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Review

Alterations in cortical interneurons and cognitive function in schizophrenia

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ABSTRACT

Certain clinical features of schizophrenia, such as working memory disturbances, appear to emerge from altered gamma oscillatory activity in the prefrontal cortex (PFC). Given the essential role of GABA neurotransmission in both working memory and gamma oscillations, understanding the cellular substrate for their disturbances in schizophrenia requires evidence from *in vivo* neuroimaging studies, which provide a means to link markers of GABA neurotransmission to gamma oscillations and working memory, and from postmortem studies, which provide insight into GABA neurotransmission at molecular and cellular levels of resolution. Here, we review findings from both types of studies which converge on the notions that 1) inhibitory GABA signaling in the PFC, especially between parvalbumin positive GABAergic basket cells and excitatory pyramidal cells, is required for gamma oscillatory activity and working memory function; and 2) disturbances in this signaling contribute to altered gamma oscillations and working memory in schizophrenia. Because the PFC is only one node in a distributed cortical network that mediates working memory, we also review evidence of GABA abnormalities in other cortical regions in schizophrenia.

1. Introduction

Schizophrenia, a debilitating psychiatric illness affecting 0.5-1% of the global population, typically presents with a constellation of positive, negative, and cognitive symptoms (Lewis and Lieberman, 2000). Although positive symptoms (hallucinations and delusions) are the most striking feature of the illness, cognitive disturbances are typically present before the onset of psychosis and are the best predictor of long-term functional outcome (Green, 1996; Kahn and Keefe, 2013). The affected domains of cognition include working memory, executive function, learning and long-term memory, visual/auditory perception, and attention (Carter et al., 2008). Among these, the deficits in working memory (i.e., the ability to transiently maintain and manipulate information for a limited period of time in order to guide thought or behavior) appear to be central to the cognitive impairments in the illness, serving as the substrate for impairments in other cognitive domains, such as visual orientation, memory for faces or objects, and executive function (Silver et al., 2003). Together, these findings suggest that working memory deficits represent a core feature of schizophrenia.

Working memory function is associated with gamma frequency (30-80 Hz) oscillations in the prefrontal cortex (PFC). The power of PFC gamma oscillations normally increases in proportion to working memory load (Howard et al., 2003; Jensen et al., 2007), but individuals with schizophrenia show lower gamma oscillatory power in response to working memory demands (Uhlhaas and Singer, 2010). Moreover, these deficits are similarly present in both subjects with chronic illness (Cho et al., 2006) and those in the first-episode of psychosis regardless of medication status (Minzenberg et al., 2010), suggesting that working memory impairments and lower gamma power reflect the disease process of schizophrenia and are not the consequence of illness chronicity or antipsychotic medications.

Gamma oscillations reflect the synchronous firing of large groups of cortical pyramidal neurons (Gonzalez-Burgos and Lewis, 2008). The role of GABA neurons in the generation of gamma oscillations was suggested by findings that pharmacological stimulation of GABA neurons (Whittington et al., 1995) or inhibition of GABA neurotransmission by a $GABA_A$ receptor antagonist (Traub et al., 1996) produced or abolished, respectively, gamma oscillatory activity *in vitro*. Consistent with the idea that gamma oscillations are the neural substrate of working memory, local administration of the same $GABA_A$ receptor antagonist into the primate PFC impaired working memory performance (Sawaguchi et al., 1989).

In the neocortex, pyramidal neurons and GABA neurons are thought to generate gamma oscillations via the pyramidal interneuron network gamma (PING) model. In this model, the asynchronous firing of pyramidal cells depolarizes GABA neurons which provide feedback

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inhibition to, and the transient silencing of, large numbers of pyramidal cells. The inhibition decays synchronously in multiple pyramidal neurons, which allows for their coordinated firing, the subsequent depolarization of GABA neurons, and recurrence of the synchronizing inhibition of pyramidal neurons. The decay rate of this inhibition (~25 msec) results in ~40 Hz or gamma frequency oscillatory activity that is sufficiently large to be measurable at the scalp by EEG or magnetoencephalography (Gonzalez-Burgos et al., 2015). Therefore, GABA neuron dysfunction in the PFC of individuals with schizophrenia could underlie reduced gamma oscillatory power and working memory deficits.

Given their crucial role in these functions, understanding interneuron alterations in individuals with schizophrenia could provide insight into the nature of the disease process. Consequently, we review both *in vivo* evidence of altered cortical GABA signaling in individuals with schizophrenia and findings from postmortem studies regarding alterations in different classes of GABA neurons in the PFC. Finally, we review emerging evidence of interneuron alterations in other cortical regions whose coordinated activity with the PFC is necessary for visuospatial working memory.

2. *In vivo* studies of cortical GABA, gamma oscillations, and working memory and their alterations in schizophrenia

Magnetic resonance spectroscopy (MRS) is one of the primary methods available to measure total brain tissue GABA concentration *in vivo*. Studies using MRS in healthy participants provide evidence consistent with the notion that cortical GABA neurotransmission is critical for both working memory and the generation of gamma oscillatory activity. For example, GABA concentration in the PFC is significantly correlated with working memory capacity in healthy individuals such that lower GABA content in the PFC predicts degradation of performance in trials with higher working memory loads (Yoon et al., 2016). Similarly, GABA concentration in the PFC of healthy subjects increases with an initial response to a working memory demand (Michels et al., 2012). GABA concentration also predicts both the gamma oscillatory frequency in the visual cortex and the ability of healthy subjects to discriminate visual stimuli (Edden et al., 2009). However, studies of the relationship between MRS measures of GABA and visually-induced peak gamma frequency produced conflicting results (Cousijn et al., 2014; Muthukumaraswamy et al., 2009).

Supporting evidence for the importance of GABA signaling in gamma oscillations comes from positron emission tomography (PET) imaging studies, which, in contrast to the total tissue concentrations of GABA measured by MRS, assesses changes in levels of extracellular GABA by measuring the tissue distribution of [^{11}C] flumazenil, a radioligand that specifically binds to $GABA_A$ receptors at the benzodiazepine site. Because the binding of GABA at $GABA_A$ receptors increases the binding affinity at the benzodiazepine site, increases in extracellular GABA are measured by PET as an increase in the binding potential of [^{11}C] flumazenil. Accordingly, administration of a GABA reuptake blocker, which increases extracellular GABA levels, resulted in increased [^{11}C] flumazenil binding (Frankle et al., 2009). Consistent with reports from MRS studies, the increase in [^{11}C] flumazenil binding after blockade of GABA reuptake was significantly correlated with gamma band power during a working memory task (Frankle et al., 2012, 2009).

Given the important role of PFC GABA signaling in gamma oscillations and working memory, multiple studies using MRS or PET have investigated GABA signaling in schizophrenia. Initial studies using 3T MRS reported lower total tissue GABA concentrations in the basal ganglia (but not in the frontal or parieto-occipital cortices) of subjects with recent-onset schizophrenia (Goto et al., 2009) and in the visual cortex of individuals with both chronic and recent-onset schizophrenia (Yoon et al., 2010). Studies of the PFC have reported mixed findings, with higher (Kegeles et al., 2012; Öngür et al., 2010), lower (Marenco et al., 2016), or unchanged (Chen et al., 2014; Rowland et al., 2016b) levels of GABA in individuals with schizophrenia. A recent meta-analysis of *in vivo* ^{1}H MRS studies confirmed that results substantially differed across studies and, accordingly, found no consistent evidence for altered GABA concentrations in patients with schizophrenia (Egerton et al., 2017). Despite the variability of these findings, it is worth noting that the two studies which found no changes in GABA levels between patient and control subjects did find significant correlations of GABA levels with performance on a verbal working memory task (Rowland et al., 2016b) and with gamma oscillation amplitude (Chen et al., 2014), providing further support for the role of GABA in these functions.

Reasons for the disparate results may include subject differences in medication status and duration of illness. For example, GABA concentration is lower in the frontal cortex in middle-aged patients with chronic schizophrenia, but not in younger patients with a recent diagnosis of schizophrenia (Rowland et al., 2016a, 2013). Furthermore, one study found increased GABA levels in unmedicated, but not in medicated, patients with schizophrenia (Kegeles et al., 2012), and another reported a negative correlation of GABA in the frontal cortex with antipsychotic dose (Tayoshi et al., 2009). A recent study using unmedicated first-episode psychosis patients found elevated GABA levels in the medial PFC, which decreased with antipsychotic treatment (de la Fuente-Sandoval et al., 2018). Other methodological issues that may contribute to the variability of findings include small sample sizes in many studies and differences in parameters (e.g., voxel size, acquisition times, and field strength) of the MRS measurement (Egerton et al., 2017).

Indeed, the methodological challenges of using MRS to measure neurotransmitter concentrations may be a significant contributor to the variability of these results. Only ^{1}H or proton MRS, compared with other isotopes measured by MRS, has sufficient resolution for the identification of neurotransmitters that exist in low concentration in the brain such glutamate, glutamine, and GABA (Kegeles et al., 1998). However, even using proton MRS, distinguishing the peaks of glutamate, glutamine, and GABA are often challenging at traditional 1.5T or 3T magnetic field strengths (Maddock and Buonocore, 2012).

To address these issues, recent studies have used 7T strength magnetic fields during MRS to better distinguish GABA from other neurotransmitters. Using 7T ^{1}H MRS, lower GABA levels were found in the medial PFC, but not in the parieto-occipital cortex, of subjects with schizophrenia. Importantly, GABA levels were also inversely correlated with cognitive functioning in these patients (Marsman et al., 2014). In another study utilizing 7T MRS, GABA levels were lower in individuals with schizophrenia, but not in their unaffected siblings; in contrast, both the schizophrenia subjects and their unaffected siblings had lower levels of glutamate (Thakkar et al., 2017). These findings are consistent with the hypothesis that the underlying genetic risk for developing schizophrenia involves glutamatergic neurotransmission (Fromer et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Thus, MRS studies utilizing the highest resolution and magnetic field strength seem to suggest that reductions in GABA concentration are conserved among patients with schizophrenia, although whether these findings hold true in the PFC remains to be determined. Consistent with these MRS studies, cerebrospinal fluid levels of GABA have been reported to be lower in first-episode psychosis patients and lower levels correlated with worse performance in a test of attention (Orhan et al., 2018).

Interpreting the results of these MRS studies is also challenging given that this method measures total tissue concentration of GABA and cannot isolate GABA associated with neurotransmission. To address this issue, PET imaging was used to measure the change in [^{11}C] flumazenil binding after administration of a drug that blocks GABA reuptake via the GABA membrane transporter (GAT1). In healthy subjects, [^{11}C] flumazenil binding in all cortical regions increased after GAT1 blockade, but this effect was attenuated in individuals with schizophrenia. The effects were significant in the dorsolateral PFC, and were

most prominent in antipsychotic naïve patients (Frankle et al., 2015). These data provide the first *in vivo* evidence suggesting that individuals with schizophrenia have a reduced capacity to increase extracellular levels of GABA, perhaps because of a deficit in GABA synthesis as discussed below.

Finally, two studies which pharmacologically manipulated GABA in subjects with schizophrenia found evidence consistent with altered GABA signaling in these patients. One study using a benzodiazepine challenge to potentiate GABA signaling at the $GABA_A$ site found a decrease in the blood-oxygen level dependent (BOLD) signal by MRI in comparison subjects, but an increase in BOLD signal in patients with schizophrenia in the PFC (Taylor et al., 2013), suggesting a reduced capacity to increase GABA signaling. Another study showed that administration of a novel positive allosteric modulator with relative selectivity for $GABA_A$ receptors containing α2/3 subunits improved performance on two working memory tasks compared to placebo in subjects with schizophrenia. Importantly, this compound was also associated with increased frontal gamma band power during a working memory task (Lewis et al., 2008). These preliminary findings from pharmacological interventions in schizophrenia subjects are consistent with the view that impaired GABA signaling underlies disturbances in working memory and the ability to generate gamma oscillations in these patients.

Although the studies summarized above all have limitations, they do provide *in vivo* support for 1) the role of cortical GABA neurotransmission in the generation of gamma oscillations and in the performance of working memory tasks and 2) the idea that impairments in GABA signaling could underlie disturbances of both gamma oscillations and working memory in individuals with schizophrenia.

3. Differential contributions of interneuron subtypes to circuit dysfunction in schizophrenia

Understanding the implications of these *in vivo* findings, which measure cortical GABA signaling globally, requires knowledge of the properties of different classes of interneurons that appear to have distinct roles in mediating working memory. Thus, their differential alteration in schizophrenia may reveal both the functional consequences of these changes and the subtypes of GABA neurons that contribute most strongly to the GABA deficit observed *in vivo*. Therefore, in this section, we briefly review the different major classes of cortical interneurons, the evidence for their differential involvement in gamma oscillations and working memory, and the alterations of these interneurons in the PFC of individuals with schizophrenia as revealed through postmortem studies.

3.1. Subtypes of interneurons and their roles in working memory

Interneurons have been classified based on differences in their electrophysiological, morphological, and biochemical properties. The latter schema is most applicable for postmortem human studies (Fig. 1). Subclasses of GABA neurons differ in their expression of specific gene products such as calcium binding proteins (i.e., parvalbumin (PV), calretinin (CR), and calbindin (CB)) and neuropeptides (i.e., somatostatin (SST), cholecystokinin (CCK), and vasoactive intestinal peptide (VIP)) (Ascoli et al., 2008; DeFelipe et al., 2013).

PV-containing interneurons have been shown to play a key role in gamma oscillations. Experimental manipulations in mice show that both knockout of the excitatory drive to PV cells (Fuchs et al., 2007) and optogenetic reduction of PV cell activity (Sohal et al., 2009) suppress gamma oscillations, whereas selective activation of PV cells amplifies gamma oscillations (Cardin et al., 2009). PV neurons can be further subdivided based on their projection targets: the axon terminals of PV basket cells (PVBCs) primarily target the perisomatic region of pyramidal cells, and the axon terminals of PV chandelier cells (ChCs) form vertical arrays termed cartridges that target the axon initial

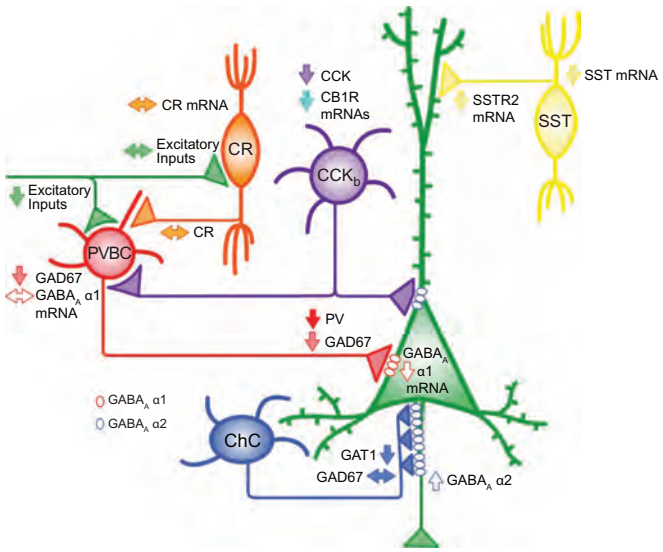

Fig. 1. Schematic summary of alterations in cortical GABA neurons in the PFC of individuals with schizophrenia as revealed in studies of postmortem human brain tissue. Arrows next to the presumptive location of the marker of inhibitory interneurons indicate increased, decreased, or unchanged levels of mRNA transcript or protein. Parvalbumin basket cells (PVBCs)-pyramidal cell microcircuits appear to be responsible for gamma oscillations, and alterations indicated here could represent the neural substrate of impaired gamma oscillatory activity seen in patients with schizophrenia. Furthermore, regulation of the activity of either of these components by other classes of interneurons, such as parvalbumin chandelier cells (ChC), somatostatin cells (SST), cholecystokinin basket cells (CCKb), or calretinin cells (CR) could alter the activity of the PVBC-pyramidal cell microcircuit responsible for this oscillatory activity and working memory.

segment (AIS) of pyramidal cells. The activity of PVBCs is tightly coupled to gamma oscillatory activity (Freund, 2003; Klausberger and Somogyi, 2008), whereas the contribution of ChCs to the generation of gamma oscillations is less clear (Gulyás et al., 2010; Massi et al., 2012; Varga et al., 2014). Notably, PVBCs and ChCs axon terminals differ in the content of their GABA synthesizing enzymes: the 67 kilodalton isoform of glutamic acid decarboxylase (GAD67) is exclusively contained in ChCs while PVBCs contain both the 65 (GAD65) and 67 kilodalton isoforms (Fish et al., 2011). These two subtypes of PV cells also differ in the principal type of $GABA_A$ receptors at their synaptic targets: $GABA_A$ receptors containing the α1 subunit, which mediate fast decay of the inhibitory postsynaptic current (IPSC), predominate at PVBC synapses onto pyramidal cells. In contrast, ChC inputs to pyramidal cells are populated by $GABA_A$ receptors containing the α2 subunit, which exhibit a slower IPSC decay (Mody and Pearce, 2004) (Fig. 1). Because gamma oscillations require the fast decay of IPSCs, these differences in postsynaptic receptors between PVBCs and ChCs may explain the stronger contribution of PVBCs to the generation of gamma oscillatory activity (Bartos et al., 2007). Thus, the available data strongly implicate the PVBC-pyramidal cell microcircuit as the neural substrate of gamma oscillations.

Another group of basket cells contain the neuropeptide CCK and target both pyramidal cells and other interneurons (Freund and Katona, 2007), including PV cells (Karson et al., 2009) (Fig. 1). Therefore, CCK basket cells are poised to strongly influence both components of the microcircuit responsible for generating gamma oscillations. However, the physiological properties of CCK basket cell firing suggest that their contribution to gamma oscillations differs from that of PVBCs. Unlike PVBCs, these cells exhibit asynchronous GABA release in response to depolarization (Daw et al., 2009) and receptors at CCK basket cell terminals are primarily populated by $GABA_A$ receptors containing the α2 subunit that mediates a slow IPSC decay as opposed to the fast

decaying IPSCs mediated by the α1 subunit-containing $GABA_A$ receptors. Furthermore, type 1 cannabinoid receptors (CB1Rs) are present at high levels in CCK axon terminals where they mediate a process known as depolarization-induced suppression of inhibition (DSI). In DSI, pyramidal cell depolarization stimulates the release of endocannabinoids which then bind to presynaptic CB1R receptors, suppressing GABA release from CCK axon terminals (Wilson and Nicoll, 2002). Together, these differences in physiological properties do not support the fast synaptic inhibition required for gamma oscillations (Bartos and Elgueta, 2012). However, the firing of CCK basket cells has been reported to be coupled to the early phase of gamma oscillatory activity (Tukker et al., 2007) and activation of CB1R receptors suppresses gamma band power (Hájos et al., 2000). Thus, CCK neurons may indirectly modulate gamma oscillations by influencing the function of the PVBC-pyramidal cell microcircuit.

This microcircuit can also be modulated by SST-containing interneurons which predominately target the distal dendritic shafts (de Lima and Morrison, 1989) of pyramidal cells (Markram et al., 2004; Melchitzky and Lewis, 2008) and PV cells (Urban-Ciecko and Barth, 2016) (Fig. 1). While the distal location of their synaptic inputs predicts that they exert a weaker influence over this microcircuit, the available evidence suggests that alterations in SST interneuron function can powerfully affect both components of the microcircuit that generates gamma oscillations. Furthermore, the functional impact of a loss of SST signaling seems to depend on the degree to which these cells innervate pyramidal cells or PV cells. For example, optogenetic inhibition of SST cells in layer 2/3 of the mouse cortex, where SST cell inputs are primarily onto pyramidal cells, results in increased pyramidal cell firing (Gentet et al., 2012; Xu et al., 2013) whereas inhibition of SST cells in layer 4, where most of the targets are PV cells, results in decreased pyramidal cell firing (Xu et al., 2013). While some evidence purports that SST cells are phase-locked to gamma oscillatory activity (Veit et al., 2017), these oscillations were slower than typical gamma bands (20–30 Hz); instead, another study suggested PV cells drive gamma oscillations while SST cells drive slower, beta range oscillations (Chen et al., 2017). However, these cells are likely still crucial for working memory, as optogenetic suppression of the activity of SST cells in the mouse medial PFC was associated with impairments in working memory tasks (Kim et al., 2016).

Finally, CR-containing interneurons, most of which also express VIP, primarily target other interneurons (Melchitzky and Lewis, 2008), including both PV and SST cells (Pi et al., 2013). Due to their inhibition of other GABA neurons, VIP interneurons can disinhibit pyramidal cells. Furthermore, they have been shown to be crucial for synaptic plasticity of PV-containing interneurons (Donato et al., 2013). Thus, VIP/CR-containing interneurons may regulate, directly or indirectly, the output of both PVBCs and pyramidal cells in the cortical microcircuit that generates gamma oscillations.

3.2. Alterations in interneuron subtypes in schizophrenia

Postmortem studies have consistently revealed alterations in components of GABAergic neurotransmission in the PFC of individuals with schizophrenia (Fig. 1). The strength of GABAergic neurotransmission is proportional to the availability of GABA in the synapse. In schizophrenia, both mRNA (Akbarian et al., 1995; Kimoto et al., 2014; Vawter et al., 2002; Volk et al., 2000; Woo et al., 2008) and protein (Curley et al., 2011; Guidotti et al., 2000) levels of GAD67, the principal enzyme responsible for cortical GABA synthesis, are lower in the PFC, consistent with the idea that the availability of presynaptic GABA is reduced in the illness. Interestingly, GAD65 does not appear to be altered in the PFC of subjects with schizophrenia but may be lower in schizoaffective disorder (Glausier et al., 2015). While the total number of neurons is not changed in the PFC in the illness (Thune et al., 2001), the density of neurons with detectable levels of GAD67 mRNA is 25-35% lower across cortical layers 1-5, while the remaining GAD67-positive neurons have mRNA levels that do not differ from control subjects (Akbarian et al., 1995; Volk et al., 2000). These findings suggest that GAD67 is markedly reduced in a subset of PFC interneurons in schizophrenia, while the remaining neurons have normal levels of GAD67, raising interesting questions about which subtypes of GABA neurons contribute to the GAD67 deficit in the illness.

3.3. PV interneurons in the PFC of schizophrenia subjects

In the PFC of individuals with schizophrenia, PV cells exhibit lower GAD67 mRNA levels such that ~50% of PV-positive interneurons lack detectable GAD67 mRNA (Hashimoto et al., 2003). Furthermore, PV mRNA expression is lower in PFC layers 3–4 of individuals with schizophrenia, the same layers where the GAD67 deficit is present (Hashimoto et al., 2003; Volk et al., 2000). These findings do not appear to be due to fewer PV neurons, as the densities of PV mRNA-positive neurons (Hashimoto et al., 2003) or PV-immunoreactive neurons (Chung et al., 2016a; Enwright et al., 2016) are not altered in the PFC of individuals with schizophrenia. In the few studies that reported a lower density of PV neurons (Beasley et al., 2002; Beasley and Reynolds, 1997), the findings may be due to a methodological confound such that low PV levels were undetectable (Stan and Lewis, 2012). Furthermore, although neither the density of presynaptic PV boutons (Glausier et al., 2014) nor of vesicular GABA transporter (vGAT)-positive axon boutons (Rocco et al., 2016) are altered in the PFC in schizophrenia, PV protein levels per terminal are lower (Glausier et al., 2014). Together, these data suggest that a subset of PV-positive interneurons are markedly affected in the PFC of individuals with schizophrenia. Consistent with the idea that only a subset of PV neurons are affected, GAD67 (Curley et al., 2011) and PV (Glausier et al., 2014) protein levels were lower in axon terminals of putative PVBCs in the PFC of subjects with schizophrenia, whereas ChC cartridges had unchanged levels of GAD67 (Rocco et al., 2016).

Further evidence that inhibition from PVBCs is altered in schizophrenia comes from studies of postsynaptic receptors. For example, transcript levels of the α1 subunit of $GABA_A$ receptors, which are found postsynaptic to PVBC inputs onto pyramidal cells, are selectively lower in pyramidal cells, but not in interneurons in layer 3 of the PFC from schizophrenia subjects (Glausier and Lewis, 2011). Furthermore, lower levels of other subunits of the $GABA_A$ receptor have been reported, including the β2 subunits. Interestingly, the reduction in the α1 and β2 subunits is most prominent in layers 3–4, the same layers where the PV and GAD67 mRNA deficits are most pronounced (Beneyto et al., 2011). Together, these findings support the notion that alterations at both the pre- and post-synaptic side of PVBC inputs onto pyramidal cells result in weakened inhibition of pyramidal cells.

Although ChCs terminals do not have lower GAD67 levels, other lines of evidence suggest that ChCs, especially those in layers 2-superficial 3, are altered in the PFC of individuals with schizophrenia. The density of ChC cartridges immunoreactive for GAT1 is 40% lower in the PFC of individuals with schizophrenia (Woo et al., 1998), and both the expression of the α2 subunit of $GABA_A$ receptors (Beneyto et al., 2011), which populate the AIS of pyramidal cells, and the density of AIS immunoreactive for the α2 subunit are increased (Volk et al., 2002). Together, normal levels of GAD67 protein (Rocco et al., 2016), lower levels of GAT1 in ChC cartridges, and upregulation of the postsynaptic $GABA_A$ α2 receptor subunit would be predicted to increase inhibitory strength onto the AIS of pyramidal cells.

Specific upstream factors might be driving the differential alterations in PVBCs (consistent with weaker GABA neurotransmission) and in ChCs (consistent with stronger GABA neurotransmission). Because both GAD67 and PV are activity-dependent gene products, their downregulated expression in PVBCs could be due to lower excitatory drive to these neurons. Indeed, the density of excitatory synapses onto PV-positive neurons in layer 4 (where PVBCs are much more common than ChCs (Miyamae et al., 2017)) is lower, and predicts the levels of

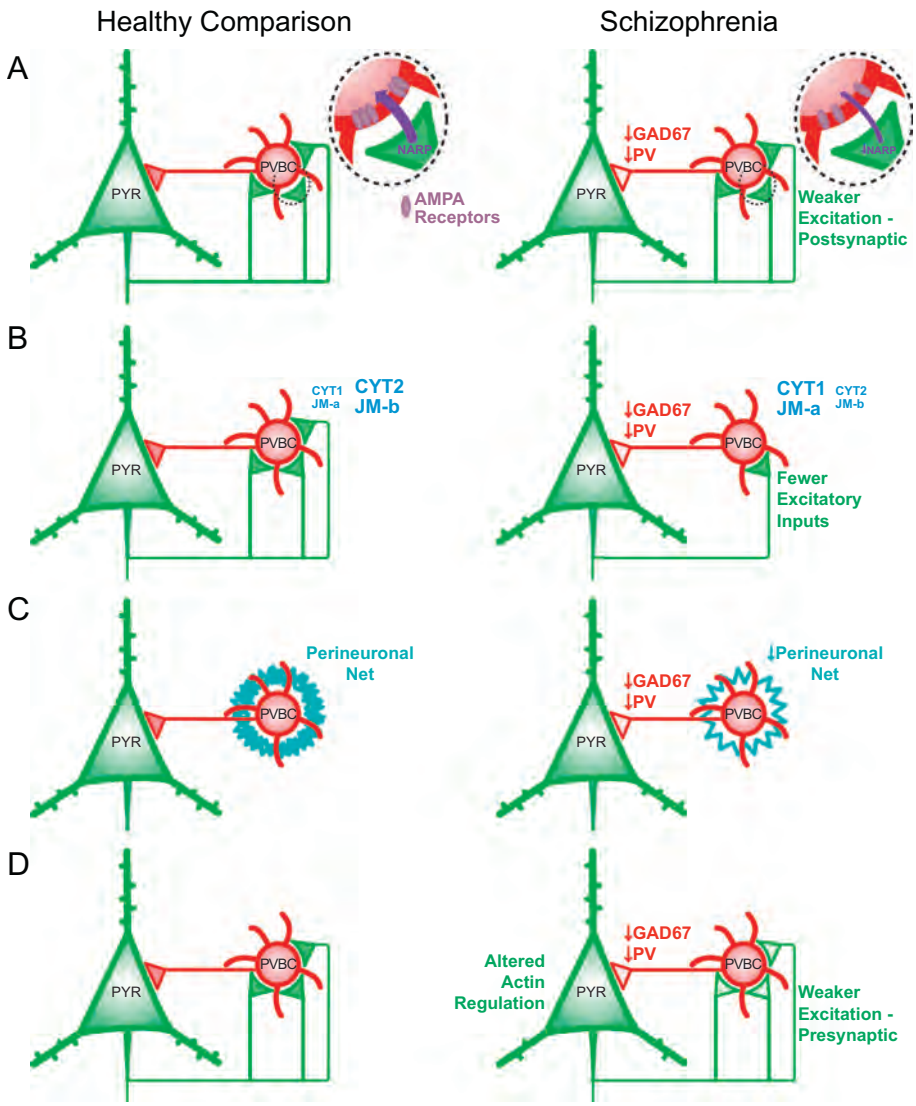

Fig. 2. Schematic summaries of four alternative hypotheses for the upstream factors that may mediate the deficit in GAD67 and PV selectively in PVBCs in the PFC of subjects with schizophrenia. Lighter shading of synaptic boutons indicates weaker presynaptic inputs. A.) Downregulation of neuronal pentraxin (NARP) at pyramidal cell inputs could lead to fewer AMPA receptors on PVBCs, and lower activity-dependent transcription of GAD67 and PV in schizophrenia. B.) ErbB4 splicing variants in PV cells regulate the density of excitatory inputs onto these cells, such that higher expression of the minor variants (CYT1 and JM-a) compared to the major variants (CYT2 and JM-b) results in fewer excitatory inputs onto PV cells in schizophrenia. Indeed, PV cells in the PFC of individuals with schizophrenia have higher expression of the minor splicing variants which may lead to the fewer excitatory inputs to PVBCs, contributing to reduced expression of the activity dependent genes, GAD67 and PV. C.) A decrease in the constituents of the perineuronal nets surrounding PVBCs, by reducing protection against oxidative stress, may lead to a downregulation of transcripts that encode for GAD67 and PV protein. D.) An intrinsic deficit in actin regulation, leading to lower density of dendritic spines and fewer excitatory inputs to pyramidal cells, results in lower excitatory drive to PVBCs and downregulation of GAD67 and PV. The resulting downregulation of feedback inhibition to hypoactive pyramidal cells may help maintain excitatory-inhibitory balance in this cortical microcircuit, but at the cost of impairing the generation of gamma oscillations (Gonzalez-Burgos et al., 2015).

PV and GAD67 mRNAs, in schizophrenia subjects (Chung et al., 2016a). The excitatory drive to PV neurons is, in part, regulated by the secretion of neuronal activity-regulated pentraxin (NARP) from pyramidal cells. After being secreted by pyramidal cells through glutamatergic synapses onto PV interneurons, NARP recruits GluR4-containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which mediate excitatory neurotransmission onto these interneurons (Chang et al., 2010) (Fig. 2A). In schizophrenia, NARP mRNA is reduced in layer 3 pyramidal cells (Kimoto et al., 2015). Thus, lower activity of layer 3 pyramidal cells (possibly due to their reduced number of dendritic spines, the principal site of excitatory synapses (Glausier and Lewis, 2013)) could result in lower NARP expression, leading to a reduction in excitatory synapses onto local PV cells in layers 3–4. The lower excitatory drive may downregulate immediate-early genes responsible for promoting GAD67 transcription, such as Zif268; indeed, lower mRNA levels of Zif268 have also been reported in schizophrenia and were found to predict GAD67 levels (Kimoto et al., 2014). Alternatively, given that the erb-b2 receptor tyrosine kinase 4 (ErbB4) splicing patterns regulate the formation of excitatory synapses onto PV neurons (Chung et al., 2017; Mei and Nave, 2014), fewer excitatory inputs to PV cells in schizophrenia may result from altered splicing patterns of ErbB4 selectively in PV cells in the illness (Chung et al., 2016b) (Fig. 2B). It is worth noting that one *in vivo* study demonstrated that genetic variation in ErbB4 predicted GABA concentrations measured by MRS in healthy subjects (Marenco et al., 2011), supporting the notion that ErbB4 variants may be driving the changes in GABA concentration seen in individuals with schizophrenia.

In contrast to the alterations in PVBCs which seem to weaken GABA input to pyramidal cells in schizophrenia, the alterations in ChC neurons might strengthen GABAergic neurotransmission at the AIS of pyramidal cells. For example, ChC inputs have been reported to be depolarizing, rather than hyperpolarizing, if the overall activity of pyramidal cells is low (Woodruff et al., 2011). Thus, although speculative, hypoactive pyramidal cells in schizophrenia, and the resulting quiescent cortical circuit, might evoke both lower presynaptic GAT1 and higher postsynaptic GABA α2 receptors that would in combination strengthen GABA neurotransmission at ChC inputs and potentially promote depolarization of the pyramidal cell. Alternatively, given that the flow of chloride ions through the $GABA_A$ receptor depends on the intracellular concentration of chloride, altered expression of chloride ion channels (Hyde et al., 2011) or altered activity of their regulators (Arion and Lewis, 2011) could change the chloride gradient and render activation of $GABA_A$ receptors less hyperpolarizing by reducing the influx of chloride ions after GABA signaling.

The distinct alterations seen in PVBCs and ChCs might also arise from disruptions in perineuronal nets (PNNs), a condensed form of extracellular matrix which appears to surround PVBCs and not ChCs (Yamada and Jinno, 2015). The PNNs that surround PVBCs play

important roles in protection against oxidative stress and the regulation of synaptic plasticity (Berretta et al., 2015). Indeed, experimental reductions in PNNs result in downregulated PV expression (Yamada et al., 2015), and reductions in PNNs have been observed in the PFC of individuals with schizophrenia (Enwright et al., 2016; Mauney et al., 2013) (Fig. 2C).Thus, a reduction in excitatory drive to PV cells, alternative splicing of ErbB4 and fewer excitatory inputs to PV cells, and/or a deficit in PNNs could all contribute to lower expression of GAD67 and PV in an affected subset of PV interneurons in schizophrenia.

3.4. Other GABA neurons affected in schizophrenia

The findings that GAD67 mRNA is lower across cortical layers 1–5 in schizophrenia, but that the PV deficit is present only in layers 3–4, suggests that other GABA subtypes contribute to lower GAD67 levels in the other cortical layers. For example, CCK basket cells are present predominately in layers 2-superficial 3, CCK mRNA expression is downregulated in these layers in schizophrenia, and the changes in CCK mRNA expression are highly correlated with the deficit in GAD67 expression in these subjects (Eggan et al., 2008; Fung et al., 2010; Hashimoto et al., 2008a). Similarly, SST-containing interneurons are present primarily in layers 2- superficial 3 and layer 5-6, deficits in SST mRNA are particularly pronounced in schizophrenia (Fung et al., 2010; Hashimoto et al., 2008a), and the changes in SST mRNA expression predict GAD67 transcript levels Morris et al., 2008. On the postsynaptic aspect of SST inhibitory signaling, reductions in the somatostatin receptor 2 mRNA in pyramidal cells have also been reported (Beneyto et al., 2012) (Fig. 1). Direct investigation of GAD67 integrity in these cells is warranted, but may be methodologically challenging given that there are marked reductions in both SST mRNA per neuron and the density of neurons with detectable levels of SST mRNA (Morris et al., 2008). Thus, another marker of SST cells, which is unaltered in the illness, is needed to directly assess GAD67 in these cells.

CR cells, which primarily target other interneurons, do not appear to be altered in the PFC of subjects with schizophrenia. Total mRNA (Chung et al., 2016b; Fung et al., 2010; Hashimoto et al., 2003) and protein levels (Fung et al., 2010) of CR are unchanged in schizophrenia. Similarly, neither the density of CR mRNA-positive neurons nor the levels of CR mRNA per neuron are changed in the illness (Hashimoto et al., 2003) and immunoreactivity for CR is unaltered in the PFC of subjects with schizophrenia (Daviss and Lewis, 1995; Reynolds and Beasley, 2001; Woo et al., 1998) (Fig. 1). Consistent with the lack of intrinsic change in CR neurons, CR neurons appear to have a normal complement of excitatory inputs, unlike PV neurons (Chung et al., 2016a). These convergent lines of evidence suggest CR may not be contributing towards the GAD67 deficit in the PFC of individuals in the illness. However, GAD67 levels in CR neurons have yet to be directly studied in schizophrenia.

4. Interneuron disturbances in other cortical regions

The convergence of findings supporting a GABA deficit in the PFC raises important questions as to whether these deficits are conserved across cortical regions or exhibit region-specific changes in schizophrenia. Thus, in this final section, we review findings of GABA alterations in other cortical regions and assess the similarity of these findings to the deficits observed in the PFC.

The temporal lobe has been extensively studied in the context of GABA alterations in schizophrenia, particularly in the hippocampus. Some of the earliest studies reported a reduced number of small interneurons in the hippocampus (Benes et al., 1998) consistent with some studies reporting an overall loss of neuronal density in this region (Falkai and Bogerts, 1986; Jeste and Lohr, 1989). In contrast to these findings, a stereological study of the hippocampus in schizophrenia failed to find evidence of neuronal loss (Heckers et al., 1991) and more recent evidence confirms a lack of change of total neuron number (Konradi et al., 2011). Furthermore, even though another study found fewer PV-immunoreactive neurons in the hippocampus (Zhang and Reynolds, 2002), this finding might represent the presence of neurons with undetectable levels of PV. Indeed, the same studies that confirmed no change of total neuron number in the hippocampus confirmed a lower number of both PV and SST immunoreactive neurons (Konradi et al., 2011). Thus, alterations of these interneurons in the hippocampus may resemble the interneuron abnormalities in the PFC, where very low levels of PV and SST expression render some neurons undetectable. Similar to findings in the PFC, recent studies suggest GAD67 is also downregulated in certain sub-regions of the hippocampus (Benes et al., 2007; Konradi et al., 2011; Ray et al., 2011), although earlier reports suggested no change in GAD67 expression (Heckers et al., 2002). Outside of the hippocampus, tissue homogenates of the temporal cortices were reported to exhibit a significant 70% reduction in GAD67 protein in subjects with schizophrenia (Impagnatiello et al., 1998). In the primary auditory cortex, GAD65 immunoreactivity per inhibitory bouton is lower without loss of the density of boutons in subjects with schizophrenia (Moyer et al., 2012); however, GAD67 levels have not been evaluated in the primary auditory cortex.

GABA deficits have also been observed in other frontal cortical regions in schizophrenia, including the anterior cingulate cortex (ACC). Some evidence suggests that the ACC has a lower density of interneurons, primarily in layer 2 (Benes et al., 1991), whereas other studies suggest no difference in the total number of neurons with an increase in the number of PV-positive soma in deeper cortical layers of the ACC (Kalus et al., 1997). Other studies have failed to replicate these changes in PV immunoreactive neuron density, reporting instead a reduction in CB containing interneurons in layer 2 of the ACC of patients with schizophrenia (Cotter et al., 2002). Consistent with the laminar localization of SST cells, the density of GAD67 mRNA-positive neurons (Woo et al., 2004) and GAD67 levels (Thompson et al., 2009) are lower in layer 2 and layer 5 of the ACC in schizophrenia subjects. Thus, the changes in GABA neurons in the ACC may not be present in PV interneurons but rather in CB interneurons, possibly leading to different functional consequences compared with the changes seen in the PFC.

To date, two studies have systematically identified differences in GAD67 expression across multiple brain regions in postmortem studies of schizophrenia. Thompson and colleagues found significant GAD67 mRNA deficits in the orbitofrontal cortex and modest, non-significant reductions in the ACC and the superior temporal gyrus (Thompson et al., 2009), suggesting that the GABA deficit is not exclusive to the PFC. Findings of marked reductions in PV, SST, and GAD67 expression across the dorsolateral PFC, ACC, primary motor cortex, and primary visual cortex (Hashimoto et al., 2008b) further support this notion.

However, only one study has systematically examined markers of GABA signaling across cortical nodes responsible for visuospatial working memory. Visuospatial working memory is carried out by communication across a distributed cortical network including the primary visual cortex (V1), visual association cortex (V2), posterior parietal cortex (PPC), and dorsolateral PFC (Miller and Cohen, 2001), with pyramidal neurons in layer 3 providing most of the projections among these regions. Examination of GABA-related markers in layer 3 of these regions found that the normal expression of these markers differed substantially across regions and the effect of schizophrenia differed across regions (Hoftman et al., 2018) (Fig. 3). Control subjects exhibited a caudal-to-rostral gradient of GABA expression, such that GABA markers were highest in the visual cortex and lowest in the dorsolateral PFC; this gradient was enhanced in schizophrenia subjects (Fig. 3). These differential alterations in GABA markers in layer 3 may contribute to visuospatial working memory deficits observed in patients with schizophrenia (Fleming et al., 1997). It is important to note that the focus of this study on layer 3, where PV neurons predominate, might contribute to certain differences in findings relative to other studies that examined total gray matter.

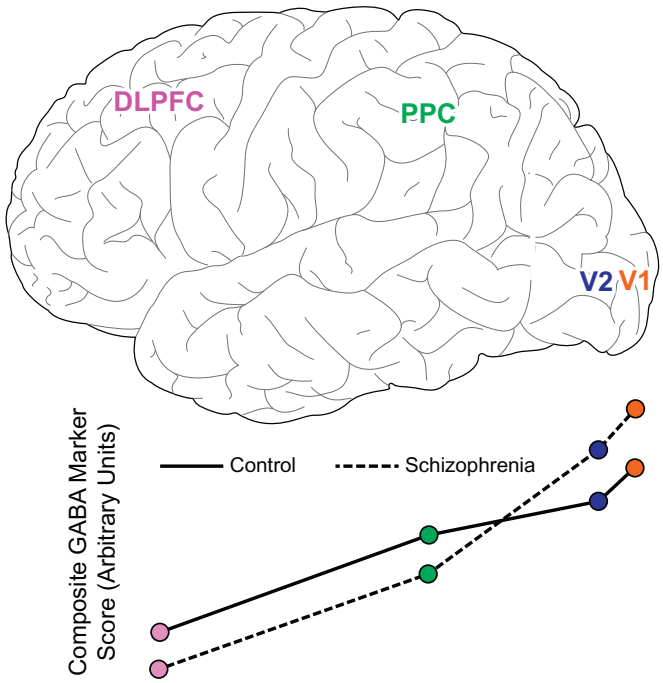

Fig. 3. Schematic summary of the results of a study that systemically investigated GABA markers in layer 3 across four cortical regions critical for visuospatial working memory. Measures of a composite GABA score were obtained by summation of normalized z-scores for the expression ratio of transcripts common to all GABA neurons in each brain region for both diagnostic groups, providing each equal weight to each transcript measured. The colors indicate each brain region studied, and the data points reflect these summated scores of GABA markers in each region by diagnosis. In healthy comparison subjects (solid line), GABA markers have lowest expression in layer 3 of the dorsolateral PFC (DLPFC), and progressively increase in the posterior parietal cortex (PPC), the visual association cortex (V2), achieving the highest expression in the primary visual cortex (V1). In individuals with schizophrenia (dashed line), this rostral to caudal gradient is enhanced, such that GABA markers are markedly downregulated in the DLPFC and upregulated in V1. Alterations in the set point of inhibition may contribute to disrupted visuospatial working memory in subjects with schizophrenia. Data in figure adapted from (Hoftman et al., 2018).

5. Conclusions

The findings reviewed above strongly indicate that interneuron signaling in the PFC is critical for the generation of gamma oscillations and the proper functioning of working memory. This notion is supported both by *in vivo* studies in healthy subjects demonstrating a relationship between cortical GABA concentration, gamma oscillations, and working memory performance and by manipulations of GABA circuitry in animal models which result in alterations of gamma band power and working memory performance. These findings provide a foundation for the inference that cortical interneuron alterations contribute to the gamma oscillation disturbances and working memory impairments in schizophrenia.

The assessment of GABA neuron function in healthy and schizophrenia subjects requires studies conducted at multiple levels of resolution. *In vivo* neuroimaging studies provide indices of GABA function in living subjects, permitting correlations between cortical GABA levels and working memory function. Most of the earlier studies produced mixed results, with markers of GABA neurotransmission reported to be increased, decreased, or unchanged in the PFC of individuals with schizophrenia. Findings from newer studies, however, using high strength magnetic field MRS or PET imaging of extracellular GABA support the notion of a cortical GABA deficit in schizophrenia; additional studies utilizing these more sensitive imaging methods are needed to confirm the presence of a GABA deficit *in vivo* in these subjects. These findings are also consistent with the results of most postmortem studies that have documented molecular alterations, at the level of both transcripts and proteins, suggestive of lower GABA neurotransmission. Indeed, such studies have reported that the deficit in GABA neurotransmission (i.e., lower levels of GAD67) is present in PVBCs.

Given the importance of PVBCs in the generation of gamma oscillations and working memory function, it is likely that deficits in PVBC signaling are key contributors to the impairments of these functions in individuals with schizophrenia. Importantly, other subtypes of interneurons also appear to be altered in schizophrenia (although it is currently unknown if these subtypes have a deficit in GABA synthesis), and alterations in at least some of these subtypes might contribute to working memory impairments via their influence on the PVBC-pyramidal cell microcircuit. For example, CCK basket cells innervate both pyramidal cells and PVBCs, and altered signaling from CCK neurons could disrupt the coordinated firing of the PVBC-pyramidal cell microcircuit (Schmidt et al., 2014). Similarly, SST cells, which target the dendrites of both pyramidal cells and PV neurons, are also markedly altered in the illness. Theoretical models predict that these dendritically-targeting GABA neurons are necessary to filter out behaviorally irrelevant distractors (Wang et al., 2004) which can interfere with the maintenance of information in working memory (Miller et al., 1996). Indeed, the inability to filter out distracting stimuli and sustain attention has been suggested to underlie cognitive disturbances in patients with schizophrenia (Silver and Feldman, 2005).

These findings raise important questions about the mechanism(s) responsible for the cortical GABA deficit in schizophrenia; for example, what factors lead to lower GAD67 expression and presumably less GABA synthesis in PVBCs? One possibility is an intrinsic deficit in PVBCs that results in fewer excitatory inputs and a lower drive for the activity-dependent expression of GAD67. For example, the splicing of ErbB4, which mediates the neuregulin-driven formation of excitatory synapses, is selectively altered in PV cells in schizophrenia, and is associated with a lower number of excitatory inputs to these cells (Chung et al., 2017, 2016b, 2016a).

Other studies have led to the hypothesis that hypofunction of the NMDA receptor on PVBCs may contribute to an activity-dependent down-regulation of GAD67 expression. For example, systemic administration of NMDA receptor antagonists in rodents was associated with a reduction in the firing of putative interneurons in the PFC followed by increased activity of putative pyramidal neurons, consistent with a disinhibition of the latter (Homayoun and Moghaddam, 2007). Other findings supporting this hypothesis include: 1) the NMDA receptor antagonist ketamine reduced the frequency and amplitude of miniature inhibitory post-synaptic currents in rodent slice cultures (Zhang et al., 2008); 2) ablation of the NR1subunit of NMDA receptors in 50% of interneurons in preadolescent mice resulted in spatial working memory deficits and lower expression of GAD67 and PV protein levels in adulthood (Belforte et al., 2009); and 3) selective mutation of the NMDA receptors on PV-positive interneurons led to impairments in the induction of gamma oscillatory activity and working memory in mice (Carlén et al., 2012). However, findings of alterations in NMDA receptors in schizophrenia subjects has been mixed (Hu et al., 2015). Interestingly, a selective decrease in the NR2A subunit of NMDA receptors in layers 3/4 of the PFC was observed in the brains of individuals with schizophrenia (Bitanihirwe et al., 2009), and cultured PV neurons show a decrease in PV and GAD67 expression following application of a specific NR2A antagonist (Kinney et al., 2006). Together, these findings suggest that a deficit of this subunit and impaired signaling through NMDA receptors on PV cells may be upstream to the GAD67 and PV deficit observed in schizophrenia.

However, other data raise important questions about the importance of NMDA receptors in mediating PV function. The ability of PVBCs to generate gamma frequency oscillations relies on fast synaptic

signaling that is unlikely to be supported by the slower kinetics of NMDA receptors (Gonzalez-Burgos and Lewis, 2012). Indeed, computational modeling demonstrates that increasing NMDA receptor-mediated currents actually decreases gamma oscillatory activity (Rotaru et al., 2011), and *in vitro* assays of hippocampal neurons show that NMDA receptor antagonists may actually increase gamma oscillatory activity (Pinault, 2008). In addition, the actual contributions of NMDA receptor-mediated excitation of PVBCs is low compared to AMPA receptors: physiologic studies suggest a ~3 times greater AMPA than NMDA contribution to PV cell firing (Gonzalez-Burgos and Lewis, 2012) and electron microscopy studies of glutamate synapses show low content of NMDA receptor subunits on PV cells compared to pyramidal cells (Nyíri et al., 2003). Furthermore, while replicating the finding that systemic ketamine administration disinhibits pyramidal cells in the PFC, administration of an NMDA receptor antagonist directly to the PFC failed to show this effect, suggesting that the effects of ketamine may be mediated by NMDA receptor blockade outside of the PFC, rather than through local inhibitory PV neurons (Wang et al., 2013).

These differences in findings regarding the role of NMDA receptors on PV neurons might reflect a developmental effect, as NMDA receptor antagonism in postpubertal stages does not reproduce the deficits in PV or GAD67 seen with prepubertal antagonism (Belforte et al., 2009).

Finally, according to the NMDA receptor hypofunction hypothesis, reduced activity of PVBCs should disinhibit pyramidal cells. However, the evidence from postmortem human studies does not support such a state in schizophrenia. For example, lower inhibition from PVBCS would be expected to result in an upregulation of α1-containing $GABA_A$ receptors in pyramidal cells that are post-synaptic to PVBCs as well as evidence of increased activity and energy production in pyramidal cells. In contrast, existing data indicate lower or unchanged levels of $GABA_A$ receptor α1 subunit transcript (Beneyto et al., 2011; Glausier and Lewis, 2011) and protein (Glausier et al., 2014) in PFC layer 3 pyramidal cells in schizophrenia, and lower markers of activity (Kimoto et al., 2015) and energy production in these neurons (Arion et al., 2015). In addition, genetic reductions of GAD67 expression specifically in PV cells in animal models failed to produce the changes in multiple other markers of GABA neurotransmission seen in schizophrenia (Curley et al., 2013; Georgiev et al., 2016). In aggregate, these findings do not support the idea of lower inhibition from PVBCs as a primary disturbance in schizophrenia and raise questions regarding the role of NMDA receptors in mediating PV cell function.

Alternatively, the deficits in PVBCs might be secondary to a primary disturbance in pyramidal cells. Consistent with this idea, layer 3 pyramidal cells in the PFC exhibit gene expression alterations in actin regulators of dendritic spines (Datta et al., 2015), fewer dendritic spines, the site of excitatory synapses (Glantz and Lewis, 2000; Glausier and Lewis, 2013), and lower expression of gene products that index activity and energy (Arion et al., 2017, 2015; Kimoto et al., 2015) (Fig. 2D). Given that the axon collaterals of layer 3 pyramidal neurons are a major source of excitatory inputs to PVBCs (Melchitzky and Lewis, 2003), this disturbance would be predicted to result in lower excitatory drive to PVBCs and a compensatory downregulation of inhibition from these neurons to restore excitatory-inhibitory balance in the circuit.

Distinguishing between these alterative hypotheses, determining whether each is operative in different subjects, or determining if disturbances in both cell types are necessary for the illness to be manifest will require a multifaceted approach involving proof-of-concept tests via manipulations in animal models and larger scale *in vivo* and postmortem human studies.

Although the PFC is crucial for proper working memory function, it is just one node in the distributed cortical network that mediates working memory. Current findings indicate that GABA interneuron alterations are present in multiple nodes in schizophrenia, suggesting that the working memory impairment in the illness could be due to alterations in any given node or emerge from a cascading effect of dysfunction across nodes. The implications of regional differences in the magnitude of GABA findings in layer 3 remains speculative (Hoftman et al., 2018); however, it is possible that these differential disturbances represent, in part, the cellular substrates of observed widespread E/I imbalances across multiple regions of the neocortex in imaging studies of schizophrenia patients (Yang et al., 2016).

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Conflict of interest

David A. Lewis currently receives investigator-initiated research support from Pfizer. In 2016-2018, he served as a consultant in the areas of target identification and validation and new compound development to Merck. Samuel Dienel declares no conflicts of interest.

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