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Alterations in Cortical Network Oscillations and Parvalbumin Neurons in Schizophrenia

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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 (PV) interneurons that are critical for gamma oscillation production and 3) results from recent postmortem human brain studies providing additional molecular bases for PV interneuron alterations in prefrontal cortical circuitry in schizophrenia.

Keywords

Gamma Oscillations; Prefrontal Cortex; Working Memory; GABA; Inhibition; Cognition

Introduction

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

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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 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 non-rhythmic 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 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 broad-band 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 post-mortem studies and show greater gamma oscillation deficits compared to 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 the gamma oscillations induced during cognitive tasks is 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 electroencephalography (EEG) and magnetoencephalography (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 which 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 post-mortem 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 which 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 which 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 (ASSR) 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 post-mortem 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 to healthy controls early in the maintenance phase (8). However, later in the maintenance phase, healthy controls 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 which 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 post-stimulus parametric increases in gamma activity for healthy controls, 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 three 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). A MEG study of mental arithmetic found lower induced left frontal gamma activity at low frequency sub-bands (30–45 Hz), but higher right frontal and fronto-temporal activity at higher frequency sub-bands (46–71 Hz) (46), suggesting disturbances of specific sub-bands of the gamma range. Although not probing prefrontal circuits specifically, ASSR paradigms provide convergent support for such frequency specificity, consistently identifying 40 Hz deficits in schizophrenia (27;29;30;47;48),

including a study that sampled sub-bands from the gamma range, and found deficits in the 30–45 Hz range for phase-locking factor and total power in patients (30). Another study combined transcranial magnetic stimulation (TMS) with EEG to probe for gamma deficits in schizophrenia; relative to healthy controls the natural frequency responses in the frontal regions of the schizophrenia subjects were lower in the gamma range (31).

The frontal gamma oscillation literature has largely reported on frontal scalp electrode data with an assumed underlying frontal source, but that this can only be indirectly inferred. FMRI studies provide convergent evidence of prefrontal cortical deficits (49), and close associations between the fMRI BOLD signal and gamma oscillations (50;51) provide indirect links to frontal cortical sources for the reported gamma oscillation disturbances. However, studies conducting source-based analyses will be required in order to make more direct claims concerning frontal sources. As a related issue, the findings reported for induced (non-phase-locked to stimulus presentation) oscillations in the gamma range are potentially confounded by electromyographic activity associated with miniature saccades (52). Although it seems unlikely that such effects could explain all task condition-related and group differences in gamma oscillations reported in the literature, refined data acquisition and analytic methods for addressing this issue will need to be adopted to more definitively exclude this potential confound (53;54).

Role of PV neurons in the production of gamma oscillations

The neural mechanisms that generate gamma oscillations are still under active investigation, but GABA-mediated inhibition appears to be a key element (4;12). Our current understanding of gamma oscillation generation is based mainly on computational modeling studies and experiments in rodent hippocampus, and the mechanisms underlying gamma oscillations in the DLPFC of humans and non-human primates have not been directly assessed. However, several lines of evidence suggest that the mechanisms of inhibition-based gamma oscillations are highly conserved across cortical regions and mammalian species (55). Consistent with this view, certain properties of perisomatic inhibitory postsynaptic currents in pyramidal neurons that are crucial for gamma oscillation production are present across cortical regions and species, including the macaque monkey DLPFC (56). The two main mechanisms proposed for the production of gamma oscillations are the Interneuron Network Gamma (ING) and Pyramidal Interneuron Network Gamma (PING) models (33). Depending on specific conditions, either ING or PING may be the prominent mechanism (12), but the aggregate data favor the PING model as the likely mechanism for the types of neocortical gamma oscillations that are altered in schizophrenia. In the PING model, strong inhibitory input from PV-containing basket interneurons transiently silences the activity of a local population of asynchronously firing pyramidal neurons; following decay of the inhibitory effect, the postsynaptic pyramidal cells fire in synchrony (Figure 1A). If synaptic inhibition is rhythmic at gamma frequency, then the pyramidal cell activity becomes rhythmic as well (33;57), generating a synchronous gamma oscillation in the network.

The PING model is favored for several reasons. For example, during the gamma oscillation cycle, whether studied in vivo or in vitro, interneurons fire a few milliseconds later than

pyramidal cells (58). This finding is consistent with the monosynaptic recruitment of interneurons in the PING model and contrasts with the synchronous firing of pyramidal cells and interneurons in ING models (59). Moreover, removing the inhibition crucial for ING by genetically deleting $GABA_A$ receptors in PV neurons does not affect gamma oscillations (60), whereas removing the phasic excitation crucial for PING (33) by AMPA receptor (AMPAR) deletion in PV cells markedly disrupts gamma oscillations (61).

Typically, both AMPAR and NMDA (NMDAR) receptors mediate the excitatory post synaptic currents (EPSCs) at glutamate synapses. Interestingly, relative to AMPAR, the NMDAR component of the EPSC is quite small in glutamate synapses onto PV neurons compared with that present in pyramidal cells and in non-PV GABA neurons (62–72). Since AMPAR EPSCs have a much shorter duration than NMDAR EPSCs, a primarily AMPAR-mediated activation of PV neurons is consistent with the narrow time window of PV neuron recruitment observed during the gamma cycle (58). Indeed, the short-lasting EPSCs produced by a much larger AMPAR than NMDAR contribution in PV neurons are critical for the recruitment of PV neurons during gamma rhythms, since prolongation of the EPSC by increasing the NMDAR component to synapses onto PV neurons in a computational PING model markedly attenuates gamma band power by reducing the temporal precision of PV cell firing (68). These data show that PING model oscillations require fast kinetics in both inhibitory postsynaptic currents (56) and in EPSCs.

Consistent with the importance of a large AMPAR contribution for the recruitment of PV neurons, both the temporal precision of oscillatory PV neuron firing and gamma oscillation power are reduced when the strength of AMPAR EPSCs in PV neurons is decreased by genetic deletion of AMPAR subunits (61). Fast and strong AMPAR-mediated excitation of PV neurons is also important for the synchronization of local gamma oscillations across distant sites (73). The fast AMPAR EPSC in PV neurons is mediated by GluA2 subunit-lacking, GluA4 subunit-containing AMPARs that generate shorter EPSCs (61;67;70). The selective expression of GluA4 AMPARs at excitatory synapses onto PV neurons may depend on the neuronal activity-regulated pentraxin (NARP) (74). NARP, an AMPAR subunit binding protein expressed by pyramidal cells, is secreted in an activity-dependent manner selectively at synapses onto PV neurons, where it promotes clustering of GluA1 and GluA4 subunit-containing AMPARs (74). Via this AMPAR clustering, NARP substantially regulates the excitatory drive onto PV neurons in response to changes in neuronal network activity (74;75). GluA4-containing AMPARs have higher Ca^{2+} permeability than GluA2-containing AMPARs, a feature that may be crucial for plasticity at synapses onto PV cells (76), which is NMDAR-independent (77;78). Plasticity at glutamate synapses on PV neurons is crucial for homeostatic changes in gamma oscillations generated in response to variations in excitatory drive onto PV cells, which, as reviewed below, may occur in schizophrenia.

PV neurons comprise two main morphological subtypes, basket cells, which target the soma and proximal dendrites of pyramidal cells, and chandelier neurons which target the initial segment of the pyramidal cell axon. Most studies reporting large AMPAR and small NMDAR EPSCs in PV neurons either focused on basket cells or did not report the morphology of the PV neurons examined (62;63;65–70). Thus, although not the case for

basket cells, it is possible that NMDARs at inputs onto chandelier neurons are important for recruiting this class of PV neurons during network activity. However, chandelier neurons may not be involved in gamma oscillations. For instance, gamma oscillation power is largely depressed by opioid receptor activation, which also markedly depresses synaptic inputs from PV basket cells onto pyramidal neurons, but leaves chandelier neuron inputs intact (79). Importantly, although both basket and chandelier neurons are active during gamma oscillations (80;81), basket cell activity is more strongly coupled with the population gamma rhythm in vivo (81), and chandelier neuron firing is not synchronized with the in vitro gamma rhythm (80). Finally, although PV neurons synchronize pyramidal cell firing via inhibition, chandelier neuron inputs may actually have an excitatory effect (82), although such an effect may depend on the cortical region (83;84) or the excitation state of the pyramidal cell network (85). Thus, it appears that PV basket cells, and not PV chandelier cells, are critical for gamma oscillations, and that the excitatory inputs to PV basket cells must have the fast decay kinetics mediated by GluA4-containing AMPARs in order to achieve the temporal precision of firing required for gamma frequency oscillations.

Temporal precision of PV neuron firing during the gamma oscillation cycle requires short-lasting fast excitatory postsynaptic potentials (EPSPs). Whereas a short EPSC duration determined by a large AMPAR to NMDAR contribution is a major mechanism for the short EPSP in PV neurons (62;68), the particular intrinsic properties of the PV neuron membrane may contribute as well. For instance, the fast EPSP decay depends on the low resistance and short time constant of the PV cell membrane, determined by the expression of inward rectifier potassium (K^+) channels and of channels of the TASK subfamily of two-pore domain-containing K^+ channels (86;87). Moreover, depolarization by the EPSPs could gate voltage-dependent K^+ channels (Kv) to shorten the EPSP duration (88–90). Interestingly, the Kv3.1 and Kv3.2 channels that are strongly expressed by PV neurons (91) and are crucial for the fast-spiking phenotype of these cells (92), may also contribute to the short EPSP duration and thus the narrow time window of EPSP summation in these cells (16;90).

Cortical parvalbumin neurons in schizophrenia

Lower mRNA and protein levels of the GABA synthesizing enzyme, glutamic acid decarboxylase 67 kD isoform (GAD67), but not of GAD65 (93), have been consistently observed in the DLPFC of schizophrenia subjects (94–102), suggesting that altered GABA synthesis is a conserved feature of the disease process. Moreover, lower cortical GAD67 mRNA levels appear to not be a consequence of illness chronicity (103), of factors that are frequently co-morbid with schizophrenia, or of medications used to treat the illness (101). Although other GABA cell types may be affected, GAD67 mRNA levels are lower in PV neurons (104) and GAD67 protein levels are lower in the axon terminals of PV basket cells (101) in schizophrenia. In addition, PV mRNA levels are lower in schizophrenia (26;104;105) as are PV protein levels, including specifically in the axon terminals of PV basket cells (106). However, PV neuron density in the DLPFC is unaltered in the illness (107), indicating that the contribution of PV neurons to cortical pathology in schizophrenia is due to alterations in their activity and not to their absence. Lower GAD67 levels in PV basket cell terminals is likely to decrease the strength of basket cell inhibitory inputs onto

pyramidal neurons (108) and could be the basis for a decrease in gamma oscillation power (Figure 1).

Two different hypotheses have been proposed to account for lower levels of GAD67 in PV neurons in the DLPFC, and thus for their potential contribution to altered gamma oscillations and cognitive deficits, in schizophrenia. One hypothesis holds that the primary problem resides in PV neurons (Figure 1B), whereas the other posits that the problem is "upstream" in the pyramidal neurons that innervate PV neurons (Figure 1C). In the former view, lower GAD67 in PV neurons leads to disinhibition of pyramidal cell firing (107). According to the latter hypothesis, a decrement in the number of dendritic spines on layer 3 DLPFC pyramidal cells (109;110), which receive most of the excitatory synapses to pyramidal cells (111), renders these neurons less active. These hypoactive pyramidal cells cause lower local network activity, leading to a homeostatic down-regulation of inhibition, which manifests, in part, as lower GAD67 expression in PV neurons (the principal class of GABA neurons receiving input from the local axon collaterals of DLPFC pyramidal neurons (112)) and consequently reducing the amount of GABA available for synaptic transmission from PV neurons. The resulting decrease in inhibition thus contributes to the partial restoration of excitatory-inhibitory balance, albeit at a lower level of both excitation and inhibition relative to the normal state (107). Although the determination of which hypothesis provides the most compelling account requires further testing, recent studies shed some additional light on each.

A primary problem in PV neurons could be manifest as altered levels of gene products that are selectively expressed in these neurons. Interestingly, KCNS3, the gene encoding the Kv9.3 voltage-gated K^+ channel modulatory α subunit, is selectively expressed in PV neurons (113). Kv9.3 subunits form heteromeric channels with Kv2.1 α subunits which are encoded by the KCNB1 gene (114–116) and are expressed by most cortical neurons including PV cells (117). Compared with Kv2.1-only channels, Kv2.1/Kv9.3 channels have faster activation, slower deactivation and inactivation, and a relatively hyperpolarized activation curve (114;115), suggesting they may be activated by subthreshold membrane depolarizations. Thus, Kv2.1/Kv9.3 channel activation may contribute to the faster decay of EPSPs in PV cells compared to other types of cortical neurons (118–120). If so, then Kv channels may shorten the time window for EPSP summation (90), favoring recruitment by synchronized versus asynchronous excitatory inputs (16). Interestingly, both KCNS3 and KCNB1 mRNAs are markedly lower in DLPFC PV neurons in schizophrenia, suggesting a down-regulation of Kv2.1/Kv9.3 channels in these neurons (121). Since Kv2.1/Kv9.3 channels may contribute to the fast EPSP decay and a narrow time window for EPSP summation, their down-regulation could lead to altered recruitment of PV neurons, specifically during the gamma oscillation cycle, contributing to impaired gamma oscillations in the DLPFC during cognitive tasks.

Alternatively, lower KCNS3 and KCNB1 mRNA levels in PV neurons could reflect overall reductions in K^+ voltage-gated channels, which might occur as a compensatory response to a lower excitatory input from pyramidal neurons. Lower pyramidal neuron activity is the expected consequence of the reduced dendritic spine number (109;110), and presumably excitatory inputs to layer 3 pyramidal neurons in the DLPFC (111). In experimental

reductions of network activity levels, both pyramidal cells and interneurons respond by increasing their excitability in order to maintain their probability of firing in the face of the lower excitatory drive (122–125). Such an increase neuronal excitability can be achieved by reducing K^+ channel expression. Although K^+ channel expression has not been studied specifically in pyramidal cells, gray matter levels of Kv3 channel proteins, crucial regulators of PV neuron excitability (92), are lower in schizophrenia (126). Reduced Kv2.1/Kv9.3 K^+ channel levels (113) could also contribute as part of a homeostatic response, as these channels likely participate in control of PV neuron firing. But since both Kv3 and Kv2.1/Kv9.3 channels may shorten EPSP duration (90;113), changes in these K^+ channels could also produce a partial loss of the capacity for coincident input detection, altering PV neuron recruitment and thus gamma oscillation power.

If the upstream problem is lower pyramidal cell activity, what mechanism might lead to reduced GAD67 expression in PV neurons? Importantly, because GAD67 expression is heavily regulated by neuronal activity (127;128), disease-related alterations in activity-dependent regulatory factors could contribute to lower GAD67 levels (107). For example, the transcriptional regulatory factor Zif268 binds to the promoter region of the GAD1 gene (129;130) and can regulate GAD67 expression (131). Zif268 mRNA levels are lower in the DLPFC of schizophrenia subjects (132–134), and expression levels of Zif268 and GAD67 mRNAs are positively correlated in these subjects (134). Furthermore, Zif268 mRNA is heavily expressed in PV neurons in the human DLPFC and its expression is lower in these neurons in schizophrenia (134). These findings suggest that reduced transcription of Zif268 may mediate the lower expression of GAD67 in PV neurons in schizophrenia in response to a deficit in excitatory drive from neighboring pyramidal cells.

How the types of shifts in excitatory-inhibitory balance described above affect network gamma oscillations is a topic of growing interest. For example, computational studies have highlighted the important role of PV cell excitability in modulating network gamma oscillations (29;68;135), including demonstrations of cell type-specific effects (135). In addition, the development of novel experimental methods in the form of optogenetics (19) and DREADD (Designer Receptors Exclusively Activated by Designer Drugs) approaches (136) have provided the basis for explicit cell type-specific empirical investigations of the effects of excitatory-inhibitory balance shifts on gamma oscillations. Together, such computational and empirical approaches could provide a powerful framework for adjudicating between competing hypotheses concerning the role of PV cells alterations in gamma oscillation disturbances in schizophrenia.

Conclusions

Substantial evidence supports 1) gamma oscillation disturbances in schizophrenia, 2) an important role of PV neurons in gamma oscillation production and 3) molecular alterations in PV neuron in the illness. How directly are these findings connected? As noted above, MRS measures of DLPFC GABA and gamma power during a working memory task were correlated across schizophrenia and control subjects (10). Indeed, MRS GABA measures and visually-induced peak gamma frequency were positively correlated in healthy subjects (137), but this association was not replicated (138) and several other MRS studies of GABA

levels in schizophrenia reported conflicting findings (139). Importantly, MRS cannot distinguish between synaptic vs. intracellular stores of GABA, nor can it index changes in GABA receptor occupancy following release. Positron emission tomography (PET) imaging can specifically index shifts in GABA receptor ligand binding (140). This "GABA shift" measure provides a direct estimation of the availability of extracellular GABA to bind to $GABA_A$ receptors, although the population of receptors assessed (e.g., activated by GABA released by PV neurons versus other interneuron subtypes) cannot be determined. Studies using the GABA shift PET paradigm and taking EEG measures from the same subjects performing a cognitive control task found 1) positive correlations between GABA receptor binding strength and delay-related EEG gamma activity in healthy controls (140;141) and 2) a deficit in the capacity to increase extracellular cortical GABA levels in subjects with schizophrenia that was associated with lower gamma oscillation power during a cognitive task (142). Application of this paradigm using GABA receptor ligands selectively acting at PV neuron output synapses may help to further assess the relation between PV neuron alterations and gamma oscillation deficits in the illness.

In vivo measures of GABA level variations have also been associated with schizophrenia-associated genetic polymorphisms in ErbB4 (143); the neuregulin 1-NRG1-ErbB4 signaling pathway plays an important role in PV interneuron development (144). Integration of such measures of genetic variation with PET and EEG approaches could yield useful in vivo information regarding the relationship between PV cell function, GABA neurotransmission and gamma oscillations. Pharmacological approaches have also been tried to ameliorate PV cell GABA neurotransmission deficits in schizophrenia. Administration of a positive allosteric modulator with relative selectivity for α2-containing GABA-A receptors demonstrated increased power of gamma oscillations during cognitive control tasks (145), but a subsequent study failed to find evidence of improvements in cognitive performance (146). Future pharmacological studies could use drugs with greater potency for GABA-A receptors containing an α2 subunit (147) or that target other PV cell receptor subtypes such as α1 subunit GABA-A receptors which are also disturbed in schizophrenia (26) and possess the fast kinetics necessary for gamma oscillations.

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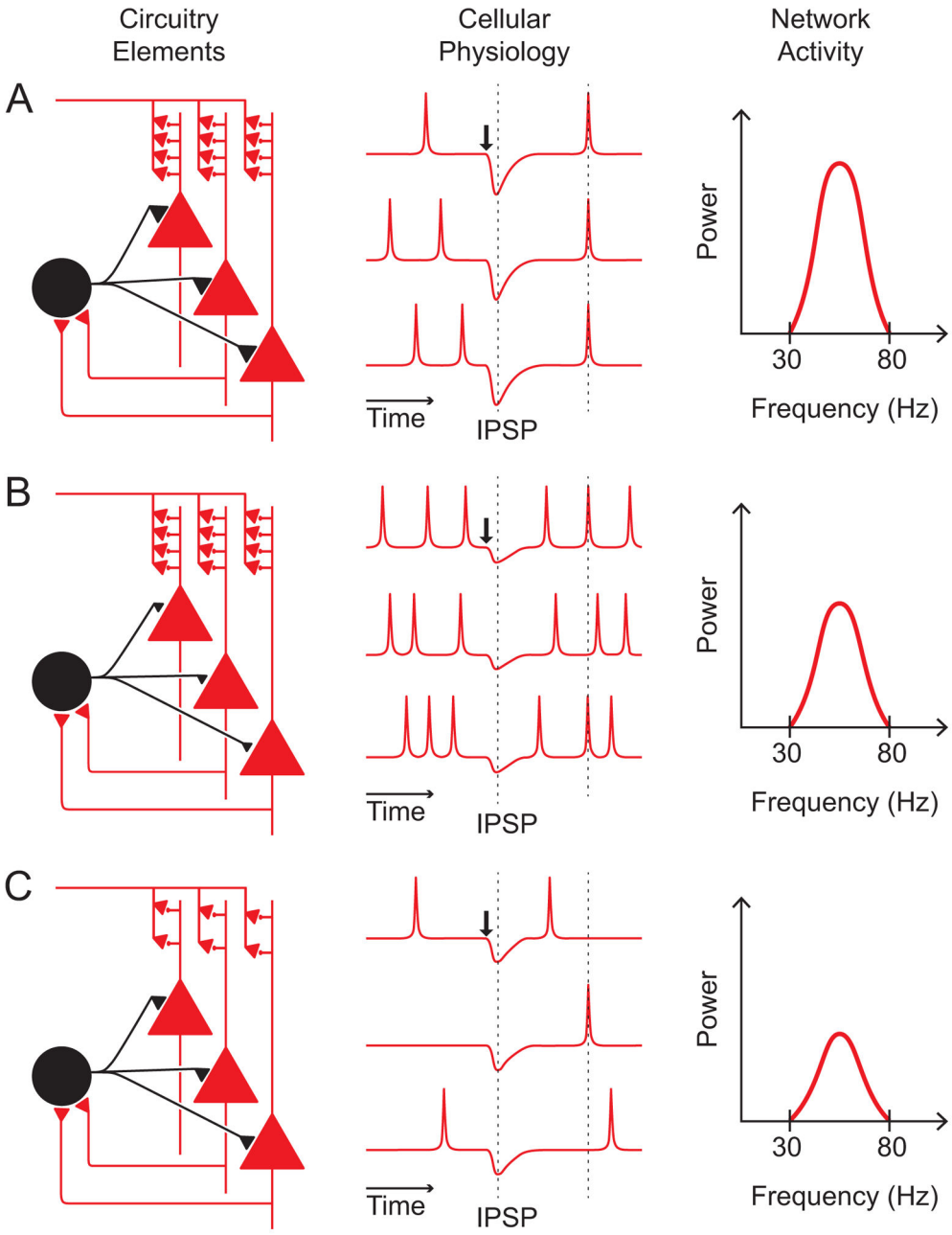

Figure 1. Hypothesized role of cortical layer 3 circuitry elements in the cellular physiology that generates gamma oscillations

A. Healthy state. Left) Excitatory inputs (small red triangles) to layer 3 pyramidal cells (red neurons), their excitatory inputs to PV basket cells (black neurons) and their distributed feedback inhibition (small black triangles) to pyramidal cells are all normal. Middle) Traces illustrate the changes in membrane potential, including spikes and inhibitory postsynaptic potentials (IPSPs), as a function of time, for the three pyramidal cells in the left panel. Under conditions (e.g., demands of a working memory task) that trigger pyramidal-interneuron gamma (PING) oscillations (black arrow), the firing of the PV basket cell produces simultaneous IPSPs in all innervated pyramidal cells. When this inhibition decays, the

pyramidal cells fire in synchrony and depolarize the PV basket cell, causing the process to repeat, producing an oscillatory pattern of synchronized pyramidal cell firing. The decay period of PV basket cell inhibition causes the oscillation to occur at 30–80 Hz or gamma frequency. The vertical dotted lines indicate the timing of the IPSP (left line) and of synchronous pyramidal cell activity (right line). Right) Due to the strength of both excitation and inhibition in the circuit, the power of the gamma oscillation is high. ***B. Schizophrenia as a state of weaker inhibition because of an alteration intrinsic to PV neurons.*** Left) Excitatory inputs to pyramidal cells are normal but feedback inhibition from PV cells is very weak (black triangles smaller than in A). Middle) At baseline (e.g., before the PING trigger), excitatory drive to pyramidal cells is normal but inhibition is very weak (IPSP size markedly reduced compared to A); as a result, pyramidal cells are “disinhibited” and overall fire more asynchronous spikes than in the healthy state. Under conditions (e.g., demands of a working memory task) that trigger PING, the small IPSPs evoked by PV basket cells are insufficient to synchronize the firing cycle of all pyramidal cells. Right) Fewer pyramidal cells firing in synchrony results in lower gamma band power. ***C. Schizophrenia as a state of weaker excitation because of an alteration intrinsic to pyramidal neurons.*** Right) Due to a reduced number of dendritic spines, excitatory drive to pyramidal cells is low, which elicits a compensatory reduction in the strength of feedback inhibition from PV basket cells. Middle) At baseline, pyramidal cells show low activity. Under conditions (e.g., demands of a working memory task) that trigger PING, the compensatory reduction in feedback inhibition provided by PV basket cells reduces the capacity of PV basket cell-mediated inhibition to synchronize pyramidal cell activity. Right) The combination of weak excitation, that reduces pyramidal cell activity, and reduced feedback inhibition in the circuit leads to very low gamma band power. Although not shown for the sake of clarity, it is important to note that the changes strength of inhibition and excitation shown in panels B and C could also have an impact on the peak frequency and bandwidth of gamma oscillations