HHS Public Access

Author manuscript

Biomark Neuropsychiatry. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Biomark Neuropsychiatry. 2020 December ; 3: . doi:10.1016/j.bionps.2020.100015.

Prefrontal cortical alterations of glutamate and GABA neurotransmission in schizophrenia: Insights for rational biomarker development

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Abstract

Certain cognitive deficits in schizophrenia, such as impaired working memory, are thought to reflect alterations in the neural circuitry of the dorsolateral prefrontal cortex (DLPFC). Gamma oscillations in the DLPFC appear to be a neural corollary of working memory function, and the power of these oscillations during working memory tasks is lower in individuals with schizophrenia. Thus, gamma oscillations represent a potentially useful biomarker to index dysfunction in the DLPFC circuitry responsible for working memory in schizophrenia. Postmortem studies, by identifying the cellular basis of DLPFC dysfunction, can help inform the utility of biomarker measures obtained *in vivo*. Given that gamma oscillations reflect network activity of excitatory pyramidal neurons and inhibitory GABA neurons, we review postmortem findings of alterations to both cell types in the DLPFC and discuss how these findings might inform future biomarker development and use.

Keywords

GABA; gamma oscillations; Glutamate; Cognition; Working memory; Schizophrenia

1. Introduction

Although positive symptoms are usually the presenting clinical feature of schizophrenia, cognitive deficits have long been regarded as core features of the illness [1]. Cognitive deficits occur with high frequency, are present prior to the initial onset of psychosis, are

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relatively stable over time, and are independent of psychotic symptoms [1,2]. Additionally, the degree of cognitive dysfunction is the best predictor of long-term functional outcome [1].

The cognitive abnormalities in schizophrenia include marked impairments in working memory [3,4], which is the ability to transiently maintain and manipulate a limited amount of information to guide thought or behavior [3,4]. Substantial empirical findings [5], confirmed by meta-analyses [3], indicate that schizophrenia is associated with large working memory deficits (~1.5–2.0 standard deviations below healthy subjects). These deficits cannot be explained by effects of IQ, duration of illness, or antipsychotic medications [3]. In fact, some studies suggest that working memory impairments contribute to disturbances in other cognitive domains in schizophrenia [6]. Thus, the development of novel interventions targeting the affected neural circuitry responsible for working memory deficits in schizophrenia remains a major unmet need.

Working memory is dependent on the integrity of neural circuitry in the dorsolateral prefrontal cortex (DLPFC) [7], and subjects with schizophrenia show altered activation of the DLPFC when performing working memory tasks [8]. Within the DLPFC, gamma oscillatory activity (30–80 Hz) appears to be a neural corollary of mental representation during working memory. For example, gamma oscillatory power scales with working memory load [9], and individuals with schizophrenia fail to increase gamma oscillatory power in the DLPFC in response to working memory demands [10].

Gamma oscillations reflect synchronous activity of large groups of glutamatergic pyramidal neurons located in cortical layers 2–3 [11]. In particular, pyramidal neurons located in layer 3 furnish horizontal connections that provide recurrent excitatory connections among pyramidal neurons and to local inhibitory neurons [12]. These inhibitory GABA neurons spatially tune this excitatory network [13] and play a key role in the generation of gamma oscillations [14] (Fig. 1A). Indeed, disturbances to either excitatory or inhibitory strength in the microcircuit disrupts gamma oscillations [15,16] and working memory function [13,17]. Thus, alterations to the neural components of this layer 3 microcircuit in the DLPFC of individuals with schizophrenia might represent the neural substrate for impaired gamma oscillations and working memory. Consequently, novel therapeutics designed to normalize the function of this circuit would be expected to improve working memory.

Assessing the potential efficacy of these novel therapeutics requires biomarkers, such as gamma oscillations, which reflect the functional integrity of the DLPFC circuitry responsible for working memory. Understanding the basis for altered gamma oscillatory activity and other biomarker measurements in schizophrenia can be informed by postmortem studies, which are able to interrogate the cellular constituents responsible for *in vivo* alterations in the disease state. Consequently, in this review, we summarize findings of altered glutamate and GABA signaling, and the affected cell types that likely give rise to this altered signaling, in the DLPFC of subjects with schizophrenia. We focus on postmortem findings which index the synaptic function, activity, and neurotransmitter synthesis in the glutamate and GABA neurotransmitter systems responsible for gamma oscillations in the DLPFC, and then consider how such findings might inform the development and use of biomarkers in schizophrenia.

2. Glutamatergic Abnormalities in the DLPFC in Schizophrenia

The primary site of glutamatergic neurotransmission, the tripartite synapse, is composed of an excitatory presynaptic bouton that releases glutamate, a postsynaptic cellular membrane loaded with glutamatergic receptors, and an astrocytic process that takes up and deactivates glutamate [18] (Fig. 2A). Glutamate is cycled through the tripartite synapse, beginning in the presynaptic bouton by the glutaminase-mediated conversion of glutamine to glutamate, which is then packaged into vesicles by vesicular glutamate transporters (vGLUTs) localized at the vesicular membrane. Following calcium influx triggered by presynaptic depolarization, these vesicles fuse with the presynaptic membrane, releasing glutamate into the synaptic cleft where it binds to postsynaptic glutamatergic receptors or is cleared by astrocytic excitatory amino acid transporters (EAATs). Within the astrocyte, glutamate is converted by glutamine synthetase to glutamine, which is then released and taken up by the presynaptic bouton via glutamine transporters, beginning the cycle once again.

2.1. Markers of glutamate in presynaptic boutons

In the DLPFC of subjects with schizophrenia, levels of glutaminase activity were found to be four-fold higher [19], suggesting greater conversion of glutamine to glutamate within the presynaptic bouton. However, DLPFC levels of glutaminase mRNA were reported to be unaltered in schizophrenia [20,21].

The two vGLUT proteins are located in different types of axonal boutons: vGLUT1 is predominantly localized within the terminals of cortical and hippocampal projections, whereas efferents from the thalamus and hypothalamus contain vGLUT2 [22,23]. vGLUT levels are a key determinant of the amount of glutamate in vesicles primed for exocytosis within the presynaptic bouton and thus also directly indicate the quantal size of glutamate release [24]. Therefore, analysis of vGLUT1 levels can provide insight into the strength of glutamatergic neurotransmission in the DLPFC. However, findings in the DLPFC of schizophrenia subjects differ across studies. Eastwood and Harrison [25] observed significantly lower vGLUT1 mRNA in layers 1–3 and a nonsignificant decrease in layers 4–6 of the DLPFC. Similarly, a study restricted to DLPFC layer 3 reported significantly lower vGLUT1 mRNA expression in schizophrenia subjects [21]. In contrast, two other investigations of total DLPFC gray matter found no change in either vGLUT1 mRNA [26,27] or protein [27]. Therefore, deficits in vGLUT1 mRNA expression may be pronounced selectively in layer 3 and thus masked when assessing all cortical layers.

2.2. Glutamatergic receptors

Glutamate can bind to any of several post-synaptic receptors upon its release: ionotropic AMPA, NMDA, and kainite receptors, as well as metabotropic receptors [28]. Ionotropic glutamate receptors are voltage-gated ion channels that quickly open and close upon the binding of glutamate.

Ionotropic AMPA receptors are tetramers composed of two GluA subunit dimers [28]. Findings of altered AMPA receptor subunit mRNA levels in schizophrenia have varied across studies, differences which might reflect the impact of age. For example, lower levels

of GluA2 and GluA4 [29], or unaltered levels of GluA2 [21], transcripts in the DLPFC were found in a middle-aged cohort of subjects with schizophrenia, whereas in an elderly cohort, higher levels of GluA2 and GluA4 mRNA were found [30]. Together, these results suggest that AMPA receptor expression level may depend on an interaction between age and disease state.

NMDA receptors are composed of two obligatory GluN1 subunits and two GluN2 and/or GluN3 subunits [28]. In adult PFC, NMDAR-containing synapses predominantly comprise di-heteromeric GluN1/GluN2A and tri-heteromeric GluN1/GluN2A/GluN2B receptors, as GluN3A expression peaks at birth and decreases progressively into adulthood [31,32]. Therefore, the glycine binding subunit GluN3A has been infrequently studied in DLPFC, with reports of elevated [33] or unaltered [34] mRNA levels. However, multiple studies have assessed the required GluN1 subunit and the glutamate binding GluN2 subunit, although these results have also been varied. Multiple studies have found lower levels of NMDA receptor mRNA and protein in the DLPFC of schizophrenia subjects. Specifically, downregulated GluN1, GluN2A, GluN2C mRNA [34–37], and GluN1 protein [34] have been observed in schizophrenia, although such findings have not always achieved statistical significance. Downregulated NMDAR subunits might contribute to working memory impairments in schizophrenia, as lower GluN1 could mean fewer functional receptor units, and lower synaptic GluN2A has been associated with poorer working memory performance [38]. Thus, lower levels of GluN1 and/or GluN2A in schizophrenia could contribute to glutamatergic signaling abnormalities and working memory deficits in the disease.

However, other studies have found elevated levels of GluN1 mRNA with no differences in other subunits [39,40], and one study found no difference in GluN1 mRNA [21]. These varied findings might stem from cohort-specific factors such as age and exposure to antipsychotic medications. For example, the studies reporting higher levels of GluN1 primarily used tissue from antipsychotic-treated, elderly subjects [39,40], whereas the studies that found levels that were lower or not different in schizophrenia [21,39,40] used tissue from middle-aged subjects. Furthermore, Sokolov and colleagues [37] found a negative relationship between duration of time off antipsychotic treatment prior to death and GluN1, such that the longer the duration of no treatment, the lower the levels of GluN1. In contrast, schizophrenia subjects treated within 72 h prior to death exhibited levels of GluN1 that were similar to unaffected comparison subjects [37]. Therefore, it appears that GluN1 may be elevated with both age and treatment duration.

Activation of the NMDA receptor is dependent upon the binding of its ligand and a co-agonist such as D-serine or glycine. Unfortunately, D-serine and its precursor L-serine, have yet to be assessed in postmortem tissue. Serine racemase, which synthesizes D-serine, has been assessed in multiple studies, but with varied results. Protein levels of the D-serine synthesis enzyme have been observed to be lower [41], unaltered [42], or elevated (but mRNA expression did not differ) [43]. In contrast, the degradation of serine racemase has consistently been reported to be unaltered in schizophrenia [41,43].

Kynurenic acid is a noncompetitive antagonist at the glycine site on NMDA receptors [44], such that the presence of kynurenic acid at the glycine site results in the receptor failing to

activate when glutamate binds. Thus, if available in excess, kynurenic acid can downregulate NMDA receptor activity. Levels of kynurenic acid protein have been reported to be elevated in the DLPFC in schizophrenia [45,46], potentially indicating higher antagonism of the NMDA receptor glycine site.

Although levels of NMDA receptor signaling in postmortem tissue are often inferred by assessing related activity-dependent markers, other approaches have been developed to assess NMDA receptor activation in postmortem tissue, including postmortem tissue-stimulation [47] and microtransplantation of postmortem cellular membranes into *Xenopus* oocytes [48]. Although glutamate receptors desensitized without additional pharmacostimulation [48], a more pronounced neuregulin-1 induced suppression of NMDA receptor activity in the postmortem prefrontal cortex of schizophrenia subjects was observed using tissue-stimulation [47]. Neuregulin-1 and its receptor erbB have been implicated in the pathology of schizophrenia [49–51] (for review please see [52]) due to their modulation of glutamatergic signaling [53,54]. Therefore, these results suggest a potential mechanism for lower NMDA receptor activation (i.e., NMDA receptor hypofunction) in the prefrontal cortex of schizophrenia subjects.

Unlike other ionotropic receptors, kainate receptors exhibit slow response recovery and are pre-synaptically localized [28]. Studies of kainate receptors in schizophrenia have produced varied findings. Assessment of the mRNA of subunits 1 −5 in a middle-aged cohort found that only GRIK1 was lower [55], but assessment in an elderly cohort revealed unaltered GRIK1, elevated GRIK3, and downregulated GRIK5 mRNA levels [56]. In a second study of elderly subjects that also assessed the role of antipsychotic treatment, schizophrenia subjects who were untreated for 6 months prior to death exhibited the lowest levels of GRIK3 and GRIK4 mRNA; subjects who had stopped treatment in the 11 weeks prior to death had intermediate mRNA levels; and schizophrenia subjects who had been treated within 72 h prior to death exhibited levels of GRIK3 and GRIK4 transcripts that did not differ from comparison subjects [37]. Therefore, like the other ionotropic receptors, the expression of kainate receptors may depend upon age and treatment status.

Metabotropic glutamate receptors are transmembrane G-protein-coupled receptors (GPCRs) that respond more slowly to glutamate binding, but can have a longer duration of action by initiating signaling cascades [28]. Metabotropic glutamate receptors are categorized into subfamilies: I, II, and III [28]. Group I mGluRs (mGluR1 and mGluR5) are primarily postsynaptic, where they modulate the activity of NMDA receptors, whereas group II (mGluR2 and mGluR3) and III (mGluR4, mGluR6–8) receptors are presynaptic and modulate presynaptic glutamatergic release [28]. Transcript and protein levels of group I receptors are higher in prefrontal cortex of schizophrenia subjects [57–59], although the tissue used in these studies were not limited to DLPFC. In contrast, one group observed downregulated mGluR5 protein in DLPFC, although these results did not reach significance [60]. Group II mGluR3 mRNA and mGluR2/3 protein were upregulated (although not always significantly so) in DLPFC [58,60,61], indicating higher presynaptic glutamatergic modulation.

Glutamatergic signaling also depends on the proper glutamate receptor localization within the synapse and the integrity of the proteins responsible for receptor clustering within postsynaptic microdomains. Intracellular molecules enriched in the postsynaptic density (PSD) target glutamate receptors to the synaptic membrane, modulate receptor activity, and regulate synaptic plasticity. The predominant PSD protein, PSD-95 (for review please see [62]) interacts with NMDA receptor subunits, AMPA receptors, tyrosine kinase receptors, ion channels, and other cytoplasmic proteins, and therefore can modulate signaling cascades that congregate within the PSD [63]. Lower levels of PSD-95 transcripts and protein have been observed in the DLPFC of schizophrenia subjects [40,62,64–71], potentially impacting PSD-related neuregulinerbB signaling [72], dendritic spine enlargement, synaptic strength, and neuronal connectivity [73].

2.3. Cortical astrocytic clearance of glutamate in schizophrenia

Synaptic glutamate is tightly regulated through several mechanisms in the tripartite synapse to maintain homeostatic balance [74]. Different subtypes of excitatory amino acid transporters (EAATs) are located on all parts of the tripartite synapse (for review please see [75]); however, astrocytic EAAT2 transports ~90% of extracellular glutamate to the intracellular space of the astrocyte, preventing hyperexcitation of nearby neurons and maintaining homeostatic balance. The density of EAAT2 at the synaptic membrane also appears to shift with changes to the excitatory/inhibitory balance as it can be increased or decreased, respectively, via pharmacological stimulation or blockade of neuronal activity *in vitro* [76,77]. Therefore, altered glutamate transport can result in glutamate spillover, potential “runaway” excitatory transmission, and the promotion of neuronal cell death (for review please see [78,79]).

Analysis of total DLPFC gray matter has not detected alterations in EAAT2 protein or mRNA levels in schizophrenia [80,81]; however, when the analysis was limited to cortical layers 3 and 5, EAAT2 transcripts were found to be lower, although non-significantly [58]. Additionally, age may influence EAAT2 expression in schizophrenia. For example, Ohnuma et al. [58] found lower EAAT2 in layer 3 of the DLPFC in elderly schizophrenia subjects, whereas higher EAAT2 mRNA levels were observed in DLPFC layer 3 in a younger (~45 years of age) cohort of schizophrenia subjects [21]. However, the effect of age may also impact EAAT2 localization, as elevated protein levels were observed in fractionated extrasynaptic membranes in a second elderly cohort [82].

Lower glutamine synthetase protein has been found in the DLPFC [83], suggesting downregulated glutamate-to-glutamine conversion within astrocytes following EAAT2 intake [84]. However, this finding was not replicated by other groups in studies of various prefrontal cortical regions [19,84,85].

2.4. Cell type-specific alterations in morphology of cortical glutamatergic neurons

Despite differences across studies for some findings, in aggregate the data reviewed above support the idea that glutamatergic signaling is altered in the DLPFC in schizophrenia subjects, especially in layer 3 (Fig. 1B). This apparent laminar-specificity is supported by evidence of pyramidal cell type-specific morphological alterations in schizophrenia. For

example, dysregulated glutamatergic activity within the DLPFC would be expected to alter cellular and dendritic spine morphology on glutamatergic pyramidal neurons. Dendritic spines, which are almost exclusively located on pyramidal neurons, are the primary site of glutamatergic receptors, and their morphology and number are activity-dependent [86]. Consistent with molecular evidence of altered glutamate signaling in DLPFC layer 3, all studies published to date observed findings of lower spine density and shorter dendritic length in DLPFC layer 3 pyramidal neurons from schizophrenia subjects [87–89] (Fig. 1B). In contrast, such alterations were not observed in layer 5 or 6 pyramidal neurons [90].

Somal size has often been considered a proxy measure for other structural and cytoskeletal abnormalities, including dendritic length and spine density [88,91,92]. Like the deficits in dendritic spine density, pyramidal neuron cell body size in schizophrenia is smaller in layer 3 [88,93,94] (Fig. 1B) but unaltered in layers 5 and 6 [90,94].

In concert, the findings from molecular studies support the provisional conclusion from molecular studies that deficits in glutamatergic signaling in DLPFC layer 3 could contribute to impaired gamma oscillations and working memory in schizophrenia.

3. Prefrontal Cortical GABA Abnormalities in Schizophrenia

Although gamma oscillations are thought to reflect the synchronized activity of large groups of pyramidal neurons, the rhythmic firing of inhibitory GABA neurons at gamma frequency is essential for this synchronized activity [95], as activation of GABA neurons is sufficient to drive oscillatory activity *in vitro* [15,96]. Altered GABA signaling in schizophrenia may therefore also contribute to impaired frontal gamma oscillations and working memory disturbances in schizophrenia.

GABA levels are technically challenging to measure directly in human postmortem tissue, but the strength of GABA neurotransmission can be inferred by measuring levels of mRNA transcripts and their cognate proteins that regulate GABA in presynaptic terminals (Fig. 2B). The availability of synaptic GABA is controlled by the 67 and 65 kDa isoforms (GAD67 and GAD65, respectively) of the synthesizing enzyme glutamic acid decarboxylase, which converts glutamic acid into GABA. Many, but not all, GABA neurons appear to contain both isoforms [97]. GAD67 is responsible for most cortical GABA synthesis [98]; GAD67 largely exists in the cofactor-saturated active form and is therefore regulated primarily by transcription. In contrast, GAD65 appears to be active only during periods of high neuronal activity [99]. In addition to the availability of GABA via synthesis, the strength of GABAergic neurotransmission is also dependent on the accumulation of GABA into synaptic vesicles, mediated by the vesicular GABA transporter (vGAT), which can serve as a key regulator of inhibitory strength in response to homeostatic signals of network activity [100,101]. Finally, the strength of GABA neurotransmission is regulated by clearance of GABA from the synaptic cleft, largely carried out by GABA transporter 1 (GAT1) on the presynaptic terminal. In the primate DLPFC, GAT1 is known to regulate the inhibitory post synaptic potentials of perisomatic GABA inhibition and to prevent GABA spillover at both perisomatic and dendritic-targeting GABA inputs [102] (Fig. 2B). Together, levels of these

three presynaptic markers of GABA neurotransmission in the postmortem brain can provide insight into the integrity of GABAergic signaling in schizophrenia.

3.1. GABA in presynaptic boutons in schizophrenia

In the DLPFC of schizophrenia subjects, lower levels of GAD67 mRNA in total gray matter have been consistently reported across cohorts of subjects and between research groups [103]. Two *in situ* hybridization studies revealed a GAD67 deficit across cortical layers 2–5, with pronounced deficits in layers 3–4 [104,105]. Protein levels of GAD67, measured by Western blot and immunofluorescence, are also lower in the disease [106], consistent with the idea that the regulation of the functional enzyme is principally through transcription. In contrast, levels of GAD65 have not been reported to be lower in the illness, although GAD65 may be lower in subjects with schizoaffective disorder [107]. Findings of lower levels of GAD67 mRNA and protein support the notion that presynaptic measures of inhibitory strength are diminished in the DLPFC of schizophrenia subjects.

Despite marked reductions in GAD67 and a likely impairment of GABA synthesis in schizophrenia, levels of vGAT mRNA appear to be normal or only modestly lower in most studies of total tissue homogenates [26,108] or in samples restricted to layer 3 [21]. Consistent with mRNA findings, levels of vGAT protein per bouton are unaltered in schizophrenia [109]. Thus, in contrast to layer-specific deficits in vGLUT1 mRNA, schizophrenia does not appear to be associated with deficits in vesicular packaging of GABA. Similar to vGAT, mRNA levels of GAT1 are not altered in total gray matter samples of DLPFC from individuals with schizophrenia [108], although a subset of GABAergic neurons may express lower levels of GAT1, suggested by a ~25% deficit in the density of GAT1 mRNA positive neurons in schizophrenia [110]. These findings highlight the importance of cell type-specific studies in schizophrenia [111], as measures of GAT1 mRNA in total tissue homogenates might mask deficits in a particular subset of neurons.

Indeed, these *in situ* hybridization findings of undetectable GAT1 [110] and GAD67 [105] mRNA in a subset of neurons suggest that specific subtypes of GABA neurons may be differentially affected in schizophrenia. GABA neurons are typically classified based on the expression of certain molecular markers that are largely distinct: the calcium binding proteins parvalbumin (PV) or calretinin (CR), and the neuropeptide somatostatin (SST). Understanding the functional consequences of alterations in transcripts and proteins related to GABA neurotransmission depends on knowing in which subtypes of GABA neurons these alterations are present. Thus, we review cell type-specific findings of altered levels of markers that index GABA neurotransmission in schizophrenia (Fig. 1B).

3.2. PV interneurons in the DLPFC are altered in schizophrenia

In the DLPFC of schizophrenia subjects, deficits in PV mRNA have been consistently replicated [112–117]. The deficit is apparent in total gray matter tissue homogenates, but laminar analysis reveals a pronounced deficit in layers 3–4, where PV cell bodies are enriched [115]. The deficits in PV mRNA are accompanied by comparable decrements in levels of PV protein in cell bodies [118] and axon terminals [119]. These changes to do not appear to reflect reduced numbers of PV neurons in the illness, as the density of PV mRNA-

positive neurons [115] and PV-immunoreactive neurons [118,120–122] are not altered in the DLPFC of schizophrenia subjects. In the few studies which report a deficit in PV neuron density in the DLPFC of schizophrenia subjects [123–125], lower levels of PV immunoreactivity per neuron may have rendered these neurons undetectable at lower levels of magnification [120]. Together, these findings of lower PV in schizophrenia suggest that PV neurons may be one of the subtypes of GABA neurons that exhibit deficits in GABA signaling in schizophrenia.

Indeed, PV neurons exhibit other alterations, including pronounced deficits in GAD67 expression such that ~45% of PV neurons lack detectable GAD67 mRNA [115]. Although PV neurons can be further subclassified based on their characteristic morphology and the targets of their axon terminals, studies of PV and GAD67 mRNA have not revealed whether both subtypes of PV neurons exhibit similar alterations, but studies at the protein level have been informative. The first subtype, the PV basket cell, primarily targets the perisomatic region of pyramidal neurons where the postsynaptic membrane is enriched in $GABA_A$ receptors containing the α1 subunit. The second subtype, PV chandelier cells, form distinctive cartridges of axon terminals that innervate the axon initial segment (AIS) of pyramidal neurons (thus termed ‘axo-axonic’ neurons) which are enriched with $GABA_A$ receptors containing the α2 subunit [126,127]. Importantly, chandelier cells exclusively use GAD67 for GABA synthesis, whereas basket cells use both GAD65 and GAD67 [97], a difference supported by single cell-transcriptomic findings [128].

Further studies of these two subtypes of PV neurons have revealed that PV basket cells, and not chandelier cells, exhibit deficits in GAD67 levels. In PV terminals that are also GAD65 positive, and therefore must represent the axon terminals of PV basket cells, protein levels of PV [119] and GAD67 [106] are lower. However, GAD67 protein levels are not altered in the distinctive axon cartridges of chandelier cells [109]. PV basket cells therefore represent a likely source of the GAD67 mRNA deficit observed in the middle layers of the DLPFC in schizophrenia subjects. The basis for the PV basket cell-selective deficits in GAD67 and PV in schizophrenia might be fewer excitatory inputs to PV basket cells in the middle layers of the DLPFC [118] or alterations in the perineuronal nets [120] that surround basket cells and not chandelier cells [129].

In addition to deficits in presynaptic GABA function in PV basket cells, most studies also report a deficit in the $GABA_A$ receptor subunits that are postsynaptic to these inputs. Both the α1 subunit and the β2 subunit, which colocalizes with the a1 subunit at basket cell inputs [130], are lower in schizophrenia especially in layers 3–4 [131], where PV basket cell terminals are highest and PV chandelier cell terminals are lowest [132]. Indeed, α1 mRNA levels are lower specifically within pyramidal neurons in deep layer 3 [133], strongly supporting the notion that in addition to deficits in presynaptic GABA function in PV basket cells, the postsynaptic efficacy of basket cell inputs to pyramidal cells is weaker in schizophrenia.

Although PV chandelier cells may not exhibit deficits in GABA synthesis, the density of chandelier cell cartridges, which are identified by the immunoreactivity of GAT1 in distinctive vertical arrays, is lower across layers 2–4 in the DLPFC of schizophrenia subjects

[134,135]. The lower density of cartridges is thought to reflect their lower detectability due to reduced GAT1 immunoreactivity, rather than an inherent structural deficit. Indeed, the density of cartridges identified by vGAT is not lower in the illness [136]. Thus, chandelier cells may be among the subtypes of GABA neurons that exhibit undetectable GAT1 mRNA levels, although this deficit is also likely present within PV basket cells: lower GAT1 is observed in samples of layer 3 PV basket cells, identified by a characteristic perineuronal net [113].

The postsynaptic side of chandelier cell inputs also appears to be altered in schizophrenia, but in ways that are distinct from alterations to the postsynaptic side of PV basket cell inputs. As previously mentioned, chandelier cell inputs tend to be populated by $GABA_A$ receptors enriched in the α2 subunit [126,127], and both the mRNA expression of this subunit and the density of cartridges positive for α2 [137] are upregulated in schizophrenia. Importantly, this upregulation is observed prominently in layer 2 [131,137], where the majority of chandelier cell inputs are located in human neocortex [132].

In sum, studies of PV neurons in schizophrenia have consistently revealed disease-associated alterations in markers that index their function in GABA neurotransmission (Fig. 1B). These studies highlight the critical importance of cell type-specific studies of the postmortem human brain, as measures at total tissue levels do not reveal in which subtypes of neurons these differences may be occurring. Together, these data strongly suggest that PV basket cells are a major contributor to the GAD67 deficit in the middle layers of the DLPFC in schizophrenia, and that impairments in GABA signaling from these neurons underlie altered gamma oscillatory function in the supragranular layers of the DLPFC in the disease.

3.3. The CR interneuron subtype does not appear to be altered in the DLPFC of schizophrenia

While PV neurons likely represent the source of the GAD67 deficit in the middle layers, GAD67 is lower in superficial layer 2 as well [105], raising the possibility that other GABA neuron subtypes contribute to this deficit. Interneurons expressing calretinin (CR) are also enriched in the superficial layers and primarily target other interneurons, disinhibiting pyramidal cells [138]. However, convergent lines of evidence suggest that this subtype may not be altered in schizophrenia. First, tissue levels of CR mRNA [112,114–116] and protein [114] are unaltered in schizophrenia (Fig. 1B). Second, neither the density of CR mRNA-expressing [115] nor of CR-immunoreactive neurons [124,139] are altered in schizophrenia. Third, alterations that are present within the PV neuron population, such as a lower complement of excitatory inputs onto the soma, are not present within the CR neuron population [118]. The lack of alteration in CR suggest that this subtype might not contribute to the alterations in markers of GABA neurotransmission, including GAD67, observed in total tissue. However, GAD67 levels have yet to be directly assessed within CR neurons.

3.4. Deficits in SST neurons in the DLPFC of schizophrenia are robust and highly replicated

Thus, another subtype of GABA neuron expressing SST, enriched in the superficial layers 2–3 as well as layer 5 and the superficial white matter, might be the source of the GAD67

deficit in these layers. SST cells primarily target the distal dendrites of pyramidal neurons and gate the excitatory inputs that pyramidal neurons receive [140,141]. However, these neurons also provide dendritic inhibition onto PV neurons, and the functional consequences of alterations to SST neurons might depend on whether they target excitatory or inhibitory cells [142,143]. SST cells in layers 2 and superficial layer 3 appear to receive a large proportion of the excitatory inputs from layer 3 pyramidal neurons [12], suggesting that SST cells participate in the layer 3 microcircuit that generates working memory and gamma oscillatory activity.

In schizophrenia, lower levels of SST mRNA have been consistently reported in the DLPFC across multiple cohorts and multiple research groups. Indeed, these deficits are robust relative to other GABA deficits and are present in a large proportion of subjects with schizophrenia [114,117,144,145]. Thus, these disease-related deficits in SST mRNA support the notion that these cells contribute to the GAD67 deficit in schizophrenia (Fig. 1B). However, identifying these and other alterations of markers related to GABA neurotransmission within SST neurons is methodologically challenging, as the density of DLPFC SST mRNA-positive neurons is 25% lower in schizophrenia [145]. Given the lack of a total neuron deficit in the illness [146] and the presence of lower mean SST mRNA levels in the remaining neurons [145], it is likely that the deficit in SST mRNA-positive neuron density in the illness reflects an inability to detect SST in some neurons, rather than a lower number of SST neurons in schizophrenia. Although this assumption has yet to be directly tested, if true, future studies should utilize proxy markers of SST neurons that are unaltered in schizophrenia in order to directly assess disease-related alterations in this population.

Although SST neurons are present across cortical gray matter layers and the subcortical white matter, both SST and GAD67 levels are lower in the superficial gray matter, but not in deep layer 6 or the superficial white matter [105,145]. This layer-specific deficit suggests that DLPFC SST neuron alterations in schizophrenia reflect alterations to the microcircuit in the superficial layers of the neocortex that involves these SST neurons as well as PV neurons and deep layer 3 pyramidal neurons. Thus, alterations in SST neurons could also contribute to impaired gamma oscillatory power in the DLPFC and working memory deficits in schizophrenia.

4. Conclusions

As reviewed above, alterations in glutamate and GABA neurotransmission in schizophrenia are most marked in the supragranular layers, and especially in a microcircuit composed of excitatory layer 3 pyramidal neurons, deep layer 3-layer 4 PV basket cells and layer 2-superficial layer 3 SST neurons (Fig. 1B). Given the apparent key role of this circuit in gamma oscillations and working memory, working memory task-related gamma oscillatory activity might represent a useful biomarker for (1) identifying which individuals with schizophrenia might benefit from pro-cognitive therapeutics targeting this circuit and (2) for assessing the efficacy of such therapeutic agents.

One example of this approach has been the investigation of a positive allosteric modulator with relative selectivity for $GABA_A$ receptors containing $\alpha 2/3$ subunits. In an initial study, a

drug with these features was associated with both greater gamma power during a task requiring working memory and improved performance on two different working memory tasks in subjects with schizophrenia [147]. A subsequent study, which did not include any biomarker measures, failed to show improvement in cognition [148], although a number of limitations in the potency of the medication and the study design may have contributed to the negative findings [149]. Non-pharmacological interventions are also using this strategy for biomarkers. For example, an ongoing clinical trial utilizing direct current stimulation to enhance frontal cognitive function in individuals with schizophrenia includes both behavioral assessments and changes in gamma oscillatory function as outcome measures (e.g., ClinicalTrials.gov identifier NCT02739347). Gamma oscillations might therefore not only be a useful physiologic measure of frontal cortical networks during working memory tasks as secondary measures in clinical trials, but also provide a translatable measure from preclinical models for the cognitive dysfunction of individuals with schizophrenia [16,150].

Other *in vivo* measures of DLPFC glutamate and GABA signaling may also serve as biomarkers in schizophrenia, but the currently available tools appear to lack the resolution needed to specifically reflect the integrity of the microcircuit. For example, magnetic resonance spectroscopy (MRS) can measure the levels of glutamate and GABA in frontal regions of the cortex. However, in contrast to consistent and replicated findings of alterations to these neurotransmitter systems reported in postmortem studies, the MRS literature on glutamate and GABA levels in schizophrenia is mixed [151,152]. This variability may be due to the fact that glutamate and GABA peaks measured in MRS are difficult to distinguish at commonly used magnetic field strengths (1.5 or 3 Tesla). Indeed, results of recent 7T MRS studies have been more consistent in reporting lower glutamate and GABA levels in the frontal cortex of subjects with schizophrenia [153,154]. However, MRS measures total tissue levels of glutamate and GABA which includes levels associated with metabolism and not just neurotransmission. Approaches utilizing novel PET radioligands may overcome these limitations by directly indexing the availability of GABA in the synapse. For example, studies utilizing this approach support the idea that GABA synthesis in the frontal cortex is impaired in schizophrenia subjects [155]. Future studies utilizing other novel PET radioligands may provide more specificity to index the neural circuitry responsible for working memory in schizophrenia subjects *in vivo*.

Another approach to indexing frontal circuit function *in vivo* is through task-related alterations in cerebral blood flow in the DLPFC, indexed by fMRI, in schizophrenia subjects. Indeed, these studies were the first to provide insight into how DLPFC dysfunction could underlie deficits in working memory [156]. However, this imaging measure is similarly less specific than task-evoked gamma, as differences in fMRI measures can be driven by numerous factors other than alterations in glutamatergic and GABAergic signaling in the superficial layers. Recent advances in laminar-specific fMRI in humans have supported the importance of supragranular layers in the maintenance of working memory function [157], raising the possibility that this technique might be applied to subjects with schizophrenia to reveal layer-specific, task-evoked alterations in fMRI measures during working memory.

As these and other approaches in *in vivo* measurements advance, they may provide greater resolution into the function of specific neural circuits and thus offer new biomarkers that are informed by the neurobiology of schizophrenia. Such biomarkers offer the promise of important linkages between circuit-based molecular targets for new medications, as revealed by postmortem studies, and the means to better index the function of the circuit targeted by pro-cognitive therapeutics.

Acknowledgment

This work was supported by NIH grant MH043784 (D.A.L) and F99/K00 MH122943 (K.E.S).

Declaration of competing interest

David A. Lewis currently receives investigator-initiated research support from Pfizer and Merck. Kirsten E. Schoonover and Samuel J. Dienel declare no conflicts of interest.

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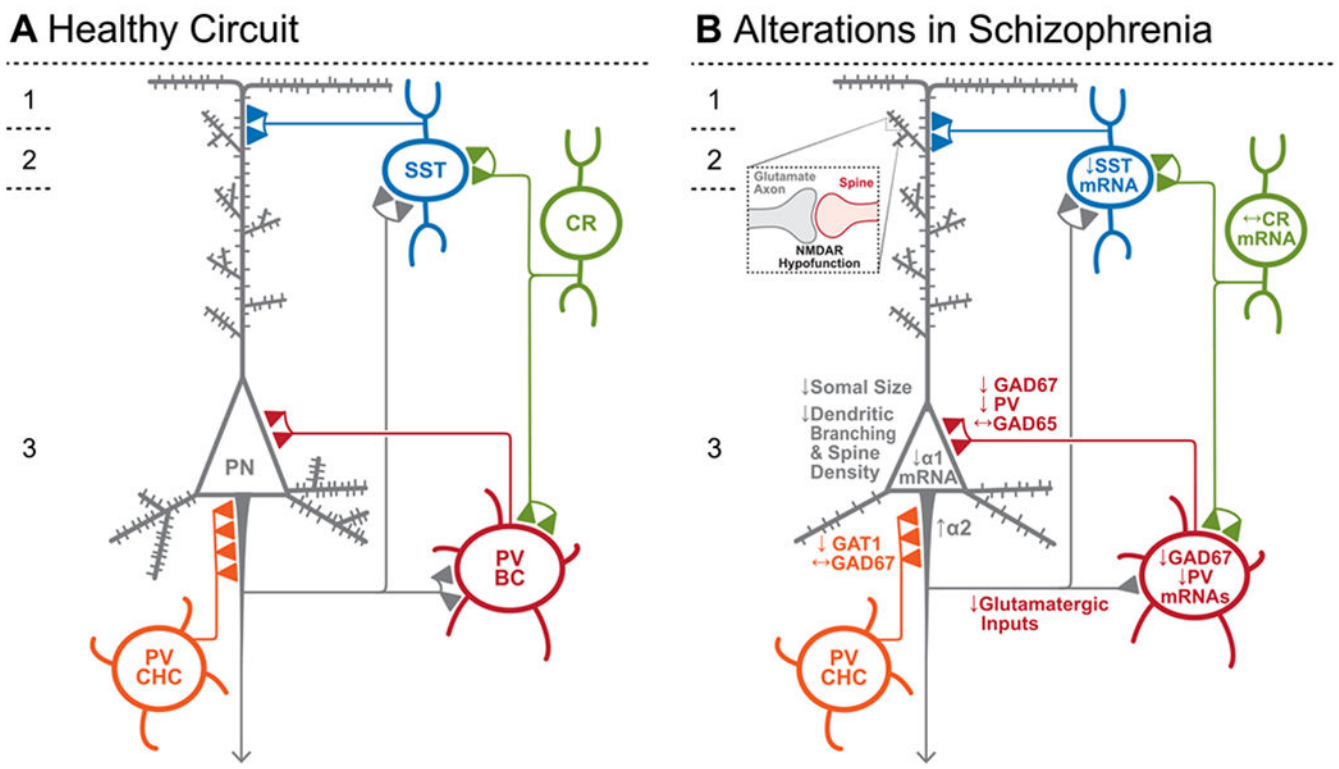

Fig. 1.

Schematic of components of the DLPFC layer 3 microcircuitry thought to be responsible for gamma oscillations and working memory. (A) In the unaffected circuit, current data support the notion that excitatory inputs recruit the activity of parvalbumin basket cells (PV BC) which inhibit large groups of pyramidal neurons (PN) simultaneously, thus synchronizing their subsequent activity. This synchronous activity occurs as gamma frequency oscillations which is thought to reflect the neural representation of working memory. Excitatory axon terminals from layer 3 pyramidal neurons also synapse onto somatostatin (SST)-expressing interneurons in layers 2–3, which target the distal dendrites of other groups of pyramidal neurons and inhibit pyramidal neurons that encode stimuli not related to the working memory memoranda. Calretinin (CR)-expressing interneurons target both PV and SST neurons, serving to disinhibit pyramidal neurons. PV chandelier cells (PV CHC) form connections directly onto the axon initial segment, and thus are poised to rapidly suppress the output of pyramidal neurons. (B) In schizophrenia, the morphological alterations to pyramidal neurons, which include a lower complement of dendritic spines, lower dendritic spine density and smaller somal sizes, suggest that these cells are hypoactive, leading to weaker recruitment of PVBCs and thus lower gamma oscillatory power. The hypoactivity of pyramidal neurons in layer 3 might arise from NMDAR hypofunction on dendrites receiving other excitatory inputs. Lower $GABA_A$ α1 receptor subunit mRNA expression in pyramidal neurons, together with lower PV and GAD67 in the PV BC terminals, suggests that both pre- and postsynaptic inhibition of PV BCs onto pyramidal neurons is lower. While the cell type-specific deficits in SST neurons are less well-defined, lower SST mRNA expression suggests these neurons may have an impaired ability to laterally inhibit other populations of pyramidal cells. CR cells do not exhibit lower levels of CR mRNA or protein in the illness,

suggesting that these cells may not be affected in schizophrenia. PV CHCs express normal levels of GAD67, but lower GAT1 in their cartridges and higher levels of the $GABA_A$ receptor α2 subunit on the axon initial segment of the pyramidal neuron. Together, these alterations suggest that GABA signaling from PV CHCs might be higher in schizophrenia.

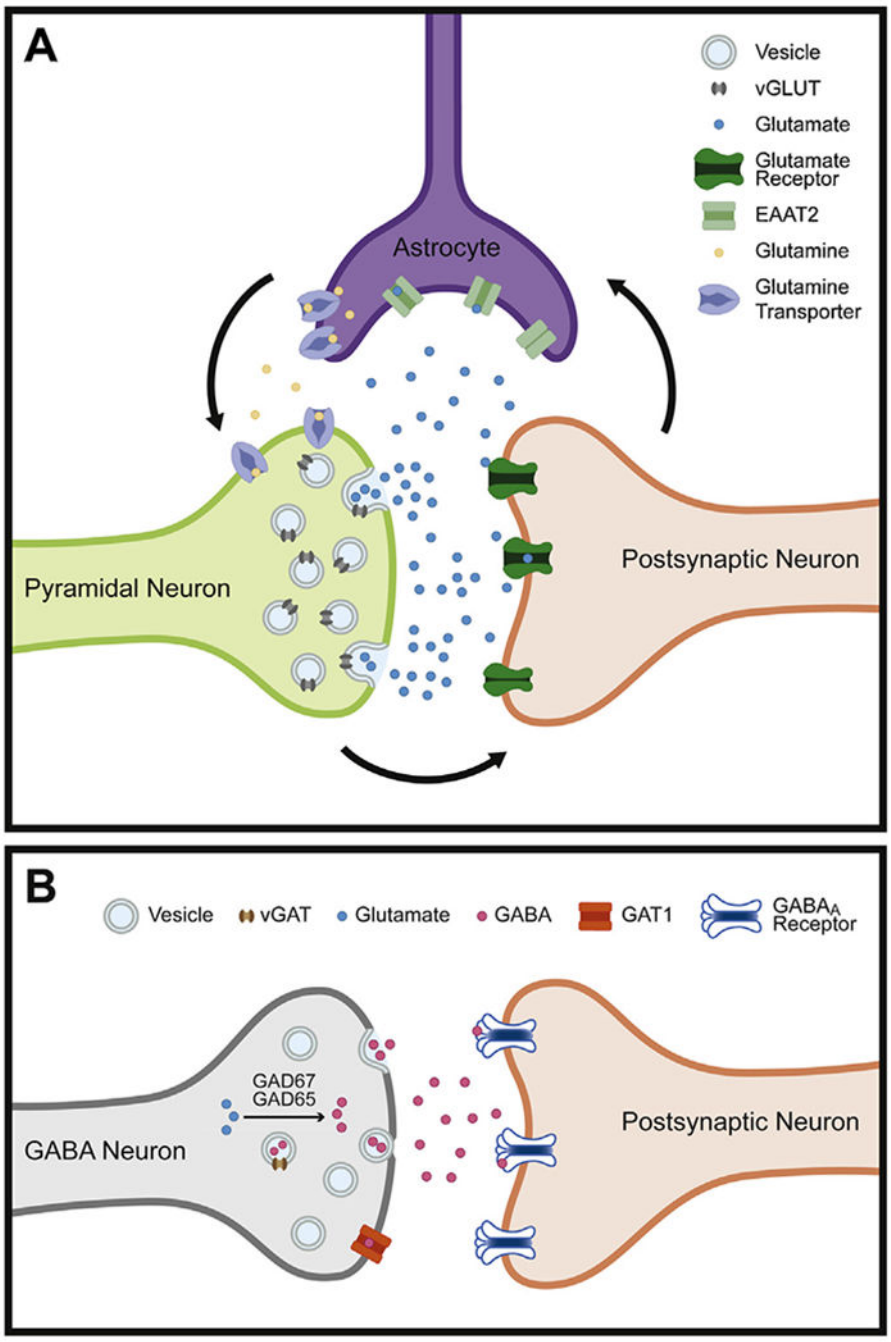

Fig. 2.

Schematic of excitatory and inhibitory synapses. (A) The tripartite glutamate synapse. In the presynaptic pyramidal neuron, glutamine is converted to glutamate by glutaminase and packaged into synaptic vesicles by the vesicular glutamate transporter (vGLUT). Following release into the synaptic cleft, glutamate binds to postsynaptic glutamate receptors located on a postsynaptic neuron. Glutamate is then cleared from the synaptic space through excitatory amino acid transporters (EAATs) on nearby astrocytes. Within the astrocyte, glutamate is converted to glutamine by glutamine synthetase before being transported to

presynaptic neurons and beginning the process again. (B) The inhibitory GABA synapse. In the presynaptic terminal of a GABA neuron, GABA is synthesized from glutamate by the enzymes glutamic acid decarboxylase 67 and 65 (GAD67 and GAD65, respectively). GABA is packaged into vesicles via the vesicular GABA transporter (vGAT). After release into the synaptic cleft, GABA acts on GABAA receptors located on the postsynaptic neuron, opening chloride channels and hyperpolarizing the membrane. The action of GABA in the synapse is terminated, in part, by the reuptake of GABA into the presynaptic axon by GABA membrane transporter 1 (GAT1).