

## Dual Perspectives

**Dual Perspectives Companion Paper: The Role of GluN2C-Containing NMDA Receptors in Ketamine's Psychotogenic Action and in Schizophrenia Models, by Elizaveta Khlestova, Jon W. Johnson, John H. Krystal, and John Lisman**

# Ketamine: NMDA Receptors and Beyond

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Human studies examining the effects of the dissociative anesthetic ketamine as a model for psychosis and as a rapidly acting antidepressant have spurred great interest in understanding ketamine's actions at molecular, cellular, and network levels. Although ketamine has unequivocal uncompetitive inhibitory effects on *N*-methyl-D-aspartate receptors (NMDARs) and may preferentially alter the function of NMDARs on interneurons, recent work has questioned whether block of NMDARs is critical for its mood enhancing actions. In this viewpoint, we examine the evolving literature on ketamine supporting NMDARs as important triggers for certain psychiatric effects and the possibility that the antidepressant trigger is unrelated to NMDARs. The rapidly evolving story of ketamine offers great hope for untangling and treating the biology of both depressive and psychotic illnesses.

**Key words:** antidepressant; hippocampus; ketamine; memantine; psychotomimetic

## Introduction

There is increasing scientific and clinical interest in understanding mechanisms underlying the psychiatric effects of ketamine and other *N*-methyl-D-aspartate receptor (NMDAR) antagonists. Current interest in ketamine stems from seminal studies of Krystal and colleagues in the early 1990s in which they demonstrated that a single 40 min infusion of a subanesthetic dose of ketamine (0.5 mg/kg) produces transient psychotic symptoms in otherwise healthy adults (Krystal et al., 1994). Ketamine infusion resulted in sensory illusions, persecutory ideas, and altered cognition, including poor attention, word finding problems, and acute learning difficulties. These symptoms were observed during ketamine infusion but abated within a few hours after the drug infusion was terminated. Subsequently, Berman et al. (2000) found that this same infusion of ketamine also produced a slower developing, but still rapid, antidepressant response in patients with major depression. This effect was manifest within a few hours after ketamine infusion and persisted up to a week or so in some individuals. Importantly, ketamine appears to have antidepressant effects, even in patients with treatment refractory major depression, including rapid beneficial effects on suicidal ideation (Zarate et al., 2006).

The psychotomimetic and antidepressant effects have spurred interest in how ketamine produces its effects at cellular, synaptic, and network levels (Abdallah et al., 2015). Studies in the 1980s showed that ketamine is a noncompetitive (uncompetitive) NMDAR antagonist (Anis et al., 1983) that acts by an open channel block mechanism (MacDonald et al., 1987). Thus, ketamine does not bind closed NMDAR channels but rather requires channels to open to antagonize (MacDonald et al., 1987). Ketamine, like its structural analogs phencyclidine and MK-801, produces a trapping type of open channel block, in which the drug binds a site that is electrically deep within the ion channel, occludes the flow of ions through the open channel, and can remain in the channel when the channel closes (Huettner and Bean, 1988). This latter property helps account for a long-lived block that is relieved by channel opening. Membrane depolarization reduces block, likely by speeding drug dissociation, but the precise mechanism of voltage dependence remains unclear and does not appear fully accounted for by an electrostatic model (MacDonald and Nowak, 1990). Ketamine is less potent than phencyclidine and MK-801 because of faster dissociation from the open channel (Johnson and Kotermanski, 2006). Although ketamine is not selective for NMDARs (Chen et al., 2009) and recent studies have questioned the role of NMDAR antagonism in antidepressant actions (Zanos et al., 2016), ketamine's effects on NMDARs appear to contribute significantly to anesthetic, analgesic, and psychotomimetic, if not also antidepressant, actions (Kavalali and Monteggia, 2012; Abdallah et al., 2015).

## Ketamine and NMDARs: alternative views

Understanding how ketamine produces its effects is an area of active investigation with important implications for understanding the pathophysiology and treatment of psychotic illnesses and

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mood disorders. Importantly, the psychiatric effects of ketamine are observed at subanesthetic doses (Li et al., 2010; Abdallah et al., 2015) that likely achieve brain concentrations in the low micromolar range, although actual brain concentrations remain uncertain (Hartvig et al., 1995; Zhao et al., 2012). At low micromolar concentrations, ketamine inhibits only a fraction of NMDARs (likely <50% block for most NMDAR subtypes at steady state under physiological conditions), leaving a significant percentage of NMDARs unblocked at peak drug effect (Dravid et al., 2007; Kotermanski et al., 2009). This latter point is important because prior studies indicate that the antidepressant-like effects of ketamine in rodents are not observed with anesthetic doses that block a higher fraction of NMDARs (Li et al., 2010). Furthermore, complete NMDAR block by high concentrations of ketamine also eliminates the complex effects of the drug on neuronal excitability and delayed metaplastic inhibition of LTP in the hippocampus of juvenile rats that are observed at low micromolar concentrations (Izumi and Zorumski, 2014). These observations raise the possibility that activation of unblocked NMDARs during subanesthetic ketamine administration, perhaps involving specific subtypes of NMDARs, may be important in determining ultimate behavioral and network outcomes.

Although ketamine is not selective for specific NMDAR subtypes, some evidence indicates threefold to fourfold higher potency for NMDARs expressing GluN1/GluN2C subunits that are preferentially expressed on GABAergic interneurons (Monyer et al., 1994; Kotermanski and Johnson, 2009). The increased potency of ketamine for GluN2C NMDARs was observed in the presence, but not absence, of extracellular  $Mg^{2+}$ . The increased potency thus does not arise as a result of differences in inherent ketamine affinity for different GluN subunits; rather, the difference appears to reflect interactions between  $Mg^{2+}$  and ketamine in the channel pore (Kotermanski and Johnson, 2009; Kotermanski et al., 2009). If ketamine achieves low micromolar concentrations in the brain during infusions, however, other  $Mg^{2+}$ -sensitive subtypes of NMDARs will also show significant block and contribute to changes in behavior and neuronal function. In particular, some effects of ketamine, including antidepressant-like effects in mice and effects on signaling pathways thought to contribute to antidepressant actions, overlap strongly with NMDARs that express GluN2B subunits (Miller et al., 2014), and more selective GluN1/GluN2B antagonists have antidepressant-like effects in rodents (Poleszak et al., 2013) and humans (Preskorn et al., 2008). Indeed, deletion of GluN2B from a subset of cortical principal neurons mimics and occludes ketamine's antidepressant-like and synaptic effects (Miller et al., 2014). Furthermore, some evidence using recombinant NMDAR subunits expressed in *Xenopus* oocytes indicates that the potency of ketamine (in the nominal absence of  $Mg^{2+}$ ) is higher at GluN2B-expressing receptors than GluN2A, GluN2C, or GluN2D (Dravid et al., 2007). Factors contributing to NMDAR subtype preference remain poorly understood, but extracellular  $Mg^{2+}$  and  $H^+$  likely contribute (Dravid et al., 2007; Kotermanski and Johnson, 2009). Other work suggests that antidepressant-like effects of NMDAR antagonists in rodents are observed with antagonism of either GluN2A- or GluN2B-type receptors, whereas psychotomimetic-like effects (stereotypies) are observed with blockade of both GluN2A and GluN2B (Jiménez-Sánchez et al., 2014). This latter finding may not translate to humans because a selective GluN2B antagonist produces dissociative symptoms in humans at higher doses (Preskorn et al., 2008).

Balanced against studies suggesting preferential GluN subunit involvement in ketamine's antidepressant actions are other stud-

ies suggesting that drugs ostensibly very similar to ketamine lack antidepressant actions. For instance, the drug memantine is pharmacodynamically similar to ketamine but does not share strong antidepressant-like actions (Gideons et al., 2014). Memantine may preferentially target extrasynaptic over synaptic NMDARs (Xia et al., 2010), although this likely arises as a result of phasic versus tonic patterns of channel opening at synaptic and extrasynaptic NMDAR populations, respectively, rather than from subunit selectivity (Wroge et al., 2012). Ketamine and memantine have indistinguishable effects on NMDARs under basal conditions in cultured hippocampal neurons, but differences in effects emerge with increases in the open channel probability of NMDARs in the presence of positive allosteric NMDAR modulators or under pathological conditions, such as oxygen-glucose deprivation, where small differences in the voltage dependence of the drugs become evident (Emnett et al., 2013, 2015). Ketamine and memantine may also differ in their interactions with  $Mg^{2+}$  at NMDARs and in their effects on spontaneous NMDAR-mediated transmission (Gideons et al., 2014); memantine also differs from ketamine in engaging a more superficial site within the NMDAR channel in addition to the electrically deep site that underlies ketamine's effects (Kotermanski et al., 2009). Thus, understanding differential effects of ketamine and other NMDAR antagonists on NMDARs and on alternative targets may be important for unraveling both the psychotomimetic and antidepressant actions of ketamine.

Two cellular hypotheses have been offered to explain subsequent persistent increases in glutamate release that apparently help to sustain antidepressant action following ketamine treatment (Miller et al., 2016). First, the indirect hypothesis alluded to above suggests preferential effects on NMDARs of GABAergic interneurons. This hypothesis is consistent with studies demonstrating that ketamine has disinhibitory effects in neocortex resulting in enhanced activity of excitatory pyramidal neurons and increases in extracellular glutamate levels (Behrens et al., 2007; Homayoun and Moghaddam, 2007; Schobel et al., 2013). Second, a direct hypothesis suggests that ketamine inhibition of NMDARs on principal cells alters ongoing cellular signaling pathways to trigger synaptic plasticity. This hypothesis is supported by recent evidence that deletion of GluN2B from cortical principal neurons mimics the effect of ketamine (Miller et al., 2014).

Regardless of initial cellular locus, because ketamine's antidepressant effects outlive both its psychotomimetic effects and its physical presence in brain, it is likely that ketamine triggers persistent biochemical, synaptic, and network effects. Consistent with this idea, ketamine has been shown to persistently enhance AMPAR-mediated excitatory synaptic function in frontal cortex and hippocampus (Li et al., 2010; Autry et al., 2011; Nosyreva et al., 2013). These latter effects may result from different actions in different brain regions but appear to involve activation of the mechanistic target of rapamycin (mTOR) kinase, inhibition of eukaryotic elongation factor 2 kinase and enhanced signaling by BDNF through trkB receptors (Li et al., 2010; Autry et al., 2011; but see Murrugh, 2016). Other work indicates that effects of ketamine on GABAergic interneurons in cortex may involve production of reactive oxygen species via NADPH oxidase (Behrens et al., 2007), whereas network effects of ketamine in the juvenile hippocampus involve nitric oxide synthase (Izumi and Zorumski, 2014). Studies in adult hippocampus also suggest that ketamine may trigger signaling events via preferential inhibition of NMDARs activated by spontaneous (rather than evoked) synaptic transmission (Autry et al., 2011; Nosyreva et al., 2013).

### Ketamine and brain maturation: a window on psychiatric effects?

An intriguing feature of ketamine that remains poorly understood is that the psychotomimetic and likely antidepressant effects change over the course of postnatal maturation; these developmental changes may be critical for understanding the role of NMDARs in psychiatry. In particular, ketamine-induced psychosis is observed in adult humans but is rare in children (Olney and Farber, 1995). Reasons for this developmental change are uncertain, but similar developmental changes have been observed in rodents for pathomorphological effects of ketamine and other NMDAR antagonists. Olney et al. (1989) found that ketamine produces vacuolar changes in posterior cingulate and retrosplenial cortices (among other regions). These vacuoles involve swelling of mitochondria and endoplasmic reticulum, and appear to result from disinhibitory effects and excessive excitation of pyramidal neurons (Farber et al., 2002). Similar to human psychiatric symptoms, vacuoles in rodent brain are rare before postnatal day 30 (PND30) (late childhood/early adolescence) but reliably observed in adulthood (Olney et al., 1991; Farber et al., 1995). It is important to note that vacuolar changes induced by ketamine in rodents are observed at higher doses than antidepressant-like effects (40 mg/kg s.c. single dose vs 3–10 mg/kg i.p. single dose) (Olney et al., 1989; Li et al., 2010; Autry et al., 2011). Further complicating these observations is the uncertainty in estimating the concentrations of ketamine that are achieved in brain with various doses and administration routes. Nevertheless, the observations highlight developmental changes that parallel those underlying ketamine psychotomimetic effects in humans.

Interestingly, treatments that dampen the neuropathological effects in rodents, including agents that enhance the actions of GABA-type A receptors (GABA<sub>A</sub>Rs), antimuscarinics, and  $\alpha$ -adrenergic agonists, also dampen psychotomimetic-like effects in animals (Olney et al., 1991; Olney and Farber, 1995). It is less clear whether these protective agents alter antidepressant effects, although a recent study found that clonidine, an  $\alpha$ 2 adrenergic agonist, dampened psychotic symptoms, but not antidepressant effects, in humans during 96 h ketamine infusions (Lenze et al., 2016).

Consistent with the above developmental changes, the ability of ketamine both to produce antidepressant-like behavioral effects in rodents and to enhance hippocampal synaptic transmission may depend on postnatal developmental age (Izumi and Zorumski, 2014; Nosyreva et al., 2014). Young rodents show neither antidepressant-like effects (PND30) nor synaptic enhancement (PND14 and PND30), whereas both effects are observed in young adult mice (6–8 weeks of age) (Nosyreva et al., 2014). Factors underlying these maturational differences are not certain but raise questions about changes in expression of NMDAR subunits and the possibility of alternative mechanisms that are age dependent.

### Are NMDARs the entire ketamine story?

Although NMDARs are the most obvious candidates to trigger antidepressant effects, recent data cast some doubt on the NMDAR hypothesis. The role of NMDARs in the psychotomimetic effects of ketamine is less controversial and is consistent with numerous studies indicating that NMDAR hypofunction may be an important contributor to schizophrenia and other psychotic illnesses (Olney and Farber, 1995; Schobel et al., 2013). Several NMDAR channel-blocking drugs, including phencyclidine and MK-801, reproduce the psychotomimetic effects of ketamine in humans and animals (Wiescholleck and Manahan-Vaughan, 2013). Furthermore, the acute psychotomimetic effects more closely parallel ketamine's pharmacokinetics and dissipate with ketamine clearance and metabo-

olism. In contrast, a recent report by Zanos et al. (2016) raises important questions about whether NMDAR blockade is critical for the slower-onset and longer-lived antidepressant-like actions. This work provides evidence that a ketamine metabolite (2S,6S;2R,6R-hydroxynorketamine (HNK) and more specifically, 2R,6R-HNK) may be the key mediator of effects on mood-related behaviors and the CA1 hippocampal network in rodents, even though HNK does not affect NMDARs. Intriguingly, HNK, particularly 2R,6R-HNK, may also lack the psychosis-inducing properties of ketamine. This recent study pursues the fact that ketamine used in clinical practice in the United States is a mixture of R,S-enantiomers, and earlier studies found that R-ketamine has more potent antidepressant-like effects in rodents than S-ketamine (Zhang et al., 2014; Yang et al., 2015), although the opposite is true at NMDARs (Liu et al., 2001). This enantioselectivity provides circumstantial evidence that NMDARs may not be the relevant trigger for antidepressant effects and prompted the focus on 2R,6R-HNK. It remains uncertain how HNK produces its effects on behavior, AMPA receptor-mediated synaptic transmission, and biochemical signaling pathways in the hippocampus, although AMPA receptors, BDNF, and eukaryotic elongation factor 2 kinase appear to be key mediators just as they are for ketamine. Despite considerable interest generated by this recent work (Zanos et al., 2016), it remains unclear whether the doses and concentrations of ketamine metabolites that produce effects in rodents are relevant to antidepressant studies in humans (Zarate et al., 2012). Further complicating the translation of this work to humans is a recent report showing that intravenous administration of S-ketamine has potent antidepressant effects in humans with treatment-resistant depression (Singh et al., 2016). Again, these recent findings highlight the major challenges in translating rodent studies of complex behaviors, particularly behaviors such as depression and psychosis, to humans.

Earlier studies reported that other ketamine metabolites, including 2S,6S-HNK and (R,S)-norketamine (NK), can activate signaling pathways, such as mTOR, thought to underlie ketamine's effects in prefrontal cortex (Paul et al., 2014). The potency of HNK and NK for activating mTOR in PC12 cells paralleled the effectiveness of these metabolites as antagonists at  $\alpha$ 7 neuronal nicotinic receptors (Moaddel et al., 2013), possibly implicating nicotinic receptors as important antidepressant triggers. However, dehydronorketamine is also a potent  $\alpha$ 7 nicotinic antagonist (Moaddel et al., 2013), but subsequent studies indicated that dehydronorketamine lacks antidepressant-like effects in rodents (Salat et al., 2015). Thus, the evidence for nicotinic receptor involvement remains equivocal. At a minimum, this set of studies raises important questions about the role of NMDAR inhibition in triggering the antidepressant actions of ketamine. If HNK proves to be a key mediator of antidepressant effects while having no psychotomimetic actions, these studies may provide ways to more definitively disentangle the two complex psychiatric effects of ketamine, perhaps even strengthening the hypothesis that NMDAR antagonism contributes to psychosis.

Because ketamine is an ion channel blocker with active metabolites, it is not surprising that the drug has actions on several receptors and channels. In particular, hyperpolarization-activated cyclic nucleotide gated cationic (HCN) channels that express the HCN1 subunit have been found to be a potential target underlying ketamine's effects on neural networks and certain clinical-like actions. HCN1-containing channels contribute to pacemaker firing in some brain regions and to the dendrosomatic coupling by which synaptic inputs in dendrites are conducted to neuronal cell bodies and axon initial segments to modulate spike firing. Ketamine inhibits HCN1-expressing channels at clinically rel-

evant concentrations with a half-maximal effective concentration of  $\sim 10 \mu\text{M}$  and greater potency of S-ketamine over R,S-ketamine (Chen et al., 2009). Mice with conditional forebrain knock-out of HCN1 in cortex and hippocampus show diminished sedation by ketamine (Zhou et al., 2013). It is presently unclear whether effects of ketamine on HCN1 contribute to psychiatric effects, and the  $\text{IC}_{50}$  for HCN block is greater than for effects at NMDARs and  $\alpha 7$  nicotinic receptors. Nonetheless, changes in dendrosomatic integration appear to contribute to some hippocampal network effects observed in the hippocampus of juvenile rats, although these effects have not been directly linked to changes in HCN function (Izumi and Zorumski, 2014).

Beyond ion channels, ketamine also has significant effects on aminergic, opioid, and cholinergic systems that could contribute to behavioral and neural network changes (Sleigh et al., 2014). Effects on dopamine turnover and opiate receptors may be particularly important for understanding the drug's various behavioral properties as a psychotomimetic, antidepressant, and agent of abuse (Sanacora and Schatzberg, 2015).

### Intracellular drug accumulation: an alternative hypothesis

As noted, studies of ketamine to date have largely focused on actions at NMDARs and downstream effects on synapses and networks thought to arise from initial NMDAR block, followed by increased extracellular glutamate levels and activation of intracellular signaling pathways. Lester et al. (2012, 2015) have raised a provocative alternative in which ketamine, a lipophilic weak base, accumulates in neurons via acid trapping in intracellular organelles and exerts its more persistent (antidepressant-like) effects via direct actions on intracellular signaling molecules independent of NMDAR block. Intracellular accumulation occurs with many CNS-active drugs because of their high membrane permeability and ability to cross the blood–brain barrier. Many psychotropic drugs are weak bases and therefore expected to accumulate in intracellular organelles with high acidity, such as lysosomes and synaptic vesicles (Sulzer and Rayport, 1990; Tischbirek et al., 2012). Actions at lysosomes could trigger mTOR signaling independent of NMDARs (Lester et al., 2015). Other direct intracellular targets of ketamine could include endoplasmic reticulum and Golgi. In these organelles, ketamine could perhaps act as a chaperone for NMDARs or other receptors, as has been shown for nicotine at nicotinic receptors (Srinivasan et al., 2011). Ketamine may also dampen endoplasmic reticulum-related stress (Lester et al., 2012), and other studies indicate that effects on cell death in some systems can be NMDAR-independent (Braun et al., 2010; Baker et al., 2016).

The direct intracellular hypothesis of ketamine takes on new meaning in light of the NMDAR-independent antidepressant-like effects of HNK described above (Zanos et al., 2016). Further tests of this hypothesis would benefit from ketamine and HNK analogs that can be tracked for intracellular localization and activity. One possibility that is currently being explored is to use norketamine derivatives that have an alkyne substitution allowing intracellular visualization with azide-alkyne condensation click chemistry (Emmett et al., 2014), ideally in combination with photoaffinity labeling of specific targets (Lapinsky, 2012; Peyrot et al., 2014; Jiang et al., 2016). A similar tandem photoaffinity labeling/click chemistry purification strategy could also be used biochemically to isolate novel ketamine protein targets (Lapinsky, 2012). Although the idea for non-NMDAR-related targets, including intracellular targets, is intriguing, ultimately these hypotheses have to contend with the data cited above suggesting that NMDAR antagonists chemically unrelated to ketamine, pre-

sumably with different cellular metabolites, different off-target effects, and different intracellular partitioning patterns, also trigger ketamine-like antidepressant effects.

In conclusion, there is little doubt that human studies of the psychotomimetic and antidepressant effects of ketamine have had a major impact on current thinking about the neuroscience and therapeutics of psychiatric illnesses. Studies of ketamine are spurring a host of new ideas about mood and psychotic illnesses, including the potential role of NMDARs and the implementation of other novel treatment strategies (Drevets et al., 2013; Nagele et al., 2015). Although the prominent effects of ketamine on NMDARs have formed the basis for much of this work and contribute to many of the major psychiatric effects of ketamine and other NMDAR antagonists, it is clear that alternative targets must be considered, including targets not involving NMDARs. These newer lines of work will benefit from better understanding of the developmental factors that contribute to ketamine's actions as well as the time course of ketamine's psychotomimetic and antidepressant actions, including efforts to understand how to prolong the mood-altering effects in patients with refractory major depression. The time course of ketamine's effects following a single infusion can also be highly instructive. Perhaps the psychotic symptoms involve initial block of NMDARs that abate over the course of a few hours while the antidepressant effects become manifest. The longer-lived changes that likely underlie the antidepressant actions may not only lead to better ways to treat depression, but also to better therapeutic interventions for psychotic illnesses, perhaps reflecting ways that neural networks correct the errors in cognition, emotion, and motivation that drive the initial psychosis. Whether these two aspects of ketamine's actions in humans can be completely disentangled remains uncertain at present. These are exciting possibilities, however, that could revolutionize the treatment of devastating and highly disabling common clinical illnesses.

### Response provided by Dual Perspectives Companion Authors—Elizaveta Khlestova, Jon W. Johnson, John H. Krystal, and John Lisman

Dr. Zorumski and coauthors have discussed many of the complexities in understanding how ketamine brings about psychotogenic action and relieves depression. We agree that there are likely to be multiple molecular targets involved. We nevertheless think it is important to understand which NMDARs are most affected by ketamine. It is fortunate that quantitative information on the pharmacological action of ketamine on NMDARs is available, and that previous studies also permit a reasonable estimate of ketamine concentration in brain during human administration. With such information, we have calculated that GluN2C-containing NMDARs are preferentially inhibited at psychotogenic doses of ketamine. Dr. Zorumski and coauthors do not contradict this conclusion but raise one point to which we reply. They note that, in the absence of  $\text{Mg}^{2+}$ , ketamine does not preferentially block GluN2C-containing receptors, and we agree. However,  $\text{Mg}^{2+}$  is normally present *in vivo*; and under these conditions, ketamine's block will be selective for GluN2C-containing receptors. This is an understandable finding because ketamine acts competitively with  $\text{Mg}^{2+}$  (MacDonald et al., 1991); thus, ketamine's

preferential block of GluN2C-containing NMDARs can be largely attributed to the weaker  $Mg^{2+}$  binding to GluN2C-containing NMDARs compared with GluN2A/B-containing NMDARs.

It may be that, if the ketamine concentration was high enough, it could also have psychotogenic effects via GluN2A/B-containing NMDARs. However, experiments with an antagonist specific for GluN2B-containing NMDARs that might provide evidence for such action remain equivocal. The authors of the only study (Preskorn et al., 2008) of this issue in humans made no claims regarding psychotogenic effects of the GluN2B-selective antagonist CP-101,606, even though psychotogenic effects were observed in some subjects at the highest concentration that was used; the reason for caution is that such effects were also sometimes observed in placebo controls.

Dr. Zorumski and coauthors cite important work from Olney and collaborators (Olney et al., 1989) demonstrating the neurotoxicity of ketamine on some cortical regions: vacuolar changes and even cell death were observed. Subsequent studies indicated that these cortical changes were not the result of ketamine action directly on cortex but rather stemmed from ketamine action in the thalamus (for review, see Sharp and Hendren, 2007). Such remote action seems surprising, but recent results (Zhang et al., 2012) provide a plausible explanation: ketamine action in the thalamus evokes  $\delta$  frequency bursting that is then transmitted to hippocampus and cortex; this strong bursting may then produce the observed cortical damage.

The task of elucidating the network and pharmacological mechanisms that underlie schizophrenia is extremely challenging, and it is important to seek converging hints using multiple approaches. We have described in our Perspectives article converging evidence that the psychotogenic action of ketamine may result from preferential inhibition of GluN2C-containing NMDARs and that the critical site of action may be the thalamus, where the inhibition evokes  $\delta$  frequency oscillations (Zhang et al., 2012). Such oscillations may be transmitted to cortex and hippocampus and produce psychotogenic effects. Related processes could cause the elevated  $\delta$  power in the EEG of patients with schizophrenia (Lehmann et al., 2014). Understanding these processes may be key to developing treatments for the disease.

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