Region-Specific Changes in Gamma and Beta2 Rhythms in NMDA Receptor Dysfunction Models of Schizophrenia

Anita K. Roopun², Mark O. Cunningham², Claudia Racca², Kai Alter², Roger D. Traub³, and Miles A. Whittington¹,²

¹Institute of Neuroscience, The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK; ²Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, NY 11203

Cognitive disruption in schizophrenia is associated with altered patterns of spatiotemporal interaction associated with multiple electroencephalogram (EEG) frequency bands in cortex. In particular, changes in the generation of gamma (30–80 Hz) and beta2 (20–29 Hz) rhythms correlate with observed deficits in communication between different cortical areas. Aspects of these changes can be reproduced in animal models, most notably those involving acute or chronic reduction in glutamatergic synaptic communication mediated by N-methyl D-aspartate (NMDA) receptors. In vitro electrophysiological and immunocytochemical approaches afforded by such animal models continue to reveal a great deal about the mechanisms underlying EEG rhythm generation and are beginning to uncover which basic molecular, cellular, and network phenomena may underlie their disruption in schizophrenia. Here we briefly review the evidence for changes in γ-amino butyric acidergic (GABAergic) and glutamatergic function and address the problem of region specificity of changes with quantitative comparisons of effects of ketamine on gamma and beta2 rhythms in vitro. We conclude, from available evidence, that many observed changes in markers for GABAergic function in schizophrenia may be secondary to deficits in NMDA receptor–mediated excitatory synaptic activity. Furthermore, the broad range of changes in cortical dynamics seen in schizophrenia—with contrasting effects seen in different brain regions and for different frequency bands—may be more directly attributable to underlying deficits in glutamatergic neuronal communication rather than GABAergic inhibition alone.

Key words: schizophrenia/EEG/gamma/beta/inhibition/NMDA

Gamma Rhythms in Schizophrenia and Models of Psychosis

Evidence that cognitive deficits in schizophrenia may be causally related to changes in cortical dynamics is growing.¹ Of the many functionally distinct classes of EEG rhythms, changes in gamma rhythmogenesis, and accompanying temporal patterns of cortical activity, may play a pivotal role in precipitating these changes. Gamma rhythms are involved in many aspects of cognitive functions from primary sensory representation² through to selective attention³ and short-term memory.⁴ They possess the ability to facilitate synchrony of neuronal activity despite long conduction delays,⁵ and this synchrony appears to be causally related to the formation of functional connections in cortex in response to sensory input.⁶ In other words, the ability of the brain to coordinate activity occurring in many, anatomically distant areas at the same time appears critically dependent on the ability of these areas to produce rhythmic outputs at gamma frequency.

The connection between gamma rhythms and schizophrenia has been made by many researchers.⁷ Changes in auditory and visual steady-state gamma rhythm generation have been seen,⁸,⁹ decreased induced-gamma power and event-related frontotemporal and parietal coherence are seen,¹⁰ and numerous studies on visual Gestalt stimuli reveal robust deficits in measures of global synchronization in cortex at gamma frequencies in schizophrenics.¹¹,¹² Similar deficits in gamma rhythmogenesis associated with early auditory processing have also been reported.¹³,¹⁴ Working memory processes involving gamma rhythms are also seen to be disrupted in schizophrenia,¹⁵ with fundamental differences in response to γ-aminobutyric acid (GABA)-modulating drugs when comparing schizophrenics with controls in target discrimination.¹⁶ This connection between changes in cortical dynamic processes involving gamma rhythms—the ability of different brain regions to coordinate their activity patterns in time—and GABAergic inhibitory synaptic transmission suggests an integral role in schizophrenic pathology. To explore this role mechanistically, we must first consider how gamma rhythms may be generated in animal models of schizophrenia-related cognitive deficits.

Animal models of some symptoms of schizophrenia exist which show highly region-specific, even cortical lamina-specific reduction in gamma rhythms. In particular,
models using noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists have been used to mimic many of the main symptoms of schizophrenia with evidence for disrupted glutameric function in growing schizophrenia. Using ketamine in rodents produces an increase in gamma rhythm generation in general frontoparietal areas that compares to specific increases in gamma auditory steady-state responses seen with ketamine administration to humans. However, it is difficult to establish the origin of rhythmic activity patterns in vivo. In vitro studies in which specific subregions of the brain are maintained in isolation have shown that ketamine has no effect on glutameric or cholinergically induced gamma rhythms in isolated hippocampus, and gamma rhythmogenesis was specifically and markedly reduced by ketamine in superficial layers of medial entorhinal cortex.

Thus, there is a general increase in gamma rhythm power with ketamine in rodent models and the human auditory steady-state response, a lack of change, or decrease, in gamma power in specific areas in vitro with ketamine, and a decrease in sensory evoked gamma power and gamma-associated measures of cortical synchrony in schizophrenics. How can we resolve these apparently contradictory data sets? If we begin with the assumption that ketamine (or NMDA blockade with other antagonists such as phencyclidine (PCP) is a good model of cognitive deficit in schizophrenia, then one possibility is that there is a complex spatiotemporal pattern to the effects of ketamine. Perhaps, NMDA receptor-mediated excitation plays different roles in modulating gamma rhythms, and other EEG rhythms, in different cortical areas. If so, then we must consider interactions between many specific brain regions and population rhythms concurrently expressed with gamma before we can make greater sense of the data available. This article makes a preliminary attempt at this, but first we need to consider just what it is about gamma rhythms that make them so labile to schizophrenic pathology and related models.

Mechanisms Possibly Relevant to Disrupted Gamma Rhythms

Gamma rhythms arise as emergent property of superficial neocortical networks. They can be generated in a number of conditions ranging from intense, transient excitation of fast-spiking interneurons via metabotropic glutamate receptors to more subtle but persistent, neuromodulatory excitation of interneurons and principal cells via cholinergic receptors. Details of relevant network behavior vary in different conditions, but the feature common to all forms of classical gamma rhythms is the presence of trains of fast, somatic inhibitory postsynaptic potentials (IPSPs) mediated by GABA<sub>A</sub> receptors in principal cells (figure 1A). The origin of these IPSPs...
is predominantly, though not exclusively, via the output from perisomatic-targeting, fast-spiking GABAergic interneurons. This rhythmic pattern of inhibitory events serves to effectively quantize and limit the times at which principal neurons may fire action potentials. It should be noted that the inhibition-based nature of gamma rhythms only applies within the range of frequencies from c.30 to c.80 Hz. Above or below these frequencies, phasic GABAergic inhibition is not sufficient to support locally coherent oscillations in experimental studies using physiologically relevant conditions in vitro. Lower frequencies can be produced by manipulations that prolong IPSP duration such as general anesthetic application. However, higher frequencies of network rhythm (eg, the “high gamma” reported in electrocorticography studies) are not consistent with the established inhibition-based mechanism of gamma rhythm generation in experiment and, as such, perhaps should not be referred to as gamma rhythms at all—though some simple computational models can be made to work beyond these limits.

In the case of inhibition-based gamma rhythms, intense transient excitation, such a pattern of activation of a network is produced by brief stimulation of afferents to that network, eg, Schaffer collateral stimulation in hippocampus or medial geniculate nucleus input to auditory cortex, thus resembling the pattern of activation of cortex by sensory inputs. In this case, predominant feedforward excitation of interneurons results in a large depolarization which lasts c.1 s. Depolarization of many interneurons together in this manner activates reciprocal inhibitory synaptic connections between interneurons. The resulting shared IPSPs constrain action potential generation in interneurons so that they all occur together (ie, synchronously) between consecutive inhibitory synaptic events. The resulting network frequency is therefore determined by the size and duration of the shared IPSP values which, in normal conditions, give frequencies within the gamma band (approximately 30–50). Because interneurons are activated by a depolarization generated by external sources (the afferent input stimulated), they do not require excitatory feedback from local excitatory neurons. In fact, in this case, spiking in local excitatory neurons can be blocked without abolishing the network gamma rhythm.

In contrast, at the other end of the range of conditions supporting gamma rhythms, reciprocal interaction from principal cells back to interneuron populations, via α-amino-3-hydroxy-s-methyl-4-isooxazole propionic acid AMPA receptors, can provide a phasic pattern of excitation of interneuron populations sufficient to generate network oscillations. In this case, depolarization of either interneurons or principal cell somata is unnecessary. Instead, ectopic action potential generation in principal cell axons, shared throughout the network via axo-axonic principal cell gap junctions, can converge on excitatory synapses onto interneurons to produce very large, compound excitatory events sufficient to generate action potentials. These action potentials then feed back onto perisomatic regions of principal cells to transiently attenuate axonal spike generation, thus resulting in a repetitive sequence of interneuron activation and principal cell inhibition, again at gamma frequencies.

Conditions in which locally generated gamma rhythms foster synchrony between spatially separate areas lie between the above 2 extremes, in situations where somatic action potential generation in principal cells can influence the degree of interneuron excitation on a period-by-period basis. Convergence of local excitatory inputs to interneurons and distal excitatory inputs from feedforward projection pathways can result in multiple interneuronal action potential generation in each gamma period. In such a case, the time difference between the multiple interneuronal spikes effectively represents the conduction delay between coactive areas. Nonlinear interaction between this interspike interval and the kinetics of intrinsic interneuronal conductances ensures that the system converges onto a pattern of spike timings whereby the delay between areas is effectively ignored—thus producing long-range synchrony.

A large proportion of perisomatic-targeting interneurons responsible for gamma rhythmogenesis in the above situations are parvalbumin (PV) immunopositive, and in some regions, in adult cortex, these PV interneurons are strongly excited by NMDA receptor activation. In these regions, acute NMDA receptor blockade results in a decrease in excitation of PV-immunopositive interneurons and a concomitant decrease in phasic IPSPs onto principal cells. Thus, the main underlying mechanism of generation of gamma frequency population rhythms is disrupted. The anatomical profile of this decrease in gamma rhythmogenesis matches directly the location of decreased PV-immunopositive interneuron numbers in the lysophosphatidic acid (LPA1) knockout model of psychiatric illness—a model that involves removal of a receptor vital for positive modulation of NMDA receptor function, thus producing a chronic deficit in NMDA signaling. The loss of PV signal in these cells, induced by ketamine, involves coupling of NMDA receptors to neuronal redox state via reduced nicotinamide adenine dinucleotide phosphate oxidase, and evidence exists to specifically implicate the NR2A subtype of NMDA receptor in this loss of PV expression. Loss of PV expression colocalizes with loss of NR2A mRNA in schizophrenia, and selective NR2A antagonism mimicked the loss of PV expression produced by ketamine in cultured interneurons.

One particular issue is raised by this correlation between decreased gamma rhythmogenesis and loss of PV signal. Decreases in PV signal are seen in key brain regions implicated in schizophrenia pathology. However, genetic models of decreased PV expression can...
generate increased gamma rhythm power, via a possible boost in action potential–elicited synaptic GABA release, in hippocampus, in contrast to the decreases seen in entorhinal cortex with acute and chronic decreases in NMDA receptor function. So it appears that loss of PV expression alone can boost gamma rhythmogenesis, but loss of PV expression secondary to reduced NMDA receptor–mediated excitation cannot compensate for the decreases in gamma rhythm generation caused by reduced interneuronal excitability. None of these mechanisms alone can explain the increase in gamma power seen in vivo with acute ketamine. However, if glutamatergic dysfunction, particularly involving NMDA receptor blockade, is present during early cortical development, then an apparently permanent loss of interneuronal function can be induced that goes beyond loss of PV expression. In this situation, there is a loss of GABA immunopositivity in neurons, suggesting a failure of some interneurons to mature appropriately (eg, see also Costa et al and Akbarian and Huang). Any decrease in PV expression would fail to boost GABA release if GABA levels were also detrimentally affected.

Beta2 Rhythms in Schizophrenia and Models of Psychosis

Gamma rhythms are certainly not the only rhythms affected in schizophrenia. One band of EEG rhythm that deserves particular attention is the beta2 band (20–29 Hz). Frequencies in this range are sometimes included as part of the gamma band in data analysis, and the basic inhibition-based mechanisms underlying gamma rhythms have been shown experimentally to extend down into this range (see above). This may complicate interpretation of findings because evidence exists to show beta2 rhythms subserve a functionally separate range of functions to gamma rhythms, and an inhibition-independent beta2 rhythm is seen to be generated at the cellular/local circuit level by very different mechanisms to gamma rhythms (see below). Decreases in phase synchrony at beta2 frequencies are seen in schizophrenics during different cognitive tasks than those that reveal changes in gamma rhythms in the same subjects. These authors demonstrated that deficits in beta2 rhythm phase synchrony represented the major change in cortical dynamics seen and conclude that long-range synchrony of neuronal activity may represent a core deficit in schizophrenia. Brief bursts of beta rhythms prior to directed motor task execution are almost absent in schizophrenics, a finding that is of particular interest given the strong relationship between beta2 rhythms and motor anticipation. However, as with gamma rhythms, sometimes increases in power in this frequency band are observed. While the majority of task-related activity studies show decreases in beta2 activity, schizophrenics with auditory hallucinations also show an increase in resting beta2 power in parietal and frontal cortices.

Mechanisms Possibly Relevant to Disrupted Beta2 Rhythms

Relative to gamma rhythms, much less is understood about the mechanisms underlying cortical beta rhythm generation. Basic models of cortical dynamics, based on hippocampal circuits, show that beta rhythms are a much more effective substrate for establishing long-range synchronization with millisecond precision, an observation that fits with the particular deficits in long-range synchrony seen at beta2 frequencies in schizophrenics. In neocortex, it appears that different cortical subregions with different primary functions (eg, primary auditory vs secondary somatosensory cortex) generate spectrally identical beta2 rhythms via different mechanisms.
Of particular interest are the mechanisms underlying beta2 rhythms in association cortex. Here gamma and beta2 rhythms coexist in a laminar-specific manner\textsuperscript{58} (figure 3) and can exist independently of each other, strongly suggesting entirely separate mechanisms of generation.

In stark contrast to the mechanisms underlying gamma rhythm generation in neocortex, beta2 rhythms in association sensory areas do not depend on excitatory or, to a large extent, inhibitory synaptic transmission (figure 4). The primary neuronal subtypes involved are the layer 5 intrinsically bursting neurons, a population representing c.50\% of all cortical output neurons that also have long-range corticocortical collaterals. During population beta2 rhythms, these neurons receive only small, erratic
GABAergic synaptic inputs (figure 4A) despite beta2 frequency outputs from layer 5 fast-spiking interneurons (figure 4B). Interneurons in this area are strongly PV immunopositive, but their outputs appear to be detrimental to beta2 rhythm generation. Blockade of GABA_A receptor–mediated IPSPs, to a degree which abolishes coexistent gamma rhythms in superficial layers, actually significantly increased the power of beta2 rhythms (figure 4A). Also, in contrast to the mechanisms underlying gamma rhythms, the layer 5 beta2 rhythms were insensitive to AMPA receptor blockade (figure 4B).

Given the apparent absence of a role for conventional synaptic transmission in generating these beta2 rhythms, we need to understand how the population rhythm may be generated nonsynaptically. Layer 5 intrinsically bursting cells generate bursts in 2 ways: (1) a large burst discharge involving depolarization of somatodendritic compartments and (2) a more brief, rhythmic burst generated by intrinsic conductances (including m-current) in axons (figure 5B). During beta2 rhythms, recordings from individual layer 5 bursting cells show bursts of axonal origin occurring rhythmically, phase locked to the local beta2 population rhythm. The mechanism of local synchronization of these axonal bursts appears to be via electrical coupling of neurons. Paired recordings of layer 5 pyramidal cells, where at least one cell is an intrinsically bursting cell, reveal strong coupling of action potential generation in both cells (figure 5A). The source of this coupling is likely to be via gap junctions. Reduction in gap junction conductance with carbenoxolone abolishes layer 5 beta2 rhythms (figure 5), and detailed computational models of populations of bursting neurons in layer 5, using coupling via axo-axonic gap junctions, reproduce the beta2 rhythm with remarkable fidelity.

How can these predominantly nonsynaptic mechanisms explain what happens to beta2 rhythms in schizophrenia and with ketamine exposure? An increase in postsynaptic GABAergic inhibition, seen with loss of PV expression alone, would be expected to decrease beta2 power. However, a decrease in output from PV-immunopositive interneurons lacking NMDA receptor–mediated excitation would be expected to increase beta2 generation (cf, the effects of GABA_A receptor blockade, figure 4A). It is also possible that reduced NMDA receptor–mediated excitation onto intrinsically bursting pyramidal cells could boost beta2 power independently from any effects on interneurons. The somatodendritic pattern of burst generation in these pyramidal cells detrimentally affects the axonal, beta2-generating, rhythmic bursting mode. Removal of factors involved in dendritic bursting (eg, NMDA input or Ih conductance) produces a large increase in field beta2 power (Kramer MA and Roopun AK, unpublished data). From the data available to date, it is not clear which mechanism or combination of interrelated mechanisms, involving NMDA receptor blockade and disrupted interneuron function, is involved in changes in cortical dynamics at beta2 frequencies. For example, the laminar-specific pattern of PV expression in prefrontal cortex closely maps onto the laminar pattern of beta2 frequency generation (figure 6). In postmortem samples from prefrontal cortex in schizophrenics, this PV expression is reduced. However, ketamine application significantly increases the ability of prefrontal cortex to generate beta2 rhythms. Whether this is directly caused by reduced NMDA drive to layer 5 pyramidal cells and/or indirectly via acute reduction in interneuronal output remains to be elucidated.

Region-Specific Effects of Ketamine on Gamma and Beta2 Frequency Rhythms

The seemingly contrasting precedents for increased/decreased gamma and beta2 rhythm generation (and associated dynamic cortical interactions) in schizophrenia suggest complex underlying mechanisms. However, the ketamine model (primarily a simple reduction in NMDA receptor–mediated events) can also produce seemingly contrasting effects on brain rhythms (see above). We therefore wished to test the hypothesis that the diverse effects of ketamine on brain rhythms are a manifestation of region-specific and EEG band-specific effects on cortical rhythm generation. We used the in vitro cortical slice preparation to ensure that the rhythms studied in each cortical area of interest were locally generated. However, in doing this, we were unable to generate realistic sensory evoked responses (the majority of central sensory pathways being removed during slice preparation). We therefore used a model of background cortical activation more analogous to persistent, rather than sensory evoked or induced, activity patterns. Cortical active states (or “upstates”) have been shown to be mediated predominantly by kainate receptor activation, and tonic activation of kainate receptors by bath application of low concentrations of kainate itself robustly generates EEG-like rhythms in the gamma and beta bands.

Materials and Methods

Horizontal cortical slices (450 μm) were prepared from adult Wistar rats in accordance with The United Kingdom Animals Scientific Procedures Act (1986). Slices were maintained at 34°C at the interface between artificial cerebro pinal fluid (ACSF; composition in mM: NaCl [126], KCl [3], NaH2PO4 [1.25], NaHCO3 [24], MgSO4 [1], CaCl2 [1.6], and glucose [10]) and warm, moist carbogen gas (95% O2:5% CO2). Oscillations were induced by bath application of 100–400 nM kainate and ketamine applied
Population rhythms were recorded with extracellular electrodes pulled from borosilicate glass filled with ACSF and had resistances in the range of 2–5 MΩ. Peak frequency and power values were obtained from power spectra generated with Fourier analysis performed off-line from digitized data (digitization frequency 10 kHz) using a 60-s epoch of recorded activity.

Fig. 5. Nonsynaptic mechanisms of beta2 rhythm generation. (A) Layer 5 pyramidal cells are nonsynaptically coupled. Left panel: paired recordings from an intrinsically bursting pyramidal cell (IB) and a nearby pyramidal cell (A) showing reciprocal coupling in the form of spikelets arising from full action potentials in the coupled neuron. Figure from Mercer et al.59 with permission. Graph shows spectra from field potential recordings in layer 4 illustrating concurrent gamma and beta2 rhythms in control conditions (con, black line). Both gamma and beta2 rhythms were abolished on reduction of gap junction conductance with carbenoxolone (gap j. block, gray line). (B) Example traces showing concurrently recorded layer 5 field potential beta2 rhythm (ec) and intracellular somatic layer 5 IB neuronal activity (IB). Expanded section of the intracellular trace shows the occurrence of rhythmic spikelet bursts and occasional antidromically generated full action potentials. Scale bars 500 ms, 0.1 mV (ec), and 15 mV (IB). Expanded section scale bars 40 ms, 10 mV. Upper right graph shows spectra for concurrently recorded IB neuronal activity (IB) and the accompanying layer 5 field potential rhythm (ec). Note the modal frequencies of both are identical. Lower right graph shows the effects of decreasing m-current conductance (with the blocker linopirdine) on the frequency of the field potential rhythm. Example traces show how the decreased frequency, with decreased m-current, is accompanied by longer burst discharges in IB neurons. Figures reproduced from Roopun et al.57

at 10–20 μM. Population rhythms were recorded with extracellular electrodes pulled from borosilicate glass filled with ACSF and had resistances in the range of 2–5 MΩ. Peak frequency and power values were obtained from
Results

The kainate model of cortical rhythmogenesis is used to generate a permanent upstate in cortex—a state in which local circuits are active and persistently generate population rhythms in the beta/gamma band. In the present study, this model failed to generate any rhythmic population activity in perirhinal and medial orbital cortical areas (figure 7) and also failed to generate beta2 rhythms in hippocampus and gamma rhythms in prefrontal areas. It should be noted that the hippocampus has been shown to generate intrinsic beta rhythms but at frequencies below the 20- to 30-Hz beta2 range. While gamma rhythms can be readily recorded from frontal cortex in patients, it remains to be seen whether these rhythms are projected from the many regions feeding into frontal cortex or generated locally.

In hippocampus, gamma rhythms (30–50 Hz) were not affected by ketamine application. However, medial entorhinal cortical gamma rhythms were reduced by 74% in this model. In contrast, gamma rhythms were significantly increased in superficial layers of primary auditory cortex (63) in the presence of ketamine. Thus, in these 3 brain regions, entirely contrasting effects of acute NMDA receptor blockade with ketamine were seen. As each region has greatly differing cytoarchitecture (from archi- to neocortical organization), this suggests that differences in local circuit connectivity and neuronal subtypes present demand different local mechanisms of gamma rhythm generation. For example, gamma rhythms in hippocampus do not depend on the activity of fast rhythmic bursting neurons (they are not present), whereas gamma rhythms in superficial layers of auditory cortex are critically dependent on the output of this subtype of principal cell. The different effects of ketamine in each area may represent a difference in the number and network connectivity patterns of PV-immunopositive interneurons driven by NMDA receptor–mediated excitation. They may equally be the result of changes in the pattern of excitatory drive to region-specific principal cells. In vivo fast rhythmic bursting cells contribute to gamma rhythms more via excitatory synaptic input patterns than intrinsic properties. However, this subtype of principal cell is present in most neocortical regions, but no significant effects of ketamine were seen on gamma rhythms in any other cortical area moving frontally from the primary auditory cortex (P > .05, figure 7).

Beta2 frequency population rhythms were seen in entorhinal cortex and primary auditory cortex at low power but were seen predominantly in deep layers of secondary somatosensory, insular, and prelimbic cortices coexistent with gamma rhythm in the former 2 regions. Ketamine application did not reduce beta2 power significantly anywhere tested in this study. However, in secondary somatosensory and prelimbic cortex, a large, significant increase in beta2 power was seen (figure 7, P < .05). It was therefore evident that region-specific differences in the effects of ketamine on beta2 rhythms were present but failed to overlap with the region-specific effects on gamma rhythms.

Discussion

The study of neuronal population rhythms in schizophrenia is providing a great deal of evidence pointing to the underlying nature of cortical dynamic deficits in this syndrome. Overall, decreases in the ability of cortex to temporally organize activity within different cortical regions, both at gamma and beta2 frequencies, are commonly found. However, changes in absolute power in these frequency bands—as a measure of the brain’s ability to generate these rhythms during cognitive tasks—reveal contrasting findings dependent on region studied and

Fig. 6. Beta2 Frequency Population Rhythms in Prefrontal Cortex (PFC) Are Enhanced by Ketamine—Loose, Negative Correlation With Changes in Parvalbumin (PV) mRNA Seen in Schizophrenics. Image shows the laminar location of parvalbumin messenger RNA (PV mRNA) in human prefrontal cortex. Middle panel shows the quantification of PV mRNA signal for each lamina in control postmortem tissue (white bars) and postmortem tissue from schizophrenics (gray bars). Left and middle panels adapted and reproduced with permission from Lewis et al. Right panel shows data from slices of adult rat prefrontal cortex in the presence of kainate (400 nM). In these conditions, only beta2 frequency field potential oscillations are observed. Laminar distribution of beta2 rhythms in control conditions (white circles) reveals peak beta2 power in layers 3–5, where PV expression is the highest. In the presence of ketamine (gray circles), beta2 power is boosted throughout all laminae, with maximal increase in layer 2, where PV expression is low.
connectivity, across the cortex. Different frequencies will fail to support strong synchronization, though if present at harmonics of each other phase synchrony is possible.65 Also, simple mismatches in the relative powers, at the same frequency, between 2 regions can have detrimental effects on synchronization. If one area is excited to a greater degree than another, then phase separation can rapidly occur.66 Similarly, with nonreciprocal connectivity between regions, increasing the power of oscillations in the subservient cortical region dramatically changes the dynamics of the system.62 This relationship between relative power and synchrony between connected areas may provide a means to resolve the discrepancy between the pattern of elevated gamma generation under ketamine and the decreases in gamma generation seen in schizophrenics, despite the similarities in accompanying cognitive deficits. It may not be the absolute power in any given frequency band in any given brain region but the ability of different cortical areas to generate equivalent powers of oscillation that is important for effective cortical communication.

Second, the more complex issue of NMDA receptor dependence of the same frequency of network oscillation in different cortical regions has many implications for understanding modulation of cortical dynamics. To date, however, not enough is understood about the nature of local rhythm-generating circuits in many cortical areas to reach an informed conclusion. For example, differences in NMDA receptor subtype distribution may play a role. NMDA receptors have a laminar distribution pattern which may differ in different cortical regions,67,68 but overall levels of the main subtype NR1 do not differ much in different areas. In addition, opposing effects of ketamine were seen on gamma rhythm generation in medial entorhinal cortex and primary auditory cortex, but these areas have approximately the same overall levels of NR2A.69 Most NMDA receptors are present on principal neurons in cortex, but there is evidence to suggest that, at least some, interneurons receive intense glutamatergic excitation with a large NMDA receptor-mediated component.41 In schizophrenia, the situation is further complicated by observations of changes in a number of NMDA receptor subunits (ref. NR3A, NR2A–D) as well as altered levels of endogenous NMDA receptor antagonists.70,71 Thus, while more detailed analysis of neuron subtype-specific dependence on NMDA receptor subtypes in different brain regions may explain region specificity of ketamine’s action and its relationship to schizophrenia, currently, this seems unlikely.

The striking differences in ketamine’s effects on gamma rhythms in entorhinal and primary auditory cortex suggest different roles for receptor-driven fast-spiking interneurons in these 2 areas. While loss of PV and GABA immunoreactivity specifically in layer 2 was associated with a reduction in gamma rhythmogenesis in

---

**Fig. 7.** Anatomical Profile of Ketamine-Induced Changes in Gamma and Beta2 Rhythms. Upper image shows a schematic representation of the horizontal cortical slices used. Recording locations for the data in the graph below are shown as white circles. Black circles show recording positions where neither gamma nor beta2 rhythms were induced with bath application of kainate (up to 400 mM). Note, in addition, that no gamma frequency rhythms (30–80 Hz) were observed in prelimbic cortex (prelimb.), and no beta2 frequency rhythms (20–29 Hz) were observed in hippocampus (Hipp.). Graph shows pooled data (n = 5–7) for the percentage change in gamma (gray line) and beta2 (black line) rhythms 1 h after ketamine application. Note the marked region dependence of effects. Significant increases in beta2 rhythm power were seen only in association cortex (2r Som) and prefrontal cortex (prelimb.). In contrast, gamma rhythm power was significantly increased in primary auditory cortex (1r Au) and decreased in medial entorhinal cortex (mEC). PeriRh., perirhinal cortex; Insula, insular cortex; MOC, medial orbital cortex.
medial entorhinal cortex, blockade of any NMDA receptor–mediated excitation of fast-spiking cells in superficial auditory cortex had the opposite effect, significantly increasing gamma power. This latter result was in keeping with the in vivo data showing a potentiation of gamma rhythm generation in rats acutely exposed to ketamine. In schizophrenia, and with genetically reduced positive modulation of NMDA responses with LP1 Receptor ablation, PV-immunoreactive cell numbers are decreased only by 30%–40%. It is feasible, therefore, that the contribution to gamma rhythmogenesis by predominantly NMDA receptor-driven interneurons is different in different local microcircuits.

One also has to question whether changes in PV expression, in general, are causal or casual to the changes in cortical dynamics associated with schizophrenia. In the PCP model, increases and decreases in PV-immunoreactive neuron numbers are seen in region-specific manner. Transient enhancement of gamma rhythmogenesis appears directly related, in a modality-specific manner, to patients with hallucinations. In contrast, decreases in auditory evoked gamma rhythms are common in schizophrenics, but evidence for reduced visual evoked gamma changes are more equivocal. Given the growing corpus of evidence linking PV expression to, specifically, NMDA receptor–mediated excitation of interneurons (see above), these data suggest that PV expression may be secondary to an underlying deficit in glutamatergic neurotransmission. In particular, reduced PV expression–induced enhancement of GABAergic transmission and gamma rhythmogenesis would seem an efficient adaptive mechanism to maintain inhibitory tone in the absence of NMDA drive to certain interneuron subtypes. However, longer term NMDA receptor dysfunction, or dysfunction during early cortical development, may cause long-lasting deficits in the ability of PV-immunopositive interneurons to generate inhibition. Evidence for a broader spectrum of markers for disrupted GABAergic inhibition, including decreases in GABA and glutamic acid decarboxylase (GAD) levels, is seen in postmortem samples from schizophrenic patients. In addition, GAD1 gene polymorphisms are associated with risk of presenting with schizophrenia. A global, net decrease in GABAergic receptor–mediated inhibition from fast-spiking interneurons may explain both decreased gamma rhythmogenesis and increased beta2 rhythmogenesis in association cortical areas but would not explain the interareal differences seen in animal models and with different sensory modalities in schizophrenics.

Additional evidence for changes in interneuron function being secondary to altered glutamatergic synaptic transmission comes from a number of sources. For example, the disrupted in schizophrenia 1 model of schizophrenia features decreased principal cell dendritic arborization. Reduced dendritic arborization can be caused directly by reduced stability of glutamatergic synapse formation—a process that is initially critically dependent on NMDA receptor function through activation of silent synapses. A failure to generate mature synaptic connections may also preserve more immature forms of neuronal communication in which gap junction–mediated intercellular communication predominates. Enhanced gap junction–mediated coupling specifically between cortical principal neurons would enhance beta2 rhythms, particularly in association cortex.

In addition, reduced NMDA receptor input to layer 5 pyramidal cells enhances intrinsic beta2 rhythmogenesis directly, a process that may be compounded in chronic NMDA hypofunction models of schizophrenia by reduced GABAergic inhibition (eg, figure 4A).

In summary, while disrupted GABAergic inhibition may be directly responsible for changes in gamma rhythmogenesis in some cortical regions associated with schizophrenia, many regions and rhythms, such as beta2 oscillations, show a more complex interrelationship. We suggest that area-specific differences in the mechanism of activation of local rhythmic circuits are exposed by underlying pathology in schizophrenia, thus generating spatial imbalance in cortical dynamics detrimental to long-range cortical communication. These changes, some of which involve interneuron function, may all be secondary to various patterns of glutamatergic activation of cortical microcircuits, in particular involving NMDA receptor–mediated synaptic excitation. Anatomically diverse effects of NMDA receptor dysfunction on cortical dynamics, modeled at least in part by acute ketamine administration, may faithfully reproduce many of the complex changes in cortical dynamics observed in schizophrenics.

Funding
The Lena Teague Bequest for research into schizophrenia; The Medical Research Council UK; the National Institutes of Health (SROINS044133–04).

Acknowledgments
We thank Nancy Kopell and Judith Ford for valuable discussion.

References


47. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci.* 2005;6:312–324.


