CNS Neuroscience & Therapeutics

REVIEW

CNS Neuroscience & Therapeutics

Impact of Ketamine on Neuronal Network Dynamics: Translational Modeling of Schizophrenia-Relevant Deficits

Bernat Kocsis,[1] Ritchie E. Brown,[2] Robert W. McCarley[2] & Mihaly Hajos[3]

1 Laboratory of Neurophysiology, Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
2 Laboratory of Neuroscience, Department of Psychiatry, VA Boston Healthcare System and Harvard Medical School, Brockton, MA, USA
3 Section of Comparative Medicine, Brady Memorial Laboratory, Yale University School of Medicine, New Haven, CT, USA

Keywords
Gamma oscillation; Mismatch negativity; *N*-methyl-D-aspartate receptors receptors; P300; Theta rhythm.

Correspondence
Bernat Kocsis, Laboratory of Neurophysiology, Department of Psychiatry Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, CLS-710, Boston, MA 02215, USA.
Tel.: +1-617-735-3301;
Fax: +1-661-554-5966;
E-mail: bernat_kocsis@hms.harvard.edu
Received 28 November 2012; revision 26 January 2013; accepted 28 January 2013.

SUMMARY

Subanesthetic doses of the psychomimetic, ketamine, have been used for many years to elicit behavioral effects reminiscent of schizophrenia in both healthy humans and in animal models of the disease. More recently, there has been a move toward the use of simple neurophysiological measures (event-related potentials, brain oscillations) to assay the functional integrity of neuronal circuits in schizophrenia as these measures can be assessed in patients, healthy controls, intact animals, and even in brain slices. Furthermore, alterations of these measures are correlated with basic information processing deficits that are now considered central to the disease. Thus, here we review recent studies that determine the effect of ketamine on these measures and discuss to what extent they recapitulate findings in patients with schizophrenia. In particular, we examine methodological differences between human and animal studies and compare *in vivo* and *in vitro* effects of ketamine. Ketamine acts on multiple cortical and subcortical sites, as well as on receptors other than the *N*-methyl-D-aspartate receptor. *Acute* ketamine models' changes correlated with psychotic states (e.g. increased baseline gamma-band oscillations), whereas chronic ketamine causes cortical circuit changes and neurophysiological deficits (e.g. impaired event-related gamma-band oscillations) correlated with cognitive impairments in schizophrenia.

doi: 10.1111/cns.12081

Contemporary views of schizophrenia have shifted from alterations in dopamine neurotransmission to impaired information processing. Cognitive impairment is regarded as the primary core deficit, resulting from dysfunction of neuronal microcircuits. The significance for pharmacology is an extension of potential therapeutic targets from neuromodulatory systems, that is, from the original D2 and the more recent combinations of aminergic receptor antagonists to neurotransmitters operating on the level of these microcicuits, that is, glutamate and GABA. Research focusing on the primary transmitters involved in neuronal network dynamics is conducted in the framework of the *N*-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis. This is one of the most powerful current models of schizophrenia, with a strong translational potential from rodents to primates to healthy subjects to patients with schizophrenia. This hypothesis originated from early observations of ketamine and other NMDA receptor (NMDAR) antagonists' ability to elicit (in healthy subjects [1]) or exacerbate (in schizophrenics [2]) positive psychotic symptoms. However, recent studies emphasize its validity to also explain cognitive deficits and negative symptoms [3–5], which has traditionally been the weak point of prior, mostly dopamine-based, models. Positive, psychotic-like symptoms elicited by ketamine (S-Ketamine, in particular), the basis for its recreational abuse, are discussed in Chapter 10 of this Special Issue. There are also excellent recent reviews of behavioral and electrophysiological studies addressing cognitive symptoms and altered neuronal network dynamics in schizophrenia using different variants of the NMDAR antagonist model [6–19].

This review will be limited to a critical comparison of the electrophysiological changes induced by ketamine and other NMDAR antagonists, for example, MK-801 and phencyclidine, with those observed in patients with schizophrenia and animal models, which can help to understand the processes involved in cognitive impairment in schizophrenia. In the past several years, there has been a rapidly growing interest in electrophysiological markers of schizophrenia fueled by major technological advancements in clinical electrophysiology and by fundamental changes in understanding the function of cortical networks and in the interpretation of EEG. This trend is expected to continue, and ketamine, which can be used both in human and animals, may play an essential role in developing the right methods and standards for detecting schizophrenia-relevant cortical dysfunction.

The Use of Ketamine as a Model of Schizophrenia-Associated Neurophysiological Abnormalities

N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamatergic receptor widely distributed in the brain from spinal cord to the cortex and implicated in numerous functions from pain to learning and memory. It is a hetero-oligomeric complex consisting primarily of two NR1 and two of several types of NR2 subunits (NR2A-NR2D). NMDAR activation requires not only binding of glutamate but also a coagonist glycine and a voltage-dependent removal of the Mg^{2+} ion blocking the channel at rest. There are numerous antagonists blocking the glutamate or the glycine binding sites, the ion pore, or allosteric binding sites. Ketamine belongs to this latter group of noncompetitive antagonists [20].

Acute administration of NMDAR antagonists to rodents impacts various CNS functions, from simple motor activity to high-level cognitive tasks [21]. In nonhuman primates, NMDAR antagonists evoke sensory, behavioral, and cognitive disturbances [22–24] similar to responses seen in humans [1]. The dose of ketamine to induce schizophrenia-relevant deficits is below the anesthetic dose, that is, 5–10 mg/kg subcutaneous injections [25–27] are used in rats and 0.3–0.5 mg/kg intravenous injections in human studies [1,28], compared with 70–80 mg/kg and 1.0–4.5 mg/kg (2 mg/kg for 5–10 min anesthesia) used for anesthesia in rodents and human, respectively. It is worth noting that the ketamine dose found effective for treatment of depression is also 0.5 mg/kg i/v [29,30]. Thus, there are efforts underway to find a way to attenuate the ketamine-induced psychotomimetic effect for the treatment of depression [31–34].

The limitations of behavioral models of schizophrenia have been recognized, and it has been argued that animal modeling of inherently human disorders, like schizophrenia, might be impossible [18]. Recently, an alternative approach emerged by recreating endophenotypes contributing to schizophrenia in preclinical animal models [9,12,35–43]. Endophenotypes are heritable, state-independent biomarkers associated and cosegregating with the illness [39]. They allow reducing complex psychiatric phenotypes into components that can be modeled in animals and make genetic and neurobiological investigation of diseases with high heterogeneity of genetic etiology and behavioral manifestation more manageable [35]. The symptoms of acute ketamine injection show a large overlap with many schizophrenia endophenotypes, but the analysis of the discrepancies is also important as it may provide additional information for understanding schizophrenia pathology. For example, one of the most firmly established schizophrenia endophenotypes, the deficit of prepulse inhibition on startle (PPI) [44–47], is reproduced by NMDAR antagonism in rodents [48–50] and primates [51,52] but not in healthy human subjects where ketamine enhances PPI [53–55].

Electrophysiological Signals

Electrophysiological signals recorded in patients can reflect abnormal neuronal functioning associated with a given disorder, genetic alteration, or clinical symptom and can be considered as endophenotypes. A number of neurophysiology-based endophenotypes, or candidate endophenotypes, have been recognized in schizophrenia [8,9,12,42,43,56–59]. Using neurophysiology-based biomarkers, for example, in evaluating drug action, can also provide unique opportunities to establish translational measures both in preclinical models and in clinical studies. Some of these biomarkers are considered to be related to abnormal glutamate neurotransmission and can be elicited with an NMDAR antagonist in healthy subjects [60]. In these studies, ketamine plays a pivotal role, as it has been approved as a drug for human administration. Many of the well-defined electrophysiological biomarkers are closely linked to NMDAR function, and abnormal neurophysiologic signals characteristic for schizophrenia can be elicited by ketamine. Among these markers are auditory gating (P50 and N100), mismatch negativity (MMN) and the P300 event-related potential.

Ketamine-Induced Disruption of Auditory Gating

Acoustic stimulation elicits several auditory-evoked potentials (AEPs) with various latencies, including a positive deflection at 50 ms (P50) and a negative deflection at 100 ms (N100) in healthy subjects. Repeating the same acoustic stimulation within sufficiently short intervals (typically at 0.5 s) significantly attenuates the AEPs associated with the second stimuli, a phenomenon known as auditory gating [61,62]. In various psychiatric and neurological disorders, auditory gating is impaired, although most likely due to different pathophysiological mechanisms. Impaired auditory gating has been described in schizophrenia using standard clinical EEG methodology, as well as by using magnetoencephalography, which confirmed the gating deficit and provided additional insight to neurological mechanisms contributing to normal and pathological gating [63,64]. In preclinical animal models, auditory gating is present, and it can be disrupted via genetic, epigenetic, and pharmacological manipulations [61]. Importantly, auditory gating can be readily disrupted by ketamine in healthy subjects [65] as well as in rodents [9,66,67].

Mismatch Negativity and P300

Recording of auditory-evoked potentials in response to deviant stimuli in an auditory "oddball" paradigm leads to a well-characterized negative deflection at 100 ms, called the MMN, and a positive deflection at 300 ms (P300). P300 is elicited by attended oddball stimuli and is generated by both frontal and parietal cortical areas. In patients with schizophrenia, a reduction in P300 amplitude has been well characterized, although abnormalities of P300 are present in many psychiatric or neurological disorders. MMN is generated by the auditory cortex, but frontal brain regions are also crucially implicated in the generation of the MMN demonstrated by EEG [68–70]and fMRI studies [71–73]. The MMN can be elicited by unattended stimuli, and abnormal MMN is considered to be the most closely related endophenotype to schizophrenia [74]. Impaired generation of both MMN and P300 has been observed after ketamine treatment in humans [75–79], resembling deficits present in patients with schizophrenic [80,81]. Importantly, the two populations showed the same relationship between the ketamine-induced MMN memory trace effect and cognitive impairments [79,80]. It has also been shown recently,

by using a model-based approach, that ketamine affects synaptic plasticity during the encoding of the MMN as expressed by a reduced forward connection from left primary auditory cortex to superior temporal gyrus and that this model-based estimate of ketamine effects on synaptic plasticity correlated significantly with ratings of ketamine-induced impairments in cognition and control [82].

Cortical Oscillations

Cortical oscillations are essential for a variety of cognitive processes impaired in schizophrenia [83]. Oscillatory synchronization organizes neuronal activity in local microcircuits and supports long-range dynamic connections, also impaired in schizophrenia [83]. They depend on a functioning network of fast-firing interneurons that show structural abnormalities in human postmortem brains [84–88] of schizophrenics, suggesting that impaired neuronal oscillations serve as a mechanistic link between deficiencies of the interneuron network and cognitive dysfunction. Developmental abnormalities of parvalbumin-positive interneurons are consistently observed in chronic animal models produced by a variety of techniques [27,89–97], and in the past several years, it has also been firmly established that the essential features of human schizophrenia recapitulated by rodent models include abnormal oscillations in low- (delta, theta) and in the high-(beta, gamma)frequency bands [25–27,48,89,98–111].

Ketamine and other NMDAR antagonists cause severe perturbations in cortical oscillations at different frequencies, which, in general, resemble those in schizophrenia. Comparison of impaired oscillations in schizophrenia and those induced by ketamine administration in humans and in a variety of animal models, however, is not always straightforward and differs in important details. Some of the differences, however, may be due to differences in the recording techniques/experimental design and might thus point to inadequacies of the recording paradigms used for assessment of oscillatory impairment in schizophrenics rather than to limited validity of the animal model.

Gamma-Band Oscillations

Significant alterations of the electrical activity in the gamma band (30–90 Hz) have been documented in patients with schizophrenia [112–122] and in most animal models studied to date [89,99,106,107] (Table 1). Extensive research in this area has clarified several key issues and led to the proposal that a "gamma oscillatory endophenotype" [8] underlies downstream phenotypic cognitive deficits characteristic of schizophrenia. Specific therapeutic targeting of gamma-band deficits has also been suggested [8], and an intermediate oscillatory phenotype has also proven a more fruitful correlation target than behavioral measures for identifying genetic biomarkers in some human imaging studies [123].

Gamma-band oscillations (GBO) alterations also appear in the acute state after administration of NMDAR antagonists to healthy humans [28,124,125] or patients with schizophrenia [125] (Table 1). They are also apparent in *in vivo* [25–27,48,100,109,126–128] and *in vitro* [129–131] preclinical studies in rodents, but there are inconsistencies between studies using different experimental paradigms. The most prominent discrepancy is that whereas NMDA blockade induces a massive increase in gamma activity, the current human schizophrenia EEG literature is dominated by reports of GBO deficits (revs. [8,83,132,133]). Until recently, animal models have also been focused on decreased GBO. These studies were designed to evaluate oscillations during cognitive tasks and postulated that a decrease in GAD67 and PV expression, the most consistent postmortem histological marker of schizophrenia, leads to attenuated GBO activity. During the past decade, a number of experimental paradigms and signal analysis methods were developed and standardized, which produced a wealth of data demonstrating the link between cognitive deficits and impaired synchrony in schizophrenia. Animal models generated by a variety of interventions also revealed a final common pattern of anatomical abnormalities of parvalbumin-expressing interneurons, cognitive deficits, and decreased gamma power in schizophrenia-relevant tasks or in sensory paradigms directly replicating those performed in humans [89,106].

However, the recent demonstration of increased gamma-band power after administration of subanesthetic doses of ketamine associated with schizophrenia-relevant behavior in rats [25] turned attention to earlier sporadic reports of increased, that is, rather than decreased, GBO activity in patients with schizophrenia. Most of these earlier studies recorded baseline activity in the high beta and gamma range in default mode or resting-state paradigms (rev.[8]), but a few also showed increased gamma activity directly associated with positive symptoms [122,134,135]. The relevance of these data is further underscored by verification of the gamma-enhancing effect of ketamine in humans [28,124] and the demonstration of increased background gamma activity in different chronic rodent models of schizophrenia, some of which showed both increased baseline and decreased task-related GBO [99,101,107,136,137]. This prompted revisiting the issue of background GBO, which should be expanded in the future using today's advanced recording and analysis techniques [138,139]. In fact, an overall increase in high-frequency EEG activity (>30 Hz) in schizophrenics compared with healthy controls was demonstrated in the dawn of computerized EEG 40 years ago, using analogue filters and the first versions of digital spectral analysis [140,141]. The pattern revealed in these 24-h EEG recordings (increased high-frequency activity along with decreased theta/alpha and increased delta-band activities) corresponds with that seen in extended EEG recordings in rodent models during the animals' natural states and behaviors [99,101,107,136,137] and with acute changes in EEG after ketamine [25,27,48,109,142]. There are current efforts to solve technical-related problems including the difficulties of the elimination of the microsaccade artifact or the problem related to the practice of standardizing evoked responses using prestimulus "background" activity. This latter was recently shown to increase in the acute NMDAR antagonist model in mice [26] and in a reanalysis of earlier data of human ASSR [112]. It is important that these studies followed similar protocols in human and animals, but the prestimulus segments they used for evaluation of background GBO remain tied to repetitive sensory test stimuli and thus might have been compromised by increased neuronal activity induced in sensory cortex by extended stimulation, especially at short interstimulus intervals [134,143,144]. Stimulus parameters may strongly affect the level of this activation as well as the ASSR itself; when using longer

Table 1 Comparison of gamma-band oscillations (GBO) in patients with schizophrenia, animal models of schizophrenia, and following applications of ketamine to healthy humans, intact animals, and rodent brain slices

	Enhanced GBO power	Attenuated GBO
Schizophrenia (human)	Background, psychosis Spontaneous [140,141] Hallucinations [122,134,135,180] Prestimulus baseline [112]	Sensory-evoked Task related (ASSR, visual stimuli, attention, working memory) [113–121] (but see [133] for ASSR GBO increase)
Chronic animal models of schizophrenia	Background Prenatal MAM rat [101] Amygdala picrotoxin rat [99] PV-Cre/NR1 mice [136] Dysbindin-1 mutant mice [107] Reduced GBO reaction to NMDAR antagonists Prenatal MAM [101,104] Neonatal VH lesion rat [208] PV-Cre/NR1 mice [136]	Sensory evoked-Task related Prenatal MAM rat (reverse learning [89]) Neonatal VH lesion rat (ASSR [105,106]) PV-Cre/NR1 mice (opto-stim [136]) Dysbindin-1 mutant mice (ERP [107])
Acute ketamine or other NMDA antagonists—human	Auditory ERP [28] ASSR [124]	Magnetoencephalography [125]
Acute ketamine or other NMDA antagonists – *in vivo* rodents	Background Spontaneous [25,109,127,128,142] (NR2A [48]) Delayed in REM sleep (NR2B [100]) Prestimulus baseline-mice [26,103]	Sensory evoked Auditory ERP-mice [26,103]
In vitro GBO in neocortex	Bath application of ketamine or other NMDAR antagonists [130,131,147] (but see [129] for negative finding)	Reductions in peak frequency with bath application of ketamine only [130,131] Reduction in peak frequency *ex vivo* following 5 daily i.p. injections [209]

stimulus duration and interstimulus interval, gamma-band ASSR was shown to increase (rather than decrease) in schizophrenics relative to healthy controls [133].

Investigation of Ketamine Effect on GBO *In Vitro*

Although GBO are generally considered to be generated within specific cortical areas, GBO abnormalities in schizophrenia or with application of NMDAR antagonists can be due to changes occurring locally in the cortical area underlying the EEG electrode or due to impaired connections with other cortical or subcortical sites involved in their state- or event-related modulation. Thus, *in vitro* studies can provide vital information, unavailable from *in vivo* preparations, regarding the cellular mechanisms of GBO generation within local cortical regions. In particular, studying oscillations in brain slices has several advantages: (1) the cellular and molecular basis for changes in the oscillations can be studied using recordings from specific cell types generating the oscillations, (2) novel genetic technologies can be used to identify particular cell types by the introduction of fluorescent markers and modulate their activity to model pathological changes observed in schizophrenic brains [130], (3) changes in oscillations can be ascribed to local changes in neuronal circuitry rather than to changes in afferent inputs, and (4) the elicited oscillations tend to be more specific for the gamma band, allowing a more precise determination of peak frequency and power. Recently, several groups, including our own, have investigated GBO alterations with ketamine or other NMDAR antagonists *in vitro*, in the hope of developing a simple translational assay for potential therapeutic agents. It remains to be seen, however, whether such experiments will have predictive value in developing effective treatments.

In vitro experiments also have several disadvantages. They are obviously not suitable for modeling psychotic symptoms in schizophrenia or any of the behavioral symptoms induced by ketamine and cannot recapitulate deficits due to impaired long-range communication between cortical and subcortical sites [145]. Thus, it is important to combine and compare the information obtained from these studies with *in vivo* animal models and human studies, as we do here.

Several studies [129–131,146,147] have examined the effect of acute, bath application of ketamine or other NMDAR antagonists on *in vitro* GBO and have identified some of the molecular and circuit changes, which may underlie both suppression and enhancement of GBO in schizophrenia. The first studies using interface-type slice chambers reported that GBO are either unaffected or reduced in the hippocampus and neocortex [129]. However, since then, several studies using different technology have shown that NMDAR antagonist administration strongly increases the power of GBO in the visual cortex, auditory cortex, and prefrontal (prelimbic) cortex [130,131,146,147]. These findings are more consistent with *in vivo* findings of increased power and imaging studies indicating increased activity in prefrontal cortex with ketamine (e.g. [148]). While *in vitro* studies have a number of advantages (described above), there are important methodological issues

related to the generation of GBO *in vitro* which make it important to compare *in vitro* findings to each other and to the findings associated with *in vivo* application of ketamine.

The major difficulty of slice studies of oscillations is that in most *in vitro* preparations, spontaneous GBO do not occur, as the afferent inputs are severed during the slicing process. Therefore, some means of increasing network activity is required to elicit the oscillations. Pioneering early work by the Whittington group in the hippocampus used tetanic electrical stimulation or application of metabotropic glutamate receptor agonists [149]. However, most groups now use application of the glutamate receptor agonist, kainate [150], application of the cholinergic receptor agonist carbachol [151], or a combination of the two. Application of kainate mimics the increased glutamatergic input caused by the activity in other cortical areas and/or from the thalamus. The application of carbachol mimics the release of acetylcholine in the hippocampus and neocortex produced by the activity of basal forebrain cholinergic neurons, during waking and rapid-eye-movement sleep [152]. Rhythmic release of GABA from perisomatic, parvalbumin-positive interneurons is required for GBO elicited by both kainate and carbachol *in vitro* [153,154].

Until recently, the majority of slice oscillation studies were performed in the hippocampus using the so-called interface or Haas-type recording chambers, together with bath application of low concentrations of kainate (typically in the high nanomolar range) or carbachol. In interface-type chambers, the upper surface of the slice is exposed to a humidified carbogen (95% O_2/5% CO_2) gas mixture, which provides excellent oxygenation. An advantage of this approach is that once induced, oscillations can be studied for many hours. While this approach has produced a large volume of high-quality and important data, it does not allow visually guided, whole-cell recordings from specific neuronal subtypes labeled using fluorescent markers, as this requires the use of high magnification, water-immersion lenses. Recent studies in recording chambers where the slices are completely submerged in artificial cerebrospinal fluid suggest that GBO require a high oxygen level [155], consistent with the correlation found between the blood-oxygenation level (BOLD) and GBO in human imaging studies [156]. Thus, improving oxygen flow to the slice by increasing the flow of artificial cerebrospinal fluid to both surfaces of the slice was found to facilitate GBO in submerged-type slice chambers. However, even with such modifications, we could not reliably induce GBO in neocortical slices [130]. Thus, we and others [157] have used a modified method involving brief, focal application of a higher (1 mM) concentration of kainate. This generates a relatively brief (10 s of seconds) burst of GBO, which can be reproducibly elicited provided sufficient time is allowed between applications. These differences in methodology (kainate vs. carbachol, interface vs. submerged and prolonged vs. brief focal application) should be born in mind when comparing different *in vitro* studies as well as between *in vitro* and *in vivo* findings.

In addition to increasing the power of GBO, we also recently found that ketamine slows the peak frequency from the gamma to the beta range [130]. These findings are intriguing, given the gamma→beta shift described in patients with schizophrenia [158] and modeling studies which suggest that beta oscillations are more effective in synchronizing activity over longer distances [159,160]. This slowing of the peak frequency was not reproduced by more selective NMDAR antagonists and was found to be an off-target effect of ketamine on $GABA_A$ receptors, causing a slowing of the decay time of inhibitory postsynaptic currents [130].

Low-Frequency Oscillations

Although recent research is primarily focusing on high-frequency oscillations, there is also evidence of disturbances in slow rhythms in the delta and theta bands in schizophrenia [161–165]. Functional deficits are most likely the consequence of parallel impairments of fast and slow rhythms as oscillations at different frequencies have overlapping neuronal substrates [166,167] and are hierarchically organized such that slow rhythms drive coordinated shifting of excitability in local neuronal ensembles and optimize gamma dynamics [168,169]. The oscillatory hierarchy operating across multiple spatial and temporal scales [170,171] is important for long-range synchronization between cortical areas and plays a critical role in various cognitive processes [168,172]. Theta–gamma cross-frequency coupling was recently found impaired in mice with genetically induced chronic NMDAR hypofunction [137,173] and in rats after acute NMDAR blockade [48]. This effect also showed subunit specificity; that is, acute elevated GBO induced by NR2A-preferring antagonists was associated with a severe impairment of low-frequency theta modulation similar to nonselective NMDAR blockade [48]. Theta-band deficits were also found in sensory gating paradigm in schizophrenics and their first-degree relatives compared with healthy controls showing a significantly higher heritability than the commonly used P50 gating endophenotype [56]. Enhanced activity in the low-frequency delta range is a common observation in schizophrenia [140,174] and is replicated by NMDAR antagonists in preclinical studies *in vivo* [110,111] and *in vitro* [175] as well as in the NMDAR hypomorphic mice model [176].

Cellular Mechanisms of Ketamine-Induced and Schizophrenia-Associated Changes in Cortical Oscillations

As discussed above, impaired oscillations in schizophrenia have been linked to GABA pathology, that is, to reductions in GAD67 and PV expression [11,84–88,177]. PV+ interneurons are involved in the generation of oscillations [178,179], suggesting a causal relationship between this histological marker and decreased oscillations documented in human schizophrenia [83,180] and in a variety of animal models [26,89,106,107,136,173,181]. NMDAR hypofunction was proposed to affect oscillations through changes brought about in the interneuron network of the schizophrenic brain [11,177]. PV+ interneurons are specifically vulnerable to NMDAR blockade. NMDARs play a specific role in the maintenance of the phenotype of PV+ interneurons. Exposure of cultured PV+ neurons to ketamine induced time- and dose-dependent decrease in PV and GAD67 [182]. Thus, NMDAR activation of genomic programs and intracellular signaling pathways [182–185] may contribute to impairment of neuronal synchronization in schizophrenia in human [83] and in NMDAR hypofunction-based chronic animal models [27,137,186,187]. In contrast to acute application of ketamine, which causes psychosis, chronic

application of ketamine and other NMDAR antagonists has been used to more closely model deficits in executive function. In rats receiving daily injections of 30 mg/kg ketamine for 5 days [186], there was a decrease in GAD67+ and PV+ cell number [27,188] and a decrease in GBO power [27], which contrasts the increases in power produced by acute ketamine. In preliminary studies, we have also found reduction in peak frequency of oscillations and a trend-level reduction in power *in vitro*[207].

In our view, NMDARs on PV+ interneurons are relatively unimportant for normal synaptic transmission (see discussion of acute effects below) but serve as a sensor for the level of network activity. Thus, GAD67 and PV may be downregulated in response to the increased network activity produced by repeated ketamine applications. This mechanism might also be relevant in producing some of the subacute effects of administration of a single dose of NMDAR antagonists, such as the delayed GBO increase observed during REM sleep, 4–5 h after injection of MK-801 [100]. In contrast to the relatively short lasting (<1 h) effect of ketamine, MK-801 elicits longer-lasting aberrant GBO elevation accompanied by stereotypic (waking) behavior, which is then followed by a second type of enhanced GBO, only occurring during REM sleep. The effect of NMDAR antagonists preferably blocking NR2A subunit-containing receptors resembles this two-component pattern [48], whereas selective NR2B blockade does not disrupt the sleep–wake cycle and elicits REM sleep-related GBO enhancement at short latencies, that is, starting right from the first REM sleep episode after injection [100]. Thus, the delayed, REM sleep-related (apparently NR2B-dependent) GBO elevation induced by MK-801 may involve subacute changes in the composition of NMDARs in interneurons generating a relative NR2B hypofunction. This is because NMDARs are regulated by receptor activity in a subtype-specific manner. Compensatory upregulation of NR2A but not NR2B subunit-containing receptors can change the NR2A/NR2B ratio as early as 4 hrs after MK-801 application to generate a relative NR2B deficit [189,190]. Acute application of selective NR2B antagonists also enhanced kainate-induced GBO *in vitro*, similar to general antagonists of the NMDAR [130]. Importantly, the NR2B subunit has been implicated as a schizophrenia-susceptibility gene [191].

Ketamine-induced increased power of GBO also has often been ascribed to a selective block of NMDAR on interneurons [192], resulting in increased excitability of pyramidal neurons, as the NMDARs on interneurons are reported to have a higher affinity for these agents than those on pyramidal neurons in the hippocampus [193]. However, at the concentrations used in *in vitro* GBO studies, most NMDARs in the slice are likely to have been blocked. Furthermore, whole-cell recordings from fast-spiking interneurons in the hippocampus and neocortex have revealed a relatively minor contribution from NMDARs to synaptic currents [194]. Thus, block of the more prominent NMDAR on low-threshold spiking, dendrite-targeting interneurons may be more important in increasing the excitability of the pyramidal neurons. Furthermore, the acute potentiating effect of NMDAR antagonism may also be due to block of the NMDAR currents on pyramidal neurons reducing jitter of synaptic currents and thereby enhancing synchrony. Selective block of NMDA on different types of neurons will ultimately be required to resolve this question. Interestingly, an additional mechanism that may account for increased power is the collapsing of high and low-gamma oscillators in deep and superficial cortical layers [131].

N-methyl-D-aspartate receptor blockade on dendritic-targeting interneurons, for example, those located in the stratum oriens of the hippocampus and projecting to lacunosum-moleculare (OLM), may also play a key role in changes of theta rhythm after ketamine administration. These cells are very sensitive to NMDA blockade [195]. They are not synchronized with gamma oscillations [196] but play a critical role in generating theta rhythm [196,197]. Theta–gamma coordination is important for cognitive processes [168,169], and OLM interneurons were shown to critically contribute to the formation of gamma-coherent cell assemblies at long distances by entrainment at theta frequency [198]. A recent computational study replicating essential features of hippocampal oscillatory activity, including cross-frequency theta–gamma modulation, explored the effect of different combinations of NMDA blockade in two pyramidal cell domains and on two types of interneurons, that is, slow-firing OLM cells and parvalbumin-positive basket cells firing at high rates and in synchrony with gamma field potentials [199]. They found that the *in vivo* pattern of reduced theta and enhanced GBO could only be elicited by selective NMDAR blockade on OLM cells, whereas NMDAR blockade on basket cells led to a decrease in gamma power.

Furthermore, since the administration of ketamine also modulates other receptors and neurotransmitter systems such as AMPA and dopamine, the effect of ketamine on cortical oscillations might include manipulations of these systems as well, for example, an excessive AMPA receptor stimulation due to glutamate spillover [200,201].

Finally, changes in cortical and hippocampal oscillations may also develop due to mechanisms potentially related to NMDARs outside of the cortex or hippocampus. Hippocampal theta power and frequency is regulated by a number of subcortical structures, including most importantly the pontine reticular formation, median raphe, supramammillary nucleus, and medial septum [202,203]. Medial septum input also amplifies GBO [199], and the involvement of medial septum and supramammillary nucleus in NMDAR antagonist-induced gamma and PPI impairment has been demonstrated [67,128]. Similarly, more caudally located basal forebrain neurons may modulate neocortical theta and gamma power [152]. In the brainstem, injection of MK-801 or AP-7 in the theta-promoting pontine reticular formation had no effect, whereas NMDAR blockade of the median raphe nucleus, normally inhibiting theta, was shown to produce theta rhythm in the hippocampus at short latencies and long duration, in urethane-anesthetized rats [204]. Local field potentials showed enhanced GBO activity in several subcortical structures, including accumbens, basalis, striatum, and thalamus [109]. An NMDAR mechanism in the thalamus was also implicated in altered cortical delta oscillations in schizophrenia [110,111,175]. In particular, the slowing and enhancement of delta waves in the prefrontal cortex observed after systemic NMDAR antagonists were replicated by local microinjections of MK-801 into the mediodorsal thalamus but not into the prefrontal cortex [110].

Conclusion

Both acute and chronic NMDAR blockade have been used in previous studies to validate the NMDAR hypofunction model. These investigations found that alterations in fast-spiking interneurons [182,188] and in cognition [50,186,205–207] were observed in both types of models and were consistent with human data. Measurement of EEG oscillations, which may serve as a link between the pathology of GABA networks and cognition deficits, presents a unique challenge, however, as the ketamine-induced acute increase has to be reconciled with more commonly reported chronic decreases of gamma activity in schizophrenics. We believe that some of the differences between human EEG data and animal models may be due to differences in the recording techniques/experimental design and might thus point to inadequacies of the recording paradigms used for assessment of oscillatory impairment in schizophrenics rather than to limited validity of the animal model. Critical comparison of the electrophysiological changes induced by ketamine and other NMDAR antagonists with those observed in patients with schizophrenia and animal models (Table 1) suggests that in schizophrenia, GBO increases and decreases may both be a consequence of NMDAR hypofunction, that is, schizophrenia and NMDAR blockade on interneurons may be associated with *increased baseline GBO* and *decreased evoked GBO*. Ketamine, which can be used both in human and animals, may play thus an essential role in developing the right methods and standards for detecting schizophrenia-relevant cortical dysfunction as well as testing novel therapeutic agents targeting GBO.

Acknowledgments

This work was supported by a Department of Veterans Affairs Medical Research Service Award (to RWM) and grants from the National Institute of Health: MH087777 (BK), HL095491 (BK and RWM), MH039683 (RWM), MH094803 (REB).

Conflict of Interest

The authors declare no conflict of interest.

References

1. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994;**51**:199–214.
2. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology* 1995;**13**:9–19.
3. Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, et al. Psychological effects of (S)-ketamine and N, N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. *Pharmacopsychiatry* 2005;**38**:301–311.
4. Vollenweider FX, Geyer MA. A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res Bull* 2001;**56**:495–507.
5. Javitt DC. Glutamate and schizophrenia: phencyclidine, *N*-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol* 2007;**78**:69–108.
6. Adell A, Jimenez-Sanchez L, Lopez-Gil X, Romon T. Is the acute NMDA receptor hypofunction a valid model of schizophrenia? *Schizophr Bull* 2012;**38**:9–14.
7. Domino EF, Luby ED. Phencyclidine/schizophrenia: one view toward the past, the other to the future. *Schizophr Bull* 2012;**38**:914–919.
8. Gandal MJ, Edgar JC, Klook K, Siegel SJ. Gamma synchrony: towards a translational biomarker for the treatment-resistant symptoms of schizophrenia. *Neuropharmacology* 2012;**62**:1504–1518.
9. Amann LC, Gandal MJ, Halene TB, et al. Mouse behavioral endophenotypes for schizophrenia. *Brain Res Bull* 2010;**83**:147–161.
10. Gilmour G, Dix S, Fellini L, et al. NMDA receptors, cognition and schizophrenia–testing the validity of the NMDA receptor hypofunction hypothesis. *Neuropharmacology* 2012;**62**:1401–1412.
11. Lisman JE, Coyle JT, Green RW, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci* 2008;**31**:234–242.
12. Javitt DC, Spencer KM, Thaker GK, Winterer G, Hajos M. Neurophysiological biomarkers for drug development in schizophrenia. *Nat Rev Drug Discov* 2008;**7**:68–83.
13. Neill JC, Barnes S, Cook S, et al. Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism. *Pharmacol Ther* 2010;**128**:419–432.
14. Gunduz-Bruce H. The acute effects of NMDA antagonism: from the rodent to the human brain. *Brain Res Rev* 2009;**60**:279–286.
15. Bubenikova-Valesova V, Horacek J, Vrajova M, Hoschl C. Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. *Neurosci Biobehav Rev* 2008;**32**:1014–1023.
16. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology* 2006;**188**:408–424.
17. Fletcher PC, Honey GD. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sci* 2006;**10**:167–174.
18. Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 2000;**23**:223–239.
19. Uhlhaas PJ, Singer W. Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. *Neuron* 2012;**75**:963–980.
20. Mion G, Villevieille T. Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). *CNS Neurosci Ther* 2013;**19**:370–380.
21. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1999;**20**:201–225.
22. Taffe MA, Davis SA, Yuan J, et al. Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. *Neuropsychopharmacology* 2002;**27**:993–1005.
23. Buccafusco JJ, Terry AV Jr. A reversible model of the cognitive impairment associated with schizophrenia in monkeys: potential therapeutic effects of two nicotinic acetylcholine receptor agonists. *Biochem Pharmacol* 2009;**78**:852–862.
24. Roberts BM, Holden DE, Shaffer CL, et al. Prevention of ketamine-induced working memory impairments by AMPA potentiators in a nonhuman primate model of cognitive dysfunction. *Behav Brain Res* 2010;**212**:41–48.
25. Pinault D. *N*-methyl D-aspartate receptor antagonists ketamine and MK-801 induce wake-related aberrant gamma oscillations in the rat neocortex. *Biol Psychiatry* 2008;**63**:730–735.
26. Lazarewicz MT, Ehrlichman RS, Maxwell CR, Gandal MJ, Finkel LH, Siegel SJ. Ketamine modulates theta and gamma oscillations. *J Cogn Neurosci* 2010;**22**:1452–1464.
27. Kittelberger K, Hur EE, Sazegar S, Keshavan V, Kocsis B. Comparison of the effects of acute and chronic administration of ketamine on hippocampal oscillations: relevance for the NMDA receptor hypofunction model of schizophrenia. *Brain Struct Funct* 2012;**217**:395–409.
28. Hong LE, Summerfelt A, Buchanan RW, et al. Gamma and delta neural oscillations and association with clinical symptoms under subanesthetic ketamine. *Neuropsychopharmacology* 2010;**35**:632–640.
29. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;**47**:351–354.
30. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;**63**:856–864.
31. Anand A, Charney DS, Oren DA, et al. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of *N*-methyl-D-aspartate receptor antagonists. *Arch Gen Psychiatry* 2000;**57**:270–276.
32. Mathews DC, Henter ID, Zarate CA. Targeting the glutamatergic system to treat major depressive disorder: rationale and progress to date. *Drugs* 2012;**72**:1313–1333.
33. Marland S, Ellerton J, Andolfatto G, et al. Ketamine: Use in Anesthesia. *CNS Neurosci Ther* 2013;**19**:381–389.
34. Salvdore G, Singh JB. Ketamine as a Fast Acting Antidepressant: Current Knowledge and Open Questions. *CNS Neurosci Ther* 2013;**19**:428–436.
35. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav* 2006;**5**:113–119.
36. O'Tuathaigh CM, Harte M, O'Leary C, et al. Schizophrenia-related endophenotypes in heterozygous neuregulin-1 'knockout' mice. *Eur J Neurosci* 2010;**31**:349–358.
37. Gornick MC, Addington AM, Sporn A, et al. Dysbindin (DTNBP1, 6p22.3) is associated with childhood-onset

psychosis and endophenotypes measured by the Premorbid Adjustment Scale (PAS). *J Autism Dev Disord* 2005;**35**:831–838.
38. Benes FM. Searching for unique endophenotypes for schizophrenia and bipolar disorder within neural circuits and their molecular regulatory mechanisms. *Schizophr Bull* 2007;**33**:932–936.
39. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;**160**:636–645.
40. Braff DL, Greenwood TA, Swerdlow NR, Light GA, Schork NJ. Advances in endophenotyping schizophrenia. *World Psychiatry* 2008;**7**:11–18.
41. Braff DL, Light GA. The use of neurophysiological endophenotypes to understand the genetic basis of schizophrenia. *Dialogues Clin Neurosci* 2005;**7**:125–135.
42. Hall MH, Taylor G, Salisbury DF, Levy DL. Sensory gating event-related potentials and oscillations in schizophrenia patients and their unaffected relatives. *Schizophr Bull* 2011;**37**:1187–1199.
43. Hall MH, Taylor G, Sham P, et al. The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia. *Schizophr Bull* 2011;**37**:778–787.
44. Swerdlow NR, Braff DL, Geyer MA. Cross-species studies of sensorimotor gating of the startle reflex. *Ann N Y Acad Sci* 1999;**877**:202–216.
45. Swerdlow NR, Braff DL, Taaid N, Geyer MA. Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. *Arch Gen Psychiatry* 1994;**51**:139–154.
46. Swerdlow NR, Weber M, Qu Y, Light GA, Braff DL. Realistic expectations of prepulse inhibition in translational models for schizophrenia research. *Psychopharmacology* 2008;**199**:331–388.
47. Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology* 2001;**156**:117–154.
48. Kocsis B. Differential role of NR2A and NR2B subunits in *N*-methyl-D-aspartate receptor antagonist-induced aberrant cortical gamma oscillations. *Biol Psychiatry* 2012;**71**:987–995.
49. Spooren W, Mombereau C, Maco M, et al. Pharmacological and genetic evidence indicates that combined inhibition of NR2A and NR2B subunit containing NMDA receptors is required to disrupt prepulse inhibition. *Psychopharmacology* 2004;**175**:99–105.
50. Manahan-Vaughan D, von Haebler D, Winter C, Juckel G, Heinemann U. A single application of MK801 causes symptoms of acute psychosis, deficits in spatial memory, and impairment of synaptic plasticity in rats. *Hippocampus* 2008;**18**:125–134.
51. Linn GS, O'Keeffe RT, Lifshitz K, Schroeder C, Javitt DC. Behavioral effects of orally administered glycine in socially housed monkeys chronically treated with phencyclidine. *Psychopharmacology* 2007;**192**:27–38.
52. Shiigi Y, Casey DE. Behavioral effects of ketamine, an NMDA glutamatergic antagonist, in non-human primates. *Psychopharmacology* 1999;**146**:67–72.
53. Abel KM, Allin MP, Hemsley DR, Geyer MA. Low dose ketamine increases prepulse inhibition in healthy men. *Neuropharmacology* 2003;**44**:729–737.
54. Duncan EJ, Madonick SH, Parwani A, et al. Clinical and sensorimotor gating effects of ketamine in normals. *Neuropsychopharmacology* 2001;**25**:72–83.
55. van Berckel BN, Oranje B, van Ree JM, Verbaten MN, Kahn RS. The effects of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. *Psychopharmacology* 1998;**137**:271–281.
56. Hong LE, Summerfelt A, Mitchell BD, et al. Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch Gen Psychiatry* 2008;**65**:1008–1016.
57. Luck SJ, Mathalon DH, O'Donnell BF, et al. A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. *Biol Psychiatry* 2011;**70**:28–34.
58. Turetsky BI, Greenwood TA, Olincy A, et al. Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. *Biol Psychiatry* 2008;**64**:1051–1059.
59. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophr Bull* 2007;**33**:69–94.
60. Javitt DC, Schoepp D, Kalivas PW, et al. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med* 2011;**3**:102mr2.
61. Hajos M. Targeting information-processing deficit in schizophrenia: a novel approach to psychotherapeutic drug discovery. *Trends Pharmacol Sci* 2006;**27**:391–398.
62. Cromwell HC, Mears RP, Wan L, Boutros NN. Sensory gating: a translational effort from basic to clinical science. *Clin EEG Neurosci* 2008;**39**:69–72.
63. Hanlon FM, Miller GA, Thoma RJ, et al. Distinct M50 and M100 auditory gating deficits in schizophrenia. *Psychophysiology* 2005;**42**:417–427.
64. Mathiak K, Ackermann H, Rapp A, et al. Neuromagnetic oscillations and hemodynamic correlates of P50 suppression in schizophrenia. *Psychiatry Res* 2011;**194**:95–104.
65. Boeijinga PH, Soufflet L, Santoro F, Luthringer R. Ketamine effects on CNS responses assessed with MEG/EEG in a passive auditory sensory-gating paradigm: an attempt for modelling some symptoms of psychosis in man. *J Psychopharmacol* 2007;**21**:321–337.
66. Cromwell HC, Klein A, Mears RP. Single unit and population responses during inhibitory gating of striatal activity in freely moving rats. *Neuroscience* 2007;**146**:69–85.
67. Ma J, Tai SK, Leung LS. Septohippocampal GABAergic neurons mediate the altered behaviors induced by *N*-methyl-D-aspartate receptor antagonists. *Hippocampus* 2012;**22**:2208–2218.
68. Garrido MI, Friston KJ, Kiebel SJ, Stephan KE, Baldeweg T, Kilner JM. The functional anatomy of the MMN: a DCM study of the roving paradigm. *Neuroimage* 2008;**42**:936–944.
69. Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: a review of underlying mechanisms. *Clin Neurophysiol* 2009;**120**:453–463.
70. Todd J, Myers R, Pirillo R, Drysdale K. Neuropsychological correlates of auditory perceptual inference: a mismatch negativity (MMN) study. *Brain Res* 2010;**1310**:113–123.
71. Doeller CF, Opitz B, Mecklinger A, Krick C, Reith W, Schroger E. Prefrontal cortex involvement in preattentive auditory deviance detection: neuroimaging and electrophysiological evidence. *Neuroimage* 2003;**20**:1270–1282.
72. Opitz B, Rinne T, Mecklinger A, von Cramon DY, Schroger E. Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. *Neuroimage* 2002;**15**:167–174.
73. Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Naatanen R. Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage* 2000;**12**:14–19.
74. Javitt DC. Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurootol* 2000;**5**:207–215.
75. Heekeren K, Daumann J, Neukirch A, et al. Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis. *Psychopharmacology* 2008;**199**:77–88.
76. Kreitschmann-Andermahr I, Rosburg T, Demme U, Gaser E, Nowak H, Sauer H. Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Brain Res Cogn Brain Res* 2001;**12**:109–116.
77. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry* 2000;**57**:1139–1147.
78. Gunduz-Bruce H, Reinhart RM, Roach BJ, et al. Glutamatergic modulation of auditory information processing in the human brain. *Biol Psychiatry* 2012;**71**:969–977.
79. Schmidt A, Bachmann R, Kometer M, et al. Mismatch negativity encoding of prediction errors predicts S-ketamine-induced cognitive impairments. *Neuropsychopharmacology* 2012;**37**:865–875.
80. Baldeweg T, Klugman A, Gruzelier J, Hirsch SR. Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr Res* 2004;**69**:203–217.
81. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res* 2005;**76**:1–23.
82. Schmidt A, Diaconescu AO, Kometer M, Friston KJ, Stephan KE, Vollenweider FX. Modeling ketamine effects on synaptic plasticity during the mismatch negativity. *Cereb Cortex* 2012; doi: 10.1093/cercor/bhs238.
83. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010;**11**:100–113.
84. Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 2001;**25**:1–27.
85. Benes FM, Lim B, Matzilevich D, Subburaju S, Walsh JP. Circuitry-based gene expression profiles in GABA cells of the trisynaptic pathway in schizophrenics versus bipolars. *Proc Natl Acad Sci U S A* 2008;**105**:20935–20940.
86. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* 2005;**6**:312–324.
87. Reynolds GP, Abdul-Monim Z, Neill JC, Zhang ZJ. Calcium binding protein markers of GABA deficits in schizophrenia–postmortem studies and animal models. *Neurotox Res* 2004;**6**:57–61.
88. Todtenkopf MS, Benes FM. Distribution of glutamate decarboxylase65 immunoreactive puncta on pyramidal and nonpyramidal neurons in hippocampus of schizophrenic brain. *Synapse* 1998;**29**:323–332.
89. Lodge DJ, Behrens MM, Grace AA. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J Neurosci* 2009;**29**:2344–2354.
90. Kaalund SS, Riise J, Broberg B, et al. Differential expression of parvalbumin interneurons in neonatal phencyclidine treated rats and socially isolated rats. *J Neurochem* 2012;**124**:548–557.
91. Turner CP, DeBenedetto D, Ware E, et al. Postnatal exposure to MK801 induces selective changes in GAD67 or parvalbumin. *Exp Brain Res* 2010;**201**:479–488.
92. Jenkins TA, Harte MK, Reynolds GP. Effect of subchronic phencyclidine administration on sucrose preference and hippocampal parvalbumin immunoreactivity in the rat. *Neurosci Lett* 2010;**471**:144–147.
93. Xi D, Zhang W, Wang HX, Stradtman GG, Gao WJ. Dizocilpine (MK-801) induces distinct changes of *N*-methyl-D-aspartic acid receptor subunits in parvalbumin-containing interneurons in young adult rat prefrontal cortex. *Int J Neuropsychopharmacol* 2009;**12**:1395–1408.
94. Francois J, Ferrandon A, Koning E, Angst MJ, Sandner G, Nehlig A. Selective reorganization of GABAergic

transmission in neonatal ventral hippocampal-lesioned rats. *Int J Neuropsychopharmacol* 2009;**12**:1097–1110.
95. Abekawa T, Ito K, Nakagawa S, Koyama T. Prenatal exposure to an NMDA receptor antagonist, MK-801 reduces density of parvalbumin-immunoreactive GABAergic neurons in the medial prefrontal cortex and enhances phencyclidine-induced hyperlocomotion but not behavioral sensitization to methamphetamine in postpubertal rats. *Psychopharmacology* 2007;**192**:303–316.
96. Penschuck S, Flagstad P, Didriksen M, Leist M, Michael-Titus AT. Decrease in parvalbumin-expressing neurons in the hippocampus and increased phencyclidine-induced locomotor activity in the rat methylazoxymethanol (MAM) model of schizophrenia. *Eur J Neurosci* 2006;**23**:279–284.
97. Gizerian SS, Morrow AL, Lieberman JA, Grobin AC. Neonatal neurosteroid administration alters parvalbumin expression and neuron number in medial dorsal thalamus of adult rats. *Brain Res* 2004;**1012**:66–74.
98. Hajos M, Hoffmann WE, Kocsis B. Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. *Biol Psychiatry* 2008;**63**:1075–1083.
99. Lanre-Amos T, Kocsis B. Hippocampal oscillations in the rodent model of schizophrenia induced by amygdala GABA receptor blockade. *Front Psychiatry* 2010;**1**:132.
100. Kocsis B. State-dependent increase of cortical gamma activity during REM sleep after selective blockade of NR2B subunit containing NMDA receptors. *Sleep* 2012;**35**:1011–1016.
101. Kocsis B, Dybvik M, Harper J, Ronnestad K. Changes in background and ketamine induced gamma oscillations in the MAM-model of schizophrenia. *Biol Psychiatry* 2012;**71**:39S.
102. Dzirasa K, Santos LM, Ribeiro S, et al. Persistent hyperdopaminergia decreases the peak frequency of hippocampal theta oscillations during quiet waking and REM sleep. *PLoS ONE* 2009;**4**:e5238.
103. Ehrlichman RS, Gandal MJ, Maxwell CR, et al. *N*-methyl-D-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia. *Neuroscience* 2009;**158**:705–712.
104. Phillips KG, Cotel MC, McCarthy AP, et al. Differential effects of NMDA antagonists on high frequency and gamma EEG oscillations in a neurodevelopmental model of schizophrenia. *Neuropharmacology* 2012;**62**:1359–1370.
105. Vohs JL, Chambers RA, Krishnan GP, et al. Auditory sensory gating in the neonatal ventral hippocampal lesion model of schizophrenia. *Neuropsychobiology* 2009;**60**:12–22.
106. Vohs JL, Chambers RA, Krishnan GP, O'Donnell BF, Berg S, Morzorati SL. GABAergic modulation of the 40 Hz auditory steady-state response in a rat model of schizophrenia. *Int J Neuropsychopharmacol* 2010;**13**:487–497.
107. Carlson GC, Talbot K, Halene TB, et al. Dysbindin-1 mutant mice implicate reduced fast-phasic inhibition as a final common disease mechanism in schizophrenia. *Proc Natl Acad Sci U S A* 2011;**108**:E962–E970.
108. Lodge DJ, Grace AA. Gestational methylazoxymethanol acetate administration: a developmental disruption model of schizophrenia. *Behav Brain Res* 2009;**204**:306–312.
109. Hakami T, Jones NC, Tolmacheva EA, et al. NMDA receptor hypofunction leads to generalized and persistent aberrant gamma oscillations independent of hyperlocomotion and the state of consciousness. *PLoS ONE* 2009;**4**:e6755.
110. Kiss T, Hoffmann WE, Scott L, et al. Role of thalamic projection in NMDA receptor-induced disruption of cortical slow oscillation and short-term plasticity. *Front Psychiatry* 2011;**2**:14.
111. Kiss T, Hoffmann WE, Hajos M. Delta oscillation and short-term plasticity in the rat medial prefrontal cortex: modelling NMDA hypofunction of schizophrenia. *Int J Neuropsychopharmacol* 2011;**14**:29–42.
112. Spencer KM. Baseline gamma power during auditory steady-state stimulation in schizophrenia. *Front Hum Neurosci* 2011;**5**:190.
113. Basar E, Rosen B, Basar-Eroglu C, Greitschus F. The associations between 40 Hz-EEG and the middle latency response of the auditory evoked potential. *Int J Neurosci* 1987;**33**:103–117.
114. Brenner CA, Sporns O, Lysaker PH, O'Donnell BF. EEG synchronization to modulated auditory tones in schizophrenia, schizoaffective disorder, and schizotypal personality disorder. *Am J Psychiatry* 2003;**160**:2238–2240.
115. Spencer KM, Niznikiewicz MA, Shenton ME, McCarley RW. Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry* 2008;**63**:744–747.
116. Brenner CA, Krishnan GP, Vohs JL, et al. Steady state responses: electrophysiological assessment of sensory function in schizophrenia. *Schizophr Bull* 2009;**35**:1065–1077.
117. Haenschel C, Linden D. Exploring intermediate phenotypes with EEG: working memory dysfunction in schizophrenia. *Behav Brain Res* 2011;**216**:481–495.
118. Barr MS, Farzan F, Tran LC, Chen R, Fitzgerald PB, Daskalakis ZJ. Evidence for excessive frontal evoked gamma oscillatory activity in schizophrenia during working memory. *Schizophr Res* 2010;**121**:1 46–152.
119. Farzan F, Barr MS, Levinson AJ, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain* 2010;**133**:1505–1514.
120. Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology* 2010;**35**:2590–2599.
121. Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol* 2007;**64**:39–45.
122. Baldeweg T, Spence S, Hirsch SR, Gruzelier J. Gamma-band electroencephalographic oscillations in a patient with somatic hallucinations. *Lancet* 1998;**352**:620–621.
123. Tan HY, Callicott JH, Weinberger DR. Intermediate phenotypes in schizophrenia genetics redux: is it a no brainer? *Mol Psychiatry* 2008;**13**:233–238.
124. Plourde G, Baribeau J, Bonhomme V. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. *Br J Anaesth* 1997;**78**:524–529.
125. Rivolta D, Sauer A, Heidegger T, et al. Effects of ketamine on gamma-band oscillations in MEG-data: a comparison with chronic schizophrenia. *Soc Neurosci Abstr* 2012;**38**:867.08.
126. Jones NC, Reddy M, Anderson P, Salzberg MR, O'Brien TJ, Pinault D. Acute administration of typical and atypical antipsychotics reduces EEG gamma power, but only the preclinical compound LY379268 reduces the ketamine-induced rise in gamma power. *Int J Neuropsychopharmacol* 2012;**15**:657–668.
127. Ma J, Leung LS. Relation between hippocampal gamma waves and behavioral disturbances induced by phencyclidine and methamphetamine. *Behav Brain Res* 2000;**111**:1–11.
128. Ma J, Leung LS. The supramammillo-septal-hippocampal pathway mediates sensorimotor gating impairment and hyperlocomotion induced by MK-801 and ketamine in rats. *Psychopharmacology* 2007;**191**:961–974.
129. Roopun AK, Cunningham MO, Racca C, Alter K, Traub RD, Whittington MA. Region-specific changes in gamma and beta2 rhythms in NMDA receptor dysfunction models of schizophrenia. *Schizophr Bull* 2008;**34**:962–973.
130. McNally JM, McCarley RW, McKenna JT, Yanagawa Y, Brown RE. Complex receptor mediation of acute ketamine application on in vitro gamma oscillations in mouse prefrontal cortex: modeling gamma band oscillation abnormalities in schizophrenia. *Neuroscience* 2011;**199**:51–63.
131. Anver H, Ward PD, Magony A, Vreugdenhil M. NMDA receptor hypofunction phase couples independent gamma-oscillations in the rat visual cortex. *Neuropsychopharmacology* 2011;**36**:519–528.
132. Spencer KM. Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. *Clin EEG Neurosci* 2008;**39**:65–68.
133. Hamm JP, Gilmore CS, Clementz BA. Augmented gamma band auditory steady-state responses: support for NMDA hypofunction in schizophrenia. *Schizophr Res* 2012;**138**:1–7.
134. Spencer KM, Nestor PG, Perlmutter R, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A* 2004;**101**:17288–17293.
135. Lee KH, Williams LM, Haig A, Gordon E. "Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. *Cogn Neuropsychiatry* 2003;**8**:57–71.
136. Carlen M, Meletis K, Siegle JH, et al. A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Mol Psychiatry* 2012;**17**:537–548.
137. Korotkova T, Fuchs EC, Ponomarenko A, von Engelhardt J, Monyer H. NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. *Neuron* 2010;**68**:557–569.
138. Kikuchi M, Hashimoto T, Nagasawa T, et al. Frontal areas contribute to reduced global coordination of resting-state gamma activities in drug-naive patients with schizophrenia. *Schizophr Res* 2011;**130**:187–194.
139. Spencer FA, Iorio A, You J, et al. Uncertainties in baseline risk estimates and confidence in treatment effects. *BMJ* 2012;**345**:e7401.
140. Itil TM, Saletu B, Davis S. EEG findings in chronic schizophrenics based on digital computer period analysis and analog power spectra. *Biol Psychiatry* 1972;**5**:1–13.
141. Itil TM. Qualitative and quantitative EEG findings in schizophrenia. *Schizophr Bull* 1977;**3**:61–79.
142. Kulikova SP, Tolmacheva EA, Anderson P, et al. Opposite effects of ketamine and deep brain stimulation on rat thalamocortical information processing. *Eur J Neurosci* 2012;**36**:3407–3419.
143. Clementz BA, Wang J, Keil A. Normal electrocortical facilitation but abnormal target identification during visual sustained attention in schizophrenia. *J Neurosci* 2008;**28**:13411–13418.
144. Wang J, Brown R, Dobkins KR, McDowell JE, Clementz BA. Diminished parietal cortex activity associated with poor motion direction discrimination performance in schizophrenia. *Cereb Cortex* 2010;**20**:1749–1755.
145. Goutagny R, Manseau F, Jackson J, Danik M, Williams S. In vitro activation of the medial septum-diagonal band complex generates atropine-sensitive and atropine-resistant hippocampal theta rhythm: an investigation using a complete septohippocampal preparation. *Hippocampus* 2008;**18**:531–535.
146. Middleton S, Jalics J, Kispersky T, et al. NMDA receptor-dependent switching between different gamma rhythm-generating microcircuits in entorhinal cortex. *Proc Natl Acad Sci U S A* 2008;**105**:18572–18577.
147. Oke OO, Magony A, Anver H, et al. High-frequency gamma oscillations coexist with low-frequency gamma oscillations in the rat visual cortex in vitro. *Eur J Neurosci* 2010;**31**:1435–1445.
148. Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D. Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *Am J Psychiatry* 1997;**154**:805–811.

149. Whittington MA, Traub RD, Jefferys JG. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 1995;**373**:612–615.
150. Fisahn A, Contractor A, Traub RD, Buhl EH, Heinemann SF, McBain CJ. Distinct roles for the kainate receptor subunits GluR5 and GluR6 in kainate-induced hippocampal gamma oscillations. *J Neurosci* 2004;**24**:9658–9668.
151. Fisahn A, Pike FG, Buhl EH, Paulsen O. Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro. *Nature* 1998;**394**:186–189.
152. Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of sleep and wakefulness. *Physiol Rev* 2012;**92**:1087–1187.
153. Hajos N, Paulsen O. Network mechanisms of gamma oscillations in the CA3 region of the hippocampus. *Neural Netw* 2009;**22**:1113–1119.
154. Whittington MA, Cunningham MO, LeBeau FE, Racca C, Traub RD. Multiple origins of the cortical gamma rhythm. *Dev Neurobiol* 2011;**71**:92–106.
155. Hajos N, Ellender TJ, Zemankovics R, et al. Maintaining network activity in submerged hippocampal slices: importance of oxygen supply. *Eur J Neurosci* 2009;**29**:319–327.
156. Scheeringa R, Fries P, Petersson KM, et al. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. *Neuron* 2011;**69**:572–583.
157. Gloveli T, Dugladze T, Saha S, et al. Differential involvement of oriens/pyramidale interneurones in hippocampal network oscillations in vitro. *J Physiol* 2005;**562**:131–147.
158. Kwon JS, O'Donnell BF, Wallenstein GV, et al. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch Gen Psychiatry* 1999;**56**:1001–1005.
159. Vierling-Claassen D, Siekmeier P, Stufflebeam S, Kopell N. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. *J Neurophysiol* 2008;**99**:2656–2671.
160. Kopell N, Ermentrout GB, Whittington MA, Traub RD. Gamma rhythms and beta rhythms have different synchronization properties. *Proc Natl Acad Sci U S A* 2000;**97**:1867–1872.
161. Ford JM, Mathalon DH, Whitfield S, Faustman WO, Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol Psychiatry* 2002;**51**:485–492.
162. Koenig T, Lehmann D, Saito N, Kuginuki T, Kinoshita T, Koukkou M. Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naive patients with schizophrenia: preliminary results. *Schizophr Res* 2001;**50**:55–60.
163. Bates AT, Kiehl KA, Laurens KR, Liddle PF. Low-frequency EEG oscillations associated with information processing in schizophrenia. *Schizophr Res* 2009;**115**: 222–230.
164. Basar-Eroglu C, Schmiedt-Fehr C, Marbach S, Brand A, Mathes B. Altered oscillatory alpha and theta networks in schizophrenia. *Brain Res* 2008;**1235**: 143–152.
165. Schmiedt C, Brand A, Hildebrandt H, Basar-Eroglu C. Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls. *Brain Res Cogn Brain Res* 2005;**25**:936–947.
166. Klausberger T, Somogyi P. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* 2008;**321**:53–57.
167. Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K. High frequency network oscillation in the hippocampus. *Science* 1992;**256**:1025–1027.
168. Lisman J, Buzsaki G. A neural coding scheme formed by the combined function of gamma and theta oscillations. *Schizophr Bull* 2008;**34**:974–980.
169. Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE. Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science* 2008;**320**:110–113.
170. Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J Neurosci* 1995;**15**:47–60.
171. Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G, Schroeder CE. An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J Neurophysiol* 2005;**94**:1904–1911.
172. Canolty RT, Edwards E, Dalal SS, et al. High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 2006;**313**:1626–1628.
173. Dzirasa K, Ramsey AJ, Takahashi DY, et al. Hyperdopaminergia and NMDA receptor hypofunction disrupt neural phase signaling. *J Neurosci* 2009;**29**:8215–8224.
174. Galderisi S, Mucci A, Volpe U, Boutros N. Evidence-based medicine and electrophysiology in schizophrenia. *Clin EEG Neurosci* 2009;**40**:62–77.
175. Zhang Y, Llinas RR, Lisman JE. Inhibition of NMDARs in the nucleus reticularis of the thalamus produces delta frequency bursting. *Front Neural Circuits* 2009;**3**:20.
176. Feng J, Hoffmann WE, Kiss K, Hajos M. Effects of AMPA receptor positive allosteric modulator in pharmacological and genetic models of schizophrenia NMDA receptor hypofunction. *Soc Neurosc Abstr* 2011;**37**:163.22.
177. Gonzalez-Burgos G, Lewis DA. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr Bull* 2008;**34**:944–961.
178. Buzsaki G. *Rhythms of the brain*. Oxford: Oxford University Press, 2006.
179. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 2009;**459**:698–702.
180. Spencer KM, Niznikiewicz MA, Nestor PG, Shenton ME, McCarley RW. Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. *BMC Neurosci* 2009;**10**:85.
181. Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature* 2010;**464**:763–767.
182. 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**:1604–1615.
183. Anastasio NC, Johnson KM. Differential regulation of the NMDA receptor by acute and sub-chronic phencyclidine administration in the developing rat. *J Neurochem* 2008;**104**:1210–1218.
184. Anastasio NC, Xia Y, O'Connor ZR, Johnson KM. Differential role of *N*-methyl-D-aspartate receptor subunits 2A and 2B in mediating phencyclidine-induced perinatal neuronal apoptosis and behavioral deficits. *Neuroscience* 2009;**163**:1181–1191.
185. Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. *Nat Rev Neurosci* 2010;**11**:682–696.
186. Becker A, Peters B, Schroeder H, Mann T, Huether G, Grecksch G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;**27**:687–700.
187. Belforte JE, Zsiros V, Sklar ER, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat Neurosci* 2010;**13**:76–83.
188. Keilhoff G, Becker A, Grecksch G, Wolf G, Bernstein HG. Repeated application of ketamine to rats induces changes in the hippocampal expression of parvalbumin, neuronal nitric oxide synthase and cFOS similar to those found in human schizophrenia. *Neuroscience* 2004;**126**:591–598.
189. von Engelhardt J, Doganci B, Seeburg PH, Monyer H. Synaptic NR2A- but not NR2B-containing NMDA receptors increase with blockade of ionotropic glutamate receptors. *Front Mol Neurosci* 2009;**2**:19.
190. Wilson MA, Kinsman SL, Johnston MV. Expression of NMDA receptor subunit mRNA after MK-801 treatment in neonatal rats. *Brain Res Dev Brain Res* 1998;**109**:211–220.
191. Allen NC, Bagade S, McQueen MB, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* 2008;**40**:827–834.
192. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* 2007;**27**:11496–11500.
193. Grunze HC, Rainnie DG, Hasselmo ME, et al. NMDA-dependent modulation of CA1 local circuit inhibition. *J Neurosci* 1996;**16**:2034–2043.
194. Rotaru DC, Yoshino H, Lewis DA, Ermentrout GB, Gonzalez-Burgos G. Glutamate receptor subtypes mediating synaptic activation of prefrontal cortex neurons: relevance for schizophrenia. *J Neurosci* 2011;**31**:142–156.
195. Hajos N, Freund TF, Mody I. Comparison of single NMDA receptor channels recorded on hippocampal principal cells and oriens/alveus interneurons projecting to stratum lacunosum-moleculare (O-LM cells). *Acta Biol Hung* 2002;**53**:465–472.
196. Klausberger T, Magill PJ, Marton LF, et al. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* 2003;**421**:844–848.
197. Gillies MJ, Traub RD, LeBeau FE, et al. A model of atropine-resistant theta oscillations in rat hippocampal area CA1. *J Physiol* 2002;**543**:779–793.
198. Tort AB, Rotstein HG, Dugladze T, Gloveli T, Kopell NJ. On the formation of gamma-coherent cell assemblies by oriens lacunosum-moleculare interneurons in the hippocampus. *Proc Natl Acad Sci U S A* 2007;**104**:13490–13495.
199. Neymotin SA, Lazarewicz MT, Sherif M, Contreras D, Finkel LH, Lytton WW. Ketamine disrupts theta modulation of gamma in a computer model of hippocampus. *J Neurosci* 2011;**31**:11733–11743.
200. 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* 1997;**17**:2921–2927.
201. Corlett PR, Frith CD, Fletcher PC. From drugs to deprivation: a Bayesian framework for understanding models of psychosis. *Psychopharmacology* 2009;**206**:515–530.
202. Vertes RP, Kocsis B. Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. *Neuroscience* 1997;**81**:893–926.
203. Kocsis B, Li S. In vivo contribution of h-channels in the septal pacemaker to theta rhythm generation. *Eur J Neurosci* 2004;**20**:2149–2158.
204. Kinney GG, Kocsis B, Vertes RP. Injections of excitatory amino acid antagonists into the median raphe nucleus produce hippocampal theta rhythm in the urethane-anesthetized rat. *Brain Res* 1994;**654**:96–104.
205. Rujescu D, Bender A, Keck M, et al. A pharmacological model for psychosis based on *N*-methyl-D-aspartate receptor hypofunction: molecular, cellular, functional and behavioral abnormalities. *Biol Psychiatry* 2006;**59**:721–729.
206. Stefani MR, Moghaddam B. Transient *N*-methyl-D-aspartate receptor blockade in early development causes

lasting cognitive deficits relevant to schizophrenia. *Biol Psychiatry* 2005;**57**:433–436.

207. Mansbach RS, Geyer MA. Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. *Neuropsychopharmacology* 1989;**2**:299–308.
208. Vohs JL, Chambers RA, O'Donnell BF, Krishnan GP, Morzorati SL. Auditory steady state responses in a schizophrenia rat model probed by excitatory/inhibitory receptor manipulation. *Int J Psychophysiol* 2012;**86**:136–142.
209. McNally JM, Kim T, Yanagawa Y, McCarley RW, Brown RE. Acute and chronic effects of ketamine on gamma oscillations in mouse prefrontal cortex. *Soc Neurosci Abstr* 2011;**37**:661.07.