Review

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# Alterations in Cortical Network Oscillations and Parvalbumin Neurons in Schizophrenia

Guillermo Gonzalez-Burgos, Raymond Y. Cho, and David A. Lewis

**ABSTRACT**

Cognitive deficits are a core clinical feature of schizophrenia but respond poorly to available medications. Thus, understanding the neural basis of these deficits is crucial for the development of new therapeutic interventions. The types of cognitive processes affected in schizophrenia are thought to depend on the precisely timed transmission of information in cortical regions via synchronous oscillations at gamma band frequency. Here, we review 1) data from clinical studies suggesting that induction of frontal cortex gamma oscillations during tasks that engage cognitive or complex perceptual functions is attenuated in schizophrenia; 2) findings from basic neuroscience studies highlighting the features of parvalbumin-positive interneurons that are critical for gamma oscillation production; and 3) results from recent postmortem human brain studies providing additional molecular bases for parvalbumin-positive interneuron alterations in prefrontal cortical circuitry in schizophrenia.

*Keywords:* Cognition, GABA, Gamma oscillations, Inhibition, Prefrontal cortex, Working memory

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The core cognitive deficits of schizophrenia (1) are poorly responsive to available medications (2). Thus, understanding the neural basis of these deficits is critical for the development of new therapeutic interventions. Cognitive neuroscience studies suggest that synchronous oscillations in network activity are essential for cortical information transfer during cognitive tasks (3,4). Oscillations, as detected by electroencephalography (EEG) and magnetoencephalography (MEG), are a measure of synchronous population activity because the contribution of single neuron activity to the EEG/MEG signal is negligible. Analysis of the EEG/MEG signal during performance of cognitive tasks has revealed oscillatory activity in various frequency bands, including theta (~4–8 Hz), alpha (~8–13 Hz), and gamma (~30–80 Hz) (4). Cortical gamma oscillations increase in power during tasks requiring complex processing of sensory information, attention, working memory, and cognitive control, suggesting that gamma oscillations are crucial for cognition (3,5,6). Importantly, substantial evidence indicates that relative to healthy comparison subjects, individuals with schizophrenia show lower power of gamma oscillations induced during the performance of cognitive tasks (7–10). Moreover, schizophrenia is associated with alterations in cortical circuitry, including gamma-aminobutyric acid (GABA) neuron-mediated synaptic inhibition (11). Given that gamma oscillations are thought to be directly dependent on synaptic inhibition (12), cognitive dysfunction in schizophrenia has been suggested to be a consequence of alterations in GABA-mediated inhibition (13).

Many GABAergic interneuron types mediate fast synaptic inhibition in neocortical circuits. Although our understanding of cortical interneuron biology is rapidly increasing, the substantial diversity of interneuron properties has precluded as yet the development of a complete GABAergic interneuron classification and the determination of the functional role of each interneuron subtype (14,15). Interneuron classes can be distinguished via the differential expression of three calcium binding proteins, calbindin, calretinin, and parvalbumin (PV), and of neuropeptides such as somatostatin, cholecystokinin, and vasoactive intestinal peptide (14,15). One of the best studied interneuron classes selectively expresses PV, does not contain any known neuropeptides, and provides perisomatic inhibition onto excitatory pyramidal cells (16). Importantly, PV-positive GABA neurons play a key role in the production of gamma oscillations (12). For example, although several classes of GABA neurons are active during gamma oscillations (17), PV neuron activity shows the strongest coupling to the gamma oscillation cycle (17,18). In addition, partially reducing PV neuron activity via optogenetic methods significantly attenuates the power of gamma oscillations (19), whereas nonrhythmic stimulation of PV neurons generates a gamma rhythm (19).

However, it is important to note that PV neuron control of pyramidal cell firing also contributes to other patterns of cortical network activity (20,21). Moreover, schizophrenia is associated not only with alterations in PV neurons (11) but also with disturbances in somatostatin- and cholecystokinin-positive interneurons (22). Thus, cognitive deficits in schizophrenia could arise from alterations in a range of sources of synaptic inhibition (23) leading to disturbances in various patterns of cortical network activity and cognition.

It is also important to note that although the PV neuron disturbances in schizophrenia are consistent with lower gamma oscillation power, some studies have reported that the power of resting state gamma oscillations (i.e., measured



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when subjects are not explicitly engaged in a behavioral task) may be increased in schizophrenia [reviewed in (24)]. However, such differences in resting state power are typically broadband and not restricted to the gamma frequency range, suggesting that they reflect different processes than those specifically engaging synaptic inhibition to generate gamma oscillations (25).

Finally, although PV cell (26) and gamma oscillation (27–30) disturbances extend across cortical regions in schizophrenia, prefrontal regions have been most thoroughly investigated in postmortem studies and show greater gamma oscillation deficits compared with more posterior cortical regions during cognitive tasks in subjects with schizophrenia (31). Thus, this review focuses on the potential mechanisms linking prefrontal cortical PV neuron and gamma oscillation disturbances in schizophrenia.

In the following sections, we review recent findings 1) in support of the idea that gamma oscillations induced during cognitive tasks are attenuated in subjects with schizophrenia; 2) on the role of PV neurons in the mechanisms of normal gamma oscillations; and 3) on molecular alterations of PV neurons in schizophrenia and how these might arise and contribute to alterations in gamma oscillations.

## FRONTAL CORTICAL GAMMA OSCILLATION DISTURBANCES IN SCHIZOPHRENIA

Gamma oscillation disturbances in schizophrenia have been reported in numerous EEG and MEG studies. These measures index the summed synchronous activity of millions of neurons, with substantial contribution from postsynaptic potentials in apical dendrites of pyramidal cells, owing to their parallel alignment that allows spatial summation (32), although the signals are also shaped by currents from other cell types and compartments (25). EEG/MEG studies thus likely assess the neurophysiological consequences of the cellular and molecular changes that have been characterized in the types of postmortem human studies described below.

Cortical circuits engage in oscillatory behavior via multiple mechanisms, but all cortical gamma oscillations are thought to emerge from network interactions (33) and to critically depend on GABA inhibition (34), as described in the next section. Studying synchronous oscillations in cortical circuits requires spectral analytic methods that index amplitude and phase information as appropriate to different contexts in which such oscillatory activity can arise [for review see (35–37)]. These include 1) activity occurring during the resting state; 2) stimulus-elicited activity that is evoked by a stimulus, is time- and phase-locked to that stimulus, and is thought to generally reflect sensory processing; and 3) induced activity that is not phase-locked to the stimulus and is thought to reflect higher order perceptual and cognitive processing. A variant of evoked activity paradigms are those that measure the auditory steady state response to periodically varying auditory stimuli. These different forms of oscillatory activity have all been studied in schizophrenia, and in most studies, the findings generally show lower power of gamma oscillations. The investigations most directly relevant to the postmortem findings in schizophrenia reviewed below (which have largely focused on the dorsolateral prefrontal cortex [DLPFC]) are the studies employing working memory and cognitive control tasks. Performance on these tasks relies critically on the integrity of DLPFC circuitry and is impaired in schizophrenia. Accordingly, these studies are the primary focus of this section.

One study employed a cognitive control task that involved cued stimulus-response mapping reversals, a paradigm that had previously revealed DLPFC deficits in a neuroimaging study of first-episode schizophrenia patients (38). In this task, healthy comparison subjects showed modulations in frontal gamma oscillations during the delay period in response to cognitive control demands, whereas patients with schizophrenia lacked such modulation in association with performance impairments (7). Similar deficits were found in first-episode schizophrenia patients performing the same task regardless of medication status (9), suggesting that these alterations in induced gamma oscillations reflect the underlying disease process and are not a consequence of illness chronicity or antipsychotic medications.

A number of studies have used classic working memory paradigms, including the Sternberg task, which induces gamma oscillations, the power of which increases parametrically with load (39). In a variant of this task, patients with schizophrenia showed modulations of gamma oscillations comparable with healthy control subjects early in the maintenance phase (8). However, later in the maintenance phase, healthy control subjects exhibited peak frontal gamma oscillations at the highest of three load conditions, whereas the peak in patients occurred with the intermediate load and failed to increase at the highest load in association with lower working memory capacity (8). A multimodal imaging study that acquired EEG during Sternberg working memory performance and magnetic resonance spectroscopy (MRS) measures of GABA in the same subjects found frontal gamma oscillation deficits in association with performance impairments in schizophrenia subjects (10). MRS GABA measures correlated with gamma activity, although this association was considered preliminary due to small sample sizes that required the pooling of patient and control data.

Other studies have investigated gamma oscillations during n-back working memory task performance, examining evoked, as opposed to induced, gamma oscillations. One n-back study reported a load-by-group interaction driven by the expected poststimulus parametric increases in gamma activity for healthy control subjects, whereas schizophrenia patients showed elevated gamma amplitudes that did not vary with load (40). However, interpretation of these findings is limited by a small sample size and the particular measure of evoked gamma activity employed (peak amplitude of event-related potentials band-passed filtered for gamma, which may or may not reflect oscillatory activity). A larger sample n-back study similarly reported elevations in evoked gamma activity in schizophrenia, though the interpretation is unclear, as the period over which evoked activity was averaged was 3 seconds (41), extending much beyond the early sensory processing that evoked responses are thought to reflect (36).

Other studies have generally shown convergent support for lower frontal gamma activity in schizophrenia. Studies using auditory oddball paradigms reported reduced evoked (42) and induced gamma activity (43) and also reduced phase-locking factor (degree of phase consistency across trials) (44,45).