which in turn lead to the release of brain-derived neurotrophic factor (BDNF). This mechanism produces a rapid plasticity activation mediated by neurotransmitter homeostasis, synapse recovery, and increased dendritic spines and therefore, it is a promising therapeutic approach to improve cognitive symptoms in MDD.

**Keywords:** *N*-methyl-D-aspartate receptors (NMDARs), ketamine, interneurons (INs), major depressive disorder (MDD), brain-derived neurotrophic factor (BDNF), hippocampus (HC)

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### Introduction

Major depressive disorder (MDD) is a growing public health concern. The World Health Organization (WHO) ranked MDD as the third leading cause of illness worldwide in 2008, and it is conceivable that it will rank first by 2030.<sup>1</sup> MDD is a complex disease in which genetic susceptibility to lifestyle plays a crucial role.<sup>2</sup> MDD causes changes in mood, behavior, and memory and induces anxiety, nervousness, exhaustion, and stress among other symptoms that severely limit psychosocial functioning and reduces quality of life.<sup>3</sup> Therefore, predisposing factors to the illness produce disability and in some cases leads to suicide.<sup>1</sup> The diagnosis of neuropsychiatric disorders has increased markedly, by more than 22%, following the COVID-19 pandemic.<sup>4</sup> People who

have overcome the disease have suffered from delusions, manic symptoms, poor memory, extreme fatigue, anxiety, and insomnia.<sup>5</sup> In practice, the diagnosis and management of MDD pose a challenge for clinicians due to its different presentations, unpredictable course, and prognosis, in addition to a highly variable treatment response.<sup>3</sup>

Limbic system brain areas such as the medial prefrontal cortex (mPFC), amygdala (AMG), and hippocampus (HC) are among the brain areas affected in MDD.<sup>6</sup> Indeed, the HC plays a direct role in declarative memory being a key modulator of prefrontal function, cooperating in the regulation of explicit memory through its connections with the dorsolateral prefrontal cortex (dlPFC). In addition to its involvement in learning and memory, the HC is also related to chronic pain management and emotional processes, mainly through

close connections with the infralimbic area (IL) located in the mPFC.<sup>7</sup>

Several studies have described a reduction in hippocampal volume in patients with chronic depression,<sup>8</sup> which in turn is related to neuronal and glial loss or cell atrophy.<sup>9</sup> Reduced levels of brain-derived neurotrophic factor (BDNF) in patients with MDD cause loss of dendritic spines of pyramidal cells (PCs) and thus decreased neuroplasticity.<sup>10</sup> These PCs are tightly interconnected with different subpopulations of interneurons (INs), establishing multiple connections with them.<sup>11</sup> The long-range inputs and outputs of PCs link the HC to several brain areas related to mood disorders, such as the frontal cortex and the anterior cingulate cortex.<sup>12,13</sup> Thus, INs are known primarily because they establish and control the local neuronal population, but it is noteworthy that long-range inhibitory INs (parvalbumin [PV]- and somatostatin [SST]-positive) have also been described between the HC and AMG, and basal ganglia and neocortical areas.<sup>11</sup>

The lack of the referred neuronal connectivity contributes to MDD.<sup>14</sup> In order to mitigate this disorder, many rapid-acting antidepressants (RAADs) are emerging in recent years as a promising therapy, including Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) antagonist that exhibits rapid and sustained effects over time.<sup>15</sup>

## Hippocampal connectivity and MDD

The hippocampal formation, constituted by Cornu Ammonis (CA1, CA2, CA3, and CA4), Dentate Gyrus (DG), and Subiculum (SB), is profusely interconnected participating various types of neurons organized in different layers. The inputs come from cortical layer II/III via the perforant pathways (PPs) or temporo-ammonic pathway (TA), reaching the unmyelinated mossy fibers of the DGs located in the granular layer or the Schaffer collaterals in CA3, respectively. CA3 transmits information to CA1, which in turn sends projections to neurons of the entorhinal cortex (EC), located mainly in deep layers V and VI.<sup>16</sup> This complex neural circuitry is part of Papez's network of memory or/and emotional circuits.<sup>17</sup> In addition, CA1 neurons project through the fimbria and fornix to return processed information to mammillary bodies located in the hypothalamus. They are also crucial of the neuroendocrine axis (hypothalamic-pituitary-adrenal, HPA) and play a key role in pathophysiology of mood disorders.<sup>18</sup>

On the contrary, there are connections along the ipsilateral longitudinal fasciculus (ILF) with ipsilateral temporal and occipital areas. Likewise, several connections also extend to contralateral areas, including in greater numbers the long-range input PV INs. These long-projection GABAergic neurons reach the EC and medial septum (MS) via the retrosplenial cortex, exerting potent regulation of behavioral control over local hippocampal circuits through numerous disinhibitory synaptic mechanisms.<sup>19</sup>

As mentioned above, impaired hippocampal function has been related to MDD. The efferent pathways of the subiculum and HC connect to critical areas such as *nucleus accumbens* (NAc) and ventral tegmental area (VTA) involved in the dopaminergic neurotransmitter-mediated reward loop, leading to alterations in the reward circuitry and affecting

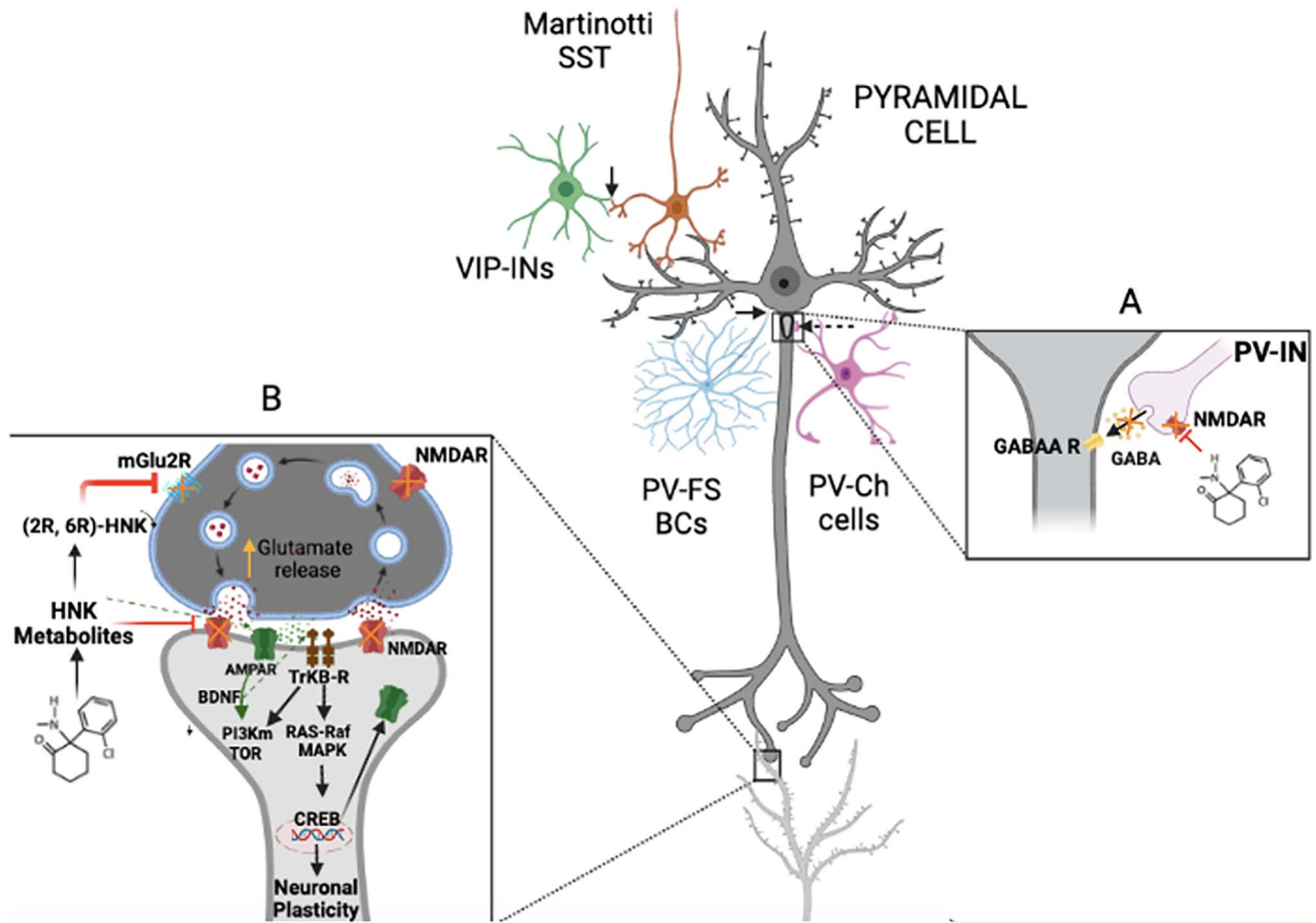
cognition and enjoyment. It has also been hypothesized that an excitatory dopaminergic projection loop between VTA and HC would enhance long-term potentiation (LTP), and in consequence, learning and memory.<sup>20</sup> Therefore, impairment of this hippocampal function could lead to reduced dopaminergic tone and contribute to anhedonia in MDD.<sup>21</sup> Finally, bed nucleus of the *stria terminalis* (BNST), located in the basal forebrain, has gained relevance because of its close relationship with the basolateral amygdala (BLA) which through the *stria terminalis* modulates the emotions of anger and fear. In addition, BNST, which presents sexual dimorphic structure, has recently been identified as an integrative center of limbic information. It presents connections with the AMG and also between the HC and the hypothalamic paraventricular nucleus (HPV). It has been observed that direct glutamatergic inputs from the ventral subiculum reached BNST, while outputs from the anterolateral, anteromedial, ventral, and posterior nuclei of the BNST also connect with the HC. Consequently, damage to the HC results in attenuation of the HPA loop and impaired hormone secretion. Therefore, this dysregulation contributed to the abnormal stress response observed in MDD.<sup>22</sup>

Finally, a decrease in neurotransmitter release has also been described in MDD.<sup>23</sup> This alteration leads to synaptic dysfunction which in turn translates into morphological changes in neurons and has been described in brain areas such as the HC and the mPFC.<sup>24,25</sup> In fact, the decrease of glutamate, serotonin, noradrenaline, or dopamine, among others, produces a lower activation of synaptic receptors accompanied by a drastic decrease of neurotrophic factors such as BDNF. The lack of monoamines and glutamate neurotransmitters release in the synaptic cleft could lead to down-regulation of excitatory synapses in multiple brain areas,<sup>26</sup> disrupting the HC and NAc and leading to several dysfunctions, mainly in reward circuits.<sup>20</sup> These patients suffer profound behavioral changes due to discouragement and fall into severe depressive states.

## Role of hippocampal INs in MDD

INs represent 20–30% of the total neurons in the central nervous system (CNS) and act on the control of the excitatory firings, plasticity, synchronization of cortical rhythms, and maintenance and modulation of circuits.<sup>11</sup> Considering the very precise function performed by INs, a possible impairment of these neurons can lead to several pathologies such as schizophrenia, depression, or anxiety.<sup>27,28</sup> In the HC, the correct activity of neural circuits is highly controlled by different types of GABAergic INs that constitute 7–11% of all hippocampal neurons.<sup>12</sup> PV, SST, and 5-HT<sub>3aR</sub> vasoactive or no vasoactive intestinal peptide (VIP/non-VIP) distinguish this population of hippocampal INs. Forty percent of the INs are PV-positive, whereas the SST and 5-HT<sub>3aR</sub> populations constitute 30% of hippocampal INs<sup>11</sup> (Figure 1).

Positive PV neurons are divided into two types: fast-spiking basket cells (FS-BCs) and chandelier cells (ChCs). Both types of cells synapse with PCs although they differ in their location. While BCs connect to the neuronal soma, ChCs synapse mainly directly with the axonal hillock.<sup>29</sup> Once inputs are received, action potentials are transmitted



**Figure 1.** Representation of the action of ketamine on NMDARs and its effect on cellular synapses and activation of molecular pathways. Ketamine blocks NMDARs in high-affinity neurons, including PV-positive interneurons. Blockade of NMDARs prevents the release of the neurotransmitter GABA (A: right square) and consequently allows PCs to release more of the excitatory neurotransmitter glutamate (evoked release) (B: left square). These changes in the synaptic cleft induced an increased activation of AMPA receptors, which in turn promotes BDNF release. BDNF binds tightly to TrkB receptors promoting neuronal plasticity by activating the Akt-mTOR pathway cascade. The metabolite HNK appears as the last metabolite of ketamine, which has the ability to bind to AMPA receptors, potentiating BDNF and plasticity. Therefore, it represents a new step with potent antidepressant action. Continuous arrows show somatostatin Martinotti cells (SST) (orange) and VIP interneurons (green). SST targets dendrites, while VIP interneurons are selectively attached to SST. Non-VIP interneurons are not represented. Dashed arrows show parvalbumin interneurons (PV-INs) synapsis. Parvalbumin basket cells (PV-FS-BCs) (light blue) target PCs (dark gray) soma, whereas chandelier cells (PV-Ch cells) (purple color) target the axonal hillock.

NMDAR: *N*-methyl-*D*-aspartate receptors; PC: pyramidal cell; AMPA:  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; PV: parvalbumin; SST: somatostatin; VIP: vasointestinal peptide; HNK: hydroxynorketamine; TrkB: tropomyosin receptor kinase B; BDNF: brain-derived neurotrophic factor; mGlu2R: metabotropic glutamate receptor type 2.

to the initial segment of the axon.<sup>30</sup> Although both types of PV + INs are capable of producing a powerful influence on target neurons<sup>31</sup> (Figure 1(A)), FS-BCs show higher speed and temporal precision and are therefore specialized for fast excitation.<sup>32</sup> Also, FS-BCs are enriched with very high amount of sodium,  $\text{Ca}^{2+}$  permeable AMPA channels,<sup>33</sup> and excess of fast repolarizing  $\text{Kv}3$  channels in fast-spiking axon neurons.<sup>11,34</sup>

Positive PV INs control basic microcircuits such as feedback and feedforward inhibition, playing a central role in the activity of complex neural network in the EC with high firing rates.<sup>35</sup> Moreover, in this context, FS-PV neurons are involved in plasticity<sup>36</sup> and stimulate reward behaviors in the mPFC. Therefore, they become the main target of emerging therapeutic treatments<sup>37</sup> appearing to be especially important in MDD.

In all anatomical structures of the HC, there are intimate connections between PCs and INs through performant pathways that exert tight functional control, especially in

the DG. PV-expressing INs reach the granular layer of the DG and activate very important feedback and feedforward inhibition of the dentate mossy fibers located in the granular layer,<sup>38</sup> providing inhibitory control of the PCs (Figure 1(A)), evoking GABAergic postsynaptic currents and allowing fast-spike phases with precise control of spike timing.<sup>39</sup> However, disruption of this homeostatic balance in depressive disorders affects downstream molecular cascades and leads to synaptic dysfunction, neuronal damage, and decreased neuroplasticity.<sup>40</sup>

### Rapid action antidepressants: ketamine as a novel treatment in MDD

Adequate antidepressant treatment should reverse the molecular and even morphological changes observed in the HC, which is one of the main structures involved in MDD, linked to other areas such as the PFC, AMG, or cingulate gyrus, all interconnected through long tracts.<sup>41</sup>

The therapeutic approach most commonly used worldwide to deal with MDD is based mainly on selective monoamine reuptake inhibitors selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). These drugs act on the synaptic cleft, preventing the reuptake of synaptic monoamines and therefore increasing the amount of monoamines, which in the clinic translates into an effective antidepressant action.<sup>42</sup> One of the limitations of this treatment is that it takes several weeks to achieve therapeutic effect and restore or alleviate symptomatology.<sup>43</sup> Another type of effective antidepressant drugs is monoamine oxidase inhibitors (MAOIs), which prevent the degradation of monoamines. Tricyclic antidepressants, such as amitriptyline, also prevent monoamine reuptake. They are prescribed in MDD, anxiety, bipolar disorders, and other pathologies such as neuropathies and pain management, but the reported side effects have been greater than monoamine reuptake inhibitors (MRI).<sup>26</sup> Furthermore, the efficacy of these commonly used antidepressants is variable, and more than one-third of patients remain depressed. These patients could eventually slip into resistant depression (RD), leading to MDD and worsening of the disease.<sup>44</sup> Consequently, there is still a need to find new strategies that can contribute to obtain rapid or immediate improvement in those patients with severe symptoms. In this field, RAADs have emerged in the last years, and ketamine has been postulated as a novel and very promising treatment for MDD.<sup>12</sup>

Ketamine hydrochloride was synthesized by Calvin Stevens in 1962 and has been used as an intravenous anesthetic since 1970, producing thalamo-cortical dissociative anesthesia and analgesia.<sup>45</sup> In addition to its use in surgery as an anesthetic, it is also used as an analgesic therapy to manage chronic pain.<sup>46</sup> Moreover, it has also been commonly used as a social drug worldwide.<sup>47</sup> As far as MDD is concerned, ketamine could improve hippocampal function by modulating INs and thus excitatory transmission, in addition to maintaining, promoting, and recovering dendritic spine loss.<sup>44</sup>

Pharmacodynamic properties of ketamine and its metabolites control glutamatergic excitatory responses by antagonizing NMDARs,<sup>48,49</sup> and it has been tested as a promising antidepressant therapy.<sup>50,51</sup> Ketamine in subanesthetic doses is able to block NMDARs in INs. The increased release of glutamate allows more intense binding of the neurotransmitter to  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), thus promoting quickly sodium and potassium permeability, and the activation of voltage-gated calcium channels (VGCCs). These channels trigger the release of BDNF, which, through binding to the receptor tyrosine kinase B (TrkB), produces the translocation of Akt to the plasmatic membrane and promotes the downstream molecular cascade through the rapamycin-mTORC1 pathway. It also regulates cellular transcription of CREB (cAMP response element binding protein) to promote neuronal survival and neuroplasticity.<sup>6</sup> The second BDNF-TrkB signaling pathway is also able to induce activation of the MAPK/Erk mTOR complex, inducing neurogenesis and dendritic growth.<sup>52</sup>

Therefore, the affinity of ketamine to bind to NMDARs leads to appropriate neurotransmitter release at the synaptic

cleft resulting in increased BDNF release and consequently increased plasticity and neuronal survival, among others, in the HC. In fact, subanesthetic ketamine administration promotes glutamate evoked release in the synaptic cleft in PCs (Figure 1(B)), triggering firing and neurotransmission and exerting a tight control and information transfer on different brain areas like PFC and HC.<sup>53</sup> Activation of these pathways is crucial in MDD as several studies have shown that postmortem tissues from suicide victims<sup>54</sup> and serum samples from MDD patients showed very low amounts of BDNF, whereas antidepressant treatment results in an increase of these values<sup>55</sup> accompanied by an improvement of symptomatology.<sup>56</sup>

In addition to the above pathway, other signaling pathways are involved in this complex process. The rapid action of ketamine also activates the calmodulin-dependent kinase eEF2K which is directly dependent on the amount of calcium and calmodulin amount.<sup>57</sup> When NMDARs are disrupted by ketamine administration, eEF2K is suppressed leading to eEF2 disinhibition. This promotes rapid and sustained protein synthesis and BDNF release and has therefore been proposed as a very effective mechanism to palliate stress and neuronal plasticity.<sup>58</sup> In fact, some authors have proposed eEF2K as the main molecular substrate that potentiates the fast-acting depressant action of ketamine that responds very rapidly during stress events.<sup>59</sup>

Furthermore, dissociation of ketamine produces extensive metabolites such as norketamine, dehydronorketamine, hydroxyketamine, and hydroxynorketamine (HNK). Recent studies have described the final metabolite of ketamine (2S, 6S; 2R, 6R)-HNK as the most present in plasma analysis in humans<sup>60</sup> and offer a promising finding due to its potentiating action of rapid antidepressant effect without side effects.<sup>61</sup> However, the mechanism of action differs from the previously mentioned NMDAR activation, and acts directly by binding specifically to the AMPAR. Consequently, it results in the direct release of BDNF into the synaptic cleft and downstream activation of TrkB. Also, it has been found that only (2R, 6R)-HNK metabolite is able to increase the levels of phosphorylated P70S6 kinase in threonine 389 position. This is potentiated by a central regulator of the mTOR pathway, inducing neuroplasticity.<sup>62</sup>

Nevertheless, to achieve the therapeutic effects of ketamine and recover the hippocampal cytoarchitecture and cognitive deficits in human patients, the dose and exposure time need to be determined.<sup>63</sup> The first ketamine trial in depressed patients was performed with a single dose of ketamine 0.5 mg/kg administered intravenously over 40 min. Significant results were found in the depressed group with respect to the placebo group, indicating that ketamine-induced potentiation and control of glutamatergic neurotransmission in human RDs were able to strongly ameliorate depressive symptoms for several hours, maintaining these effects over several days.<sup>48</sup> Since then, different trials have been conducted with subanesthetic doses for MDD in rodents and humans.

Recently, favorable results have also been described for an adjusted intranasal dose of the (S)-ketamine enantiomer (28–84 mg) administered twice weekly for two weeks in combination with oral antidepressant treatment in patients with

RD.<sup>64</sup> Similar results were obtained with a single infusion of the same dose with racemic ketamine (0.5 mg/kg) for 40 min in humans.<sup>65</sup> On the contrary, an intraperitoneal ketamine dose of 20 mg/kg was necessary to achieve antidepressant actions in mice.<sup>66</sup> In contrast, very low doses of ketamine (3–10 mg/kg) injected once in rodents also showed behavioral changes accompanied by recovery of spinal density compared to wild-type rodents.<sup>67</sup> It also has been reported that intraperitoneal infusion of 3, 10, or 30 mg/kg ketamine produced an immediate increase in glutamate, glutamine, and GABA in the mPFC of mice.<sup>68</sup> In relation to the observed GABAergic deficits and loss of glutamatergic homeostatic state described in MDD, the application of subanesthetic doses of ketamine (3 mg/kg) has also shown positive effects both in behavioral test and at structural and molecular levels.<sup>69</sup>

Finally, increased synaptogenesis after ketamine treatment has also been described in rodents.<sup>70</sup> Likewise, *in vivo* two-photon images taken in the mPFC showed increased dendritic density with a single dose of 10 mg/kg of ketamine.<sup>71</sup> Other authors demonstrated that a single subanesthetic dose in rodents is able to exhibit increased dendritic density in brain areas such as the PFC through mTOR signaling. Two hours after a low dose of ketamine, induction of spine formation could already be observed, and after 24 h, maintenance of spine stability was observed through neurotransmitter-induced excitatory postsynaptic currents (EPSCs). This demonstrates that ketamine was able to increase nerve impulse frequency and amplitude.<sup>72</sup>

## Effects of ketamine on PV+ INs

Imbalance of PV+ neurons is related to pathologies such as anxiety, depression, and also schizophrenia.<sup>73</sup> These GABAergic INs play a crucial role in the control of local microcircuits as they perform direct inhibitory synapses on excitatory somatic neurons.<sup>74</sup> In fact, PV+ fast-spiking INs are known to have faster excitatory postsynaptic firing patterns than PCs, being better recruited by excitatory inputs.<sup>75</sup> Because of these characteristics, it is suggested that an NMDAR antagonist such as ketamine modifies FS-PV cell receptors more rapidly than excitatory PCs.<sup>76</sup> Indeed, inhibition of GABA release by PV-positive INs in CA1 or subiculum restores recurrent seizures.<sup>27</sup> Therefore, NMDAR dysfunction in FS-PV+ INs could be the main target in the treatment of patients with RD, and the non-competitive allosteric modulator ketamine appears as a key regulator of NMDAR in FS-PV+ to reduce severe depressive symptoms.<sup>77</sup>

Ketamine shows high affinity for Ca<sup>2+</sup>-related influx channels, such as NMDARs, whereas its final metabolite HNK is a potent modulator of AMPAR. The relationship between both receptors is one of the links for the prevention of MDD by ketamine. In fact, ketamine plays a decisive role in PV+ INs due to the affinity shown by ketamine for NMDARs present in this type of INs<sup>78</sup> and the large amount of glutamate receptor 1 (GluR1) containing Ca<sup>2+</sup>-permeable AMPARs.<sup>33</sup> Calcium influx involves the activation of downstream molecular pathways involving BDNF, and as previously mentioned, they provide potent and stable control over PV+ INs, providing synaptic modulation.<sup>79</sup>

PV FS-BCs seem to respond more rapidly to ketamine because they present the highest number of NMDA2A subtype receptors, as well as much more than pyramidal neurons.<sup>80</sup> NMDA2A receptors appear predominantly in the synaptic cleft, whereas extra-synaptic receptors present other types of subunits such as NMDA2B/2C/2D. NMDA2B receptors are bound to Ca<sup>2+</sup>-dependent calmodulin kinase II (CaMKII),<sup>81</sup> and together with NMDA2A receptors are considered the most important receptor subtype for transmitting burst, which in turn accounts for the majority of Ca<sup>2+</sup> permeability subtype receptors among NMDARs.<sup>82</sup> This is an essential point to increase the efficiency and speed of inhibitory output.<sup>37</sup> In fact, recent work has shown that a low dose of ketamine (8 mg/kg, i.p.) enhanced NMDA2A receptor-mediated cortical activity in PV+ cells.<sup>83</sup> Furthermore, electrophysiological studies demonstrated antidepressant actions through the disinhibition hypothesis.<sup>84</sup> Initially, low doses of ketamine (10 mg/kg, i.p.) were administered 24 h prior to animal testing, which led to a rapid blockade of NMDA2B in GABAergic INs. Consequently, sustained excitatory postsynaptic currents were generated and recorded in layer V PCs together with the BLA and provided therapeutic effects to mice. Although different types of INs were involved in these neuronal circuits, all of them showed a high density of NMDA2B subtype receptors. In fact, a recent study has shown that ketamine has no antidepressant effects in the absence of this receptor on GABAergic INs in knock-down mice.<sup>85</sup>

On the contrary, NMDA2D subunits are expressed in some PV INs in the neocortex, neostriatum, and HC.<sup>86</sup> Some authors have described that Mg<sup>2+</sup> does not provide a special blockade of NMDA2D channels, giving electrophysiological properties of fast spiking compared to another class of INs.<sup>87,88</sup> This evidence supports that ketamine and other NMDAR antagonists such as MK-801 act with especially high affinity on NMDA2DRs in FS-PV cells, also supporting the role of this INs in the hypothesis of tightly controlled disinhibition of PCs.

Positive PV neurons are also related to the correct generation of gamma waves in the HC.<sup>89</sup> These oscillations are critical for neural network maintenance and cognitive phenomena.<sup>90</sup> Altered gamma waves with involvement of PV+ cells have been described in mood disorders or schizophrenia.<sup>91</sup> In this regard, other authors demonstrated that a single dose of 10 mg/kg, i.p. ketamine administered for seven days was able to potentiate evoked action potentials in PV+ cells, counteracting the loss of axonal boutons induced in chronically stressed mice.<sup>92</sup> In this study, substantial evoked action potentials were also observed in PV+ INs 10 min after ketamine administration (10 μM, i. p.). This effect was maintained for 50 min, supporting that ketamine binds NMDAR in PV+ INs increasing their excitability after stress exposure.<sup>92</sup>

## Conclusions

In conclusion, very low doses of ketamine, called hormesis, have shown a promising approach in MDD. The main activation pathway studied has been BDNF-TrkB-mTOR, promoting rapid neuronal plasticity. The changes in neurotrophic

factors involve INs, and among them, PV+ INs play a pivotal role. They provide synaptic changes in different brain areas through the hypothesis of disinhibition, producing a rapid recovery in patients suffering from MDD. In only a few minutes, sustained antidepressant therapeutic effects are achieved during several hours or days.

Nevertheless, the beneficial effects of ketamine in MDD depend on the dose and time of exposure. While ketamine administered in a single dose may be very effective due to its action as RAAD, if administered repeatedly, it may produce stereotyped behaviors because of the loss of INs, and in particular, of PV+ neurons. Therefore, it is necessary to determine these variables for a safe approach to this promising treatment for MDD patients.

#### AUTHORS' CONTRIBUTIONS

JVL and PAG designed the project. IBA with the collaboration of MAG, AV-R, and MP-G researched data for the article and bibliography. Figure was designed by IBA in collaboration with NO and HB. IBA wrote the first draft. NO, HB, PAG, and JVL contributed to discussion of the content and reviewed and edited this paper before submission. All authors have read and agreed to the published version of the manuscript due to the knowledge and experience in the study of depressive disorders.

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#### REFERENCES

- Bachmann S. Epidemiology of suicide and the psychiatric perspective. *Int J Environ Res Public Health* 2018;**15**:1425
- Lopizzo N, Bocchio Chiavetto L, Cattane N, Plazzotta G, Tarazi FI, Pariante CM, Riva MA, Cattaneo A. Gene-environment interaction in major depression: focus on experience-dependent biological systems. *Front Psychiatry* 2015;**6**:68
- Malhi GS, Mann JJ. Depression. *Lancet* 2018;**392**:2299–312
- Nalleballe K, Reddy Onteddu S, Sharma R, Dandu V, Brown A, Jasti M, Yadala S, Veerapaneni K, Siddamreddy S, Avula A, Kapoor N, Mudassar K, Kovvuru S. Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav Immun* 2020;**88**:71–4
- Garg RK. Spectrum of neurological manifestations in Covid-19: a review. *Neurol India* 2020;**68**:560–72
- Björkholm C, Monteggia LM. BDNF – a key transducer of antidepressant effects. *Neuropharmacology* 2016;**102**:72–9
- Jefferson T, Kelly CJ, Martina M. Differential rearrangement of excitatory inputs to the medial prefrontal cortex in chronic pain models. *Front Neural Circuits* 2021;**15**:791043
- Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *Am J Psychiatry* 2020;**157**:115–8
- Park SC. Neurogenesis and antidepressant action. *Cell Tissue Res* 2019;**377**:95–106
- Radley JJ, Rocher AB, Miller M, Janssen WG, Liston C, Hof PR, McEwen BS, Morrison JH. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. *Cereb Cortex* 2006;**16**:313–20
- Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. *Neuron* 2016;**91**:260–92
- Maller JJ, Welton T, Middione M, Callaghan FM, Rosenfeld JV, Grieve SM. Revealing the hippocampal connectome through super-resolution 1150-direction diffusion MRI. *Sci Rep* 2019;**9**:2418
- Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 2010;**35**:192–216
- Holmes SE, Scheinost D, Finnema SJ, Naganawa M, Davis MT, DellaGioia N, Nabulsi N, Matuskey D, Angarita GA, Pietrzak RH, Duman RS, Sanacora G, Krystal JH, Carson RE, Esterlis I. Lower synaptic density is associated with depression severity and network alterations. *Nat Commun* 2019;**10**:1529
- Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, Hu H. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature* 2018;**554**:317–22
- Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci* 2010;**11**:339–50
- Papez JW. A proposed mechanism of emotion. *J Neuropsychiatry Clin Neurosci* 1995;**7**:103–12
- Keller J, Gomez R, Williams G, Lembke A, Lazzeroni L, Murphy GM Jr, Schatzberg AF. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol Psychiatry* 2017;**22**:527–36
- Urrutia-Piñones J, Morales-Moraga C, Sanguinetti-González N, Escobar AP, Chiu CQ. Long-range GABAergic projections of cortical origin in brain function. *Front Syst Neurosci* 2022;**16**:841869
- Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 2015;**46**:703–13
- Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 2006;**16**:239–49
- Lebow MA, Chen A. Overshadowed by the amygdala: the bed nucleus of the stria terminalis emerges as key to psychiatric disorders. *Mol Psychiatry* 2016;**21**:450–63
- Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* 2016;**22**:238–49
- Belleau EL, Treadway MT, Pizzagalli DA. The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. *Biol Psychiatry* 2019;**85**:443–53
- Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord* 2012;**138**:9–18
- Thompson SM, Kallarackal AJ, Kvarita MD, Van Dyke AM, LeGates TA, Cai X. An excitatory synapse hypothesis of depression. *Trends Neurosci* 2015;**38**:279–94
- Drexel M, Romanov RA, Wood J, Weger S, Heilbronn R, Wulff P, Tasan-RO, Harkany T, Sperk G. Selective silencing of hippocampal parvalbumin interneurons induces development of recurrent spontaneous limbic seizures in mice. *J Neurosci* 2017;**37**:8166–79
- Fee C, Banasr M, Sibille E. Somatostatin-positive gamma-aminobutyric acid interneuron deficits in depression: cortical microcircuit and therapeutic perspectives. *Biol Psychiatry* 2017;**82**:549–59
- Hemmings HC, Egan TD. *Pharmacology and physiology for anesthesia e-book: foundations and clinical application*. Amsterdam: Elsevier Health Sciences, 2012

30. Clark BD, Goldberg EM, Rudy B. Electrotonic tuning of the axon initial segment. *Neuroscientist* 2009;15:651–68
31. Fishell G, Rudy B. Mechanisms of inhibition within the telencephalon: “where the wild things are.” *Annu Rev Neurosci* 2011;34:535–67
32. Massi L, Lagler M, Hartwich K, Borhegyi Z, Somogyi P, Klausberger T. Temporal dynamics of parvalbumin-expressing axo-axonic and basket cells in the rat medial prefrontal cortex in vivo. *J Neurosci* 2012;32:16496–502
33. Hull C, Isaacson JS, Scanziani M. Postsynaptic mechanisms govern the differential excitation of cortical neurons by thalamic inputs. *J Neurosci* 2009;29:9127–36
34. Hu H, Jonas P. A supercritical density of Na(+) channels ensures fast signaling in GABAergic interneuron axons. *Nat Neurosci* 2014;17:686–93
35. Buetfering C, Allen K, Monyer H. Parvalbumin interneurons provide grid cell-driven recurrent inhibition in the medial entorhinal cortex. *Nat Neurosci* 2014;17:710–8
36. Sparta DR, Hovelsø N, Mason AO, Kantak PA, Ung RL, Decot HK, Stuber GD. Activation of prefrontal cortical parvalbumin interneurons facilitates extinction of reward-seeking behavior. *J Neurosci* 2014;34:3699–705
37. Hu H, Gan J, Jonas P. Interneurons. Fast-spiking, parvalbumin+ GABAergic interneurons: from cellular design to microcircuit function. *Science* 2014;345:1255263
38. Pi H-JJ, Hangya B, Kvitsiani D, Sanders JL, Huang ZJ, Kepecs A. Cortical interneurons that specialize in disinhibitory control. *Nature* 2013;503:521–4
39. Vaden RJ, Gonzalez JC, Tsai MC, Niver AJ, Fusilier AR, Griffith CM, Kramer RH, Wadiche JL, Overstreet-Wadiche L. Parvalbumin interneurons provide spillover to newborn and mature dentate granule cells. *eLife* 2020;9:e54125
40. Melzer S, Michael M, Caputi A, Eliava M, Fuchs EC, Whittington MA, Monyer H. Long-range-projecting GABAergic neurons modulate inhibition in hippocampus and entorhinal cortex. *Science* 2012;335:1506–10
41. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology* 2008;33:88–109
42. Iadarola ND, Niciu MJ, Richards EM, Vande Voort JL, Ballard ED, Lundin NB, Nugent AC, Machado-Vieira R, Zarate CA Jr. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Ther Adv Chronic Dis* 2015;6:97–114
43. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR\*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv* 2009;60:1439–45
44. Gould TD, Zarate CA Jr, Thompson SM. Molecular pharmacology and neurobiology of rapid-acting antidepressants. *Annu Rev Pharmacol Toxicol* 2019;59:213–36
45. Müller J, Pentyala S, Dilger J, Pentyala S. Ketamine enantiomers in the rapid and sustained antidepressant effects. *Ther Adv Psychopharmacol* 2016;6:185–92
46. Barrevelde AM, Correll DJ, Liu X, Max B, McGowan JA, Shovel L, Wasan AD, Nedeljkovic SS. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain Med* 2013;14:925–34
47. Reynaud-Maurupt C, Bello PY, Akoka S, Toufik A. Characteristics and Behaviors of Ketamine Users in France in 2003. *J Psychoactive Drugs* 2007;39:1–11
48. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47:351–4
49. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;63:856–64
50. Granry JC, Dube L, Turroques H, Conreux F. Ketamine: new uses for an old drug. *Curr Opin Anaesthesiol* 2000;13:299–302
51. Singh NS, Zarate CA Jr, Moaddel R, Bernier M, Wainer IW. What is hydroxynorketamine and what can it bring to neurotherapeutics? *Expert Rev Neurother* 2014;14:1239–42
52. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology* 2012;62:35–41
53. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* 2007;27:11496–500
54. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 2003;60:804–15
55. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry* 2003;54:70–5
56. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry* 2014;76:970–6
57. Taha E, Gildish I, Gal-Ben-Ari S, Rosenblum K. The role of eEF2 pathway in learning and synaptic plasticity. *Neurobiol Learn Mem* 2013;105:100–6
58. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 2011;475:91–5
59. Ryazanov AG. Elongation factor-2 kinase and its newly discovered relatives. *FEBS Lett* 2002;514:26–9
60. Zarate CA, Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, Moaddel R, Wainer IW. Relationship of ketamine’s plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* 2012;72:331–8
61. Leung LY, Baillie TA. Comparative pharmacology in the rat of ketamine and its two principal metabolites, norketamine and (Z)-6-hydroxynorketamine. *J Med Chem* 1986;29:2396–9
62. Fukumoto K, Fogaça MV, Liu RJ, Duman C, Kato T, Li XY, Duman RS. Activity-dependent brain-derived neurotrophic factor signaling is required for the antidepressant actions of (2R,6R)-hydroxynorketamine. *Proc Natl Acad Sci* 2019;116:297–302
63. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA, Jr. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* 2012;37:1526–33
64. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H, Drevets WC. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression. *JAMA Psychiatry* 2018;75:139–48
65. Farmer CA, Gilbert JR, Moaddel R, George J, Adejo L, Lovett J, Nugent AC, Kadriu B, Yuan P, Gould TD, Park LT, Zarate CA Jr. Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression. *Neuropsychopharmacology* 2020;45:1398–404
66. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr, Gould TD. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 2016;533:481–6
67. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 2010;329:959–64
68. Chowdhury GM, Zhang J, Thomas M, Banasr M, Ma X, Pittman B, Bristow L, Schaeffer E, Duman RS, Rothman DL, Behar KL, Sanacora G. Transiently increased glutamate cycling in rat PFC is associated with rapid onset of antidepressant-like effects. *Mol Psychiatry* 2017;22:120–6
69. Ren Z, Pribiag H, Jefferson SJ, Shorey M, Fuchs T, Stellwagen D, Luscher B. Bidirectional homeostatic regulation of a depression-related brain state by gamma-aminobutyric acid deficits and ketamine treatment. *Biol Psychiatry* 2016;80:457–68

70. Duman CH, Duman RS. Spine synapse remodeling in the pathophysiology and treatment of depression. *Neurosci Lett* 2015;**601**:20–9
71. Phoumthipphavong V, Barthas F, Hassett S, Kwan AC. Longitudinal effects of ketamine on dendritic architecture in vivo in the mouse medial frontal cortex. *eNeuro* 2016;**3**
72. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry* 2011;**69**:754–61
73. Marín O. Interneuron dysfunction in psychiatric disorders. *Nat Rev Neurosci* 2012;**13**:107–20
74. Pozzi L, Pollak Dorocic I, Wang X, Carlén M, Meletis K. Mice lacking NMDA receptors in parvalbumin neurons display normal depression-related behavior and response to antidepressant action of NMDAR antagonists. *PLoS One* 2014;**9**:e83879
75. Povysheva NV, Gonzalez-Burgos G, Zaitsev AV, Kröner S, Barrionuevo G, Lewis DA, Krimer LS. Properties of excitatory synaptic responses in fast-spiking interneurons and pyramidal cells from monkey and rat prefrontal cortex. *Cereb Cortex* 2006;**16**:541–52
76. Constantinidis C, Goldman-Rakic PS. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. *J Neurophysiol* 2002;**88**:3487–97
77. Zhou ZQ, Zhang GF, Li XM, Yang C, Yang JJ. Fast-spiking interneurons and gamma oscillations may be involved in the antidepressant effects of ketamine. *Med Hypotheses* 2012;**79**:85–6
78. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1007;**17**:2921–7
79. Cornford JH, Mercier MS, Leite M, Magloire V, Häusser M, Kullmann DM. Dendritic NMDA receptors in parvalbumin neurons enable strong and stable neuronal assemblies. *eLife* 2019;**8**:e49872
80. Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM. A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. *J Neurosci* 2006;**26**:1604–15
81. Lisman J, Yasuda R, Raghavachari S. Mechanisms of CaMKII action in long-term potentiation. *Nat Rev Neurosci* 2012;**13**:169–82
82. Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci* 2013;**14**:383–400
83. Picard N, Takesian AE, Fagiolini M, Hensch TK. NMDA 2A receptors in parvalbumin cells mediate sex-specific rapid ketamine response on cortical activity. *Mol Psychiatry* 2019;**24**:828–38
84. Ghosal S, Duman CH, Liu RJ, Wu M, Terwilliger R, Girgenti MJ, Wohleb E, Fogaca MV, Teichman EM, Hare B, Duman RS. Ketamine rapidly reverses stress-induced impairments in GABAergic transmission in the prefrontal cortex in male rodents. *Neurobiol Dis* 2020;**134**:104669
85. Gerhard DM, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, Taylor SR, Duman CH, Delpire E, Picciotto M, Wohleb ES, Duman RS. GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest* 2020;**130**:1336–49
86. Standaert DG, Landwehrmeyer GB, Kerner JA, Penney JB Jr, Young AB. Expression of NMDAR2D glutamate receptor subunit mRNA in neurochemically identified interneurons in the rat neostriatum, neocortex and hippocampus. *Brain Res Mol Brain Res* 1996;**42**:89–102
87. Garst-Orozco J, Malik R, Lanz TA, Weber ML, Xi H, Arion D, Enwright JF 3rd, Lewis DA, O'Donnell P, Sohal VS, Buhl DL. GluN2D-mediated excitatory drive onto medial prefrontal cortical PV+ fast-spiking inhibitory interneurons. *PLoS One* 2020;**15**:e0233895
88. Sapkota K, Mao Z, Synowicki P, Lieber D, Liu M, Ikezu T, Gautam V, Monaghan DT. GluN2D N-Methyl-d-aspartate receptor subunit contribution to the stimulation of brain activity and gamma oscillations by ketamine: implications for schizophrenia. *J Pharmacol Exp Ther* 2016;**356**:702–11
89. Antonoudiou P, Tan YL, Kontou G, Upton AL, Mann EO. Parvalbumin and somatostatin interneurons contribute to the generation of hippocampal gamma oscillations. *J Neurosci* 2020;**40**:7668–87
90. Tukker JJ, Lasztóczy B, Katona L, Roberts JD, Pissadaki EK, Dalezios Y, Márton L, Zhang L, Klausberger T, Somogyi P. Distinct dendritic arborization and in vivo firing patterns of parvalbumin-expressing basket cells in the hippocampal area CA3. *J Neurosci* 2013;**33**:6809–25
91. Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biol Psychiatry* 2015;**77**:1031–40
92. Ng LHL, Huang Y, Han L, Chang RC, Chan YS, Lai CSW. Ketamine and selective activation of parvalbumin interneurons inhibit stress-induced dendritic spine elimination. *Transl Psychiatry* 2018;**8**:272