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Cell and Receptor Type-Specific Alterations in Markers of GABA Neurotransmission in the Prefrontal Cortex of Subjects with Schizophrenia

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Abstract

Impairments in cognitive control, such as those involved in working memory, are associated with dysfunction of the dorsolateral prefrontal cortex (DLPFC) in individuals with schizophrenia. This dysfunction appears to result, at least in part, from abnormalities in GABA-mediated neurotransmission. In this paper, we review recent findings indicating that the altered DLPFC circuitry in subjects with schizophrenia reflects changes in the expression of genes that encode selective presynaptic and postsynaptic components of GABA neurotransmission. Specifically, using a combination of methods, we found that subjects with schizophrenia exhibited expression deficits in GABA-related transcripts encoding presynaptic regulators of GABA neurotransmission, neuropeptide markers of specific subpopulations of GABA neurons, and certain subunits of the $GABA_A$ receptor. In particular, alterations in the expression of the neuropeptide somatostatin suggested that GABA neurotransmission is impaired in the Martinotti subset of GABA neurons that target the dendrites of pyramidal cells. In contrast, none of the GABA-related transcripts assessed to date were altered in the DLPFC of monkeys chronically exposed to antipsychotic medications, suggesting that the effects observed in the human studies reflect the disease process and not its treatment. In concert with previous findings, these data suggest that working memory dysfunction in schizophrenia may be attributable to altered GABA neurotransmission in specific DLPFC microcircuits.

Keywords

Postmortem; Neuropeptides; Somatostatin; $GABA_A$ receptor

Introduction

Although psychosis is usually the presenting and most striking clinical feature of schizophrenia, disturbances in cognition have been regarded as central to the illness since its initial description as dementia praecox. These impairments are thought to be the core features of the illness (Elvevåg and Goldberg, 2000) for the following reasons. First, a characteristic pattern of cognitive deficits occurs with high frequency, is relatively stable over time, and is independent of the psychotic symptoms of the illness (Gold, 2004). Indeed, if cognitive deficits are defined as the failure to achieve the expected level of cognitive functioning, then almost all patients with schizophrenia are cognitively impaired (Keefe *et al.*, 2005). Second, cognitive abnormalities have been found throughout the life span of affected individuals, including

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during childhood and adolescence and at the initial onset of psychosis (Saykin *et al.*, 1994; Green, 1998; Davidson *et al.*, 1999; Cosway *et al.*, 2000). Third, the unaffected relatives of individuals with schizophrenia also exhibit similar, although milder, cognitive deficits (Egan *et al.*, 2001; Sitskoorn *et al.*, 2004). Finally, the degree of cognitive dysfunction is the best predictor of long-term functional outcome for affected individuals (Green, 1996; Harvey *et al.*, 1998). Thus, the development and implementation of effective treatments for cognitive deficits remains a major goal in schizophrenia research (Hyman and Fenton, 2003).

Of the demonstrated types of cognitive impairments in schizophrenia, substantial research has focused on working memory, typically defined as the ability to transiently maintain and manipulate a limited amount of information in order to guide thought or behavior (Miller and Cohen, 2001). Working memory involves several component processes including storage buffers for different domains of information [*e.g.*, visuo-spatial scratch pad (short-term storage of visual information) and phonological loop (articulatory rehearsal and phonological coding of verbal information)] and a central executive component that controls the manipulation of information within the storage buffers (Baddeley, 1992). Although more work is needed to understand the functional integrity of all working memory components in schizophrenia (*e.g.*, visuo-spatial scratchpad and episodic buffer), research in this area suggests two robust conclusions. First, individuals with schizophrenia exhibit relatively little impairment on tasks that depend primarily on the phonological loop and have intact activation of the brain regions (*e.g.*, ventral lateral prefrontal cortex and posterior parietal cortex) that mediate the components of the phonological loop (Barch, 2006). Second, in contrast, measures of central executive function or cognitive control, especially the manipulation of transiently stored information, are clearly disturbed in subjects with schizophrenia (Cannon *et al.*, 2005; Tan *et al.*, 2005). Thus, the widely-reported alterations in working memory function in schizophrenia may be considered representative of deficits in a larger class of cognitive control processes.

Working memory impairments in schizophrenia are accompanied by altered activation of the dorsolateral prefrontal cortex (DLPFC), a brain region known to be associated with cognitive control (Goldman-Rakic, 1999; Weinberger *et al.*, 2001; Callicott *et al.*, 2003). For example, under appropriate conditions of cognitive activation, decreased blood flow or glucose utilization in the DLPFC appears to be a robust finding in schizophrenia (Weinberger *et al.*, 1986; 1988; Taylor, 1996), although these disturbances are less reliably found in the resting state (Buchsbaum, 1990; Andreasen *et al.*, 1992; Gur and Gur, 1995). Most interpretations of these results converge on the idea that DLPFC dysfunction in schizophrenia is task-specific and related to working memory impairment or cognitive control (Goldman-Rakic, 1987; Carter *et al.*, 1998; Smith and Jonides, 1999). Studies examining neural activity using fMRI indicate that during working memory tasks, subjects with schizophrenia exhibit an altered relationship between working memory load, behavioral performance and DLPFC activation (Van Snellenberg *et al.*, 2006). Although a direct experimental demonstration is still needed, the available data are consistent with the hypothesis that subjects with schizophrenia exhibit a left-shifted, inverted-U function between task difficulty and DLPFC activation (Callicott *et al.*, 2003; Manoach, 2003). That is, schizophrenia is not associated with a simple increase or decrease in the degree of DLPFC activation while performing a working memory task; instead, subjects with schizophrenia exhibit greater DLPFC activation at relatively low working memory loads and relatively intact performance, but reduced activation at relatively high loads and impaired performance, perhaps reflecting differences in how subjects manage the demands of the task.

Several findings support the relevance of these alterations in DLPFC function to the disease process of schizophrenia. First, subjects with other psychotic disorders (MacDonald *et al.*, 2005) or major depression (Barch *et al.*, 2003) show normal activation of the DLPFC when performing working memory tasks, which indicates that the abnormalities observed in

schizophrenia are, at least in part, specific to the clinical syndrome of schizophrenia. Second, deficits in activation of the DLPFC, but not of other cortical regions, during working memory tasks predict the severity of cognitive disorganization symptoms in subjects with schizophrenia (Perlstein *et al.*, 2001). Third, reduced working memory capacity has been suggested to be rate limiting in the performance of other cognitive tasks in schizophrenia (Silver *et al.*, 2003). Thus, working memory deficits seem to be a central feature of schizophrenia, and identifying the neural alterations in the DLPFC that produce these functional alterations is essential for understanding the underlying disease process.

GABA Neurotransmission and DLPFC Dysfunction in Schizophrenia

The dysfunction of the DLPFC in schizophrenia could reflect, at least in part, disturbances in inhibitory circuitry mediated by GABA-containing interneurons (Lewis *et al.*, 2005) since studies in monkeys indicate that normal working memory function depends upon GABA-mediated circuitry in the DLPFC (Sawaguchi *et al.*, 1989; Rao *et al.*, 2000). The idea that alterations in GABA neurotransmission might contribute to cortical dysfunction in schizophrenia was initially suggested by findings of decreased glutamic acid decarboxylase (GAD) activity (Bird *et al.*, 1979) and decreased GABA reuptake (Simpson *et al.*, 1989) in postmortem studies. Over the past decade, studies across multiple labs, using DNA microarray, real-time quantitative PCR or *in situ* hybridization, have consistently found reduced levels of the transcript for the 67 kilodalton isoform of glutamic acid decarboxylase (GAD67), the principal synthesizing enzyme for GABA, in the DLPFC of subjects with schizophrenia (Akbarian *et al.*, 1995; Guidotti *et al.*, 2000; Mirnics *et al.*, 2000; Volk *et al.*, 2000; Vawter *et al.*, 2002; Hashimoto *et al.*, 2005; 2008; Straub *et al.*, 2007). Indeed, reduced GAD67 mRNA expression in the DLPFC is perhaps the most widely and consistently replicated pathological disturbance in schizophrenia (Torrey *et al.*, 2005; Akbarian and Huang, 2006). The deficit in GAD67 mRNA seems to be accompanied by a corresponding decrease in the cognate protein, although this has been less extensively studied (Guidotti *et al.*, 2000). In contrast, cortical mRNA and protein levels of the other synthesizing enzyme for GABA, GAD65, are not changed in schizophrenia (Guidotti *et al.*, 2000), nor is the density of GAD65-immunoreactive axon terminals (Benes *et al.*, 2000). GAD67 accounts for the majority of GABA synthesis in the cortex (Mason *et al.*, 2001; Battaglioli *et al.*, 2003), whereas GAD65 contributes to GABA synthesis only under conditions of high synaptic demand (Battaglioli *et al.*, 2003; Patel *et al.*, 2006). Consistent with these findings, elimination of the GAD65 gene in mice does not alter cortical levels of GABA (Asada *et al.*, 1996), whereas reductions in GAD67 mRNA are associated with marked decreases in cortical GAD activity and GABA content (Asada *et al.*, 1997). In addition, levels of the mRNA for the GABA membrane transporter (GAT1), a protein responsible for reuptake of released GABA into nerve terminals, is also decreased in the DLPFC of subjects with schizophrenia (Ohnuma *et al.*, 1999; Volk *et al.*, 2001; Hashimoto *et al.*, 2008). In concert, these findings suggest that schizophrenia is accompanied by reductions in both the synthesis and re-uptake of cortical GABA.

As in other cortical regions and species (McBain and Fisahn, 2001; Markram *et al.*, 2004), GABA neurons in the primate DLPFC comprise subclasses that can be distinguished on the basis of molecular, electrophysiological and anatomical properties. For example, the calcium-binding proteins, parvalbumin (PV) and calretinin (CR), and the neuropeptide somatostatin (SST) are, with a few exceptions, expressed in separate populations of primate cortical GABA neurons (Condé *et al.*, 1994; Gabbott and Bacon, 1996; DeFelipe, 1997). These subtypes tend to exhibit different membrane firing properties (Kawaguchi and Kubota, 1993; Krimer *et al.*, 2005; Zaitsev *et al.*, 2005) and to have axons with different arborization patterns and synaptic targets (DeFelipe, 1997). For example, the axon terminals of fast-spiking, PV-containing chandelier and basket neurons principally target the axon initial segments and cell body/proximal dendrites, respectively, of pyramidal neurons (Williams *et al.*, 1992; Melchitzky *et*

al., 1999), the low-threshold spiking, SST-containing Martinotti cells innervate the distal dendrites of pyramidal neurons (DeLima and Morrison, 1989; Kawaguchi and Kubota, 1996; Ma *et al.*, 2006), and GABA neurons that express CR (Condé *et al.*, 1994; Gabbott and Bacon, 1996) have a regular-spiking, adaptive firing pattern (Kawaguchi, 1995; Zaitsev *et al.*, 2005) and give rise to axon terminals that target other GABA neurons or the dendritic spines and shafts of pyramidal cells (Melchitzky *et al.*, 2005). Thus, the functional consequences of a deficit in GAD67 in schizophrenia depend on the specific subpopulations of GABA neurons that are affected.

At the cellular level, the density of neurons with detectable levels of GAD67 mRNA was significantly decreased in schizophrenia subjects (Akbarian *et al.*, 1995; Volk *et al.*, 2000), whereas in neurons with detectable levels of GAD67 mRNA, the expression level per neuron did not differ from control values (Volk *et al.*, 2000). These observations suggest that the majority of DLPFC GABA neurons express normal levels of GAD67 mRNA in subjects with schizophrenia, but approximately 25-35% of GABA neurons lack detectable levels of this transcript. Levels of PV mRNA, which is expressed in ~25% of primate DLPFC GABA neurons (Condé *et al.*, 1994), were significantly decreased in layers 3 and 4, but not in layers 2 or 5-6, of the DLPFC in subjects with schizophrenia (Hashimoto *et al.*, 2003). The expression of PV mRNA per neuron was significantly decreased, but neither the density of neurons with detectable levels of PV mRNA nor the density of PV-immunoreactive neurons (Woo *et al.*, 1997; Beasley *et al.*, 2002) was changed in subjects with schizophrenia. These findings indicate that the neurons are still present and suggest that GAD67 mRNA expression is markedly reduced in PV-expressing neurons that also have reduced, but still detectable, levels of PV mRNA. This interpretation was confirmed by dual label *in situ* hybridization studies which found that ~50% of PV mRNA+ neurons lacked detectable levels of GAD67 mRNA in the DLPFC of subjects with schizophrenia (Hashimoto *et al.*, 2003). In contrast, neither the expression of calretinin (CR) mRNA (which is found in ~50% of primate DLPFC GABA neurons (Condé *et al.*, 1994)), the density of CR-immunoreactive neurons, nor the density of CR-immunoreactive axon terminals was changed in subjects with schizophrenia (Woo *et al.*, 1997; Cotter *et al.*, 2002; Hashimoto *et al.*, 2003). These cell type-specific differences have been suggested to be a consequence of hypofunction of the NMDA receptor on PV neurons in schizophrenia (Lisman *et al.*, 2008), but other findings suggest that the effects of NMDA receptor antagonists on the phenotype of cortical PV neurons are more likely to be mediated by NMDA receptors on other neurons (Gonzalez-Burgos and Lewis, 2008). In either case, it is important to note that abnormalities in PV neurons alone might not completely account for the deficits in expression of GAD67 and GAT1 mRNAs, as such changes were also observed in cortical layers 1, 2 and 5, where relatively few PV-expressing GABA neurons are located (Condé *et al.*, 1994), and where no changes in the expression of PV mRNA were found (Hashimoto *et al.*, 2003).

In addition, the levels of $GABA_A$ receptors in the DLPFC also appear to be abnormal in subjects with schizophrenia. For example, increased musci-mol-binding in pyramidal neuron cell bodies (Hanada *et al.*, 1987; Benes *et al.*, 1996) and increased $GABA_A$ receptor α2 subunits in the axon initial segments of pyramidal neurons (Volk *et al.*, 2002) might represent compensatory receptor upregulation in response to decreased GABA release from GABA neurons, especially those that express PV (Lewis *et al.*, 2005). However, the reports of decreased mRNA levels for the $GABA_A$ receptor γ2 and δ subunits (Huntsman *et al.*, 1998; Vawter *et al.*, 2002) suggest that the downregulation of $GABA_A$ receptors containing these subunits might also contribute to disturbances in DLPFC inhibitory circuitry in schizophrenia.

Alterations in Markers of GABA Neurotransmission are Cell and Receptor Subtype Specific

Together, the findings reviewed above suggested that the working memory impairments and DLPFC dysfunction in schizophrenia might reflect shifts in the expression of genes that encode selective presynaptic and postsynaptic components of GABA neurotransmission, but that the extent of the abnormalities might be broader than those described above. Consistent with this hypothesis, we found selective transcript alterations in the DLPFC of subjects with schizophrenia in a study of 80 GABA-related transcripts using a customized DNA microarray platform with enhanced sensitivity (Hashimoto *et al.*, 2008). Specifically, we found significant expression deficits of GABA-related mRNAs whose protein products can be classified into three groups: 1) presynaptic regulators of GABA neurotransmission (GAD67 and GAT1), 2) neuropeptides [somatostatin (SST), neuropeptide Y (NPY) and cholecystokinin (CCK)], and 3) $GABA_A$ receptor subunits (α1, α4, β3, γ2 and δ). These differences by microarray were confirmed by parallel studies using real-time qPCR and/or *in situ* hybridization in the same subjects.

These gene expression deficits appear to reflect the disease process of schizophrenia, or at least not to be the consequence of other factors commonly associated with the illness, such as treatment with antipsychotic medications. For example, the expression of GAD67, GAT1 and SST mRNAs was unaltered in the DLPFC of monkeys chronically exposed to haloperidol and benztropine (Volk *et al.*, 2000; 2001; Morris *et al.*, 2008); long-term exposure of monkeys to typical (haloperidol) or atypical (olanzapine) antipsychotics did not alter mRNA levels for GAD67, SST, or $GABA_A$ α1 subunit in the DLPFC (Hashimoto *et al.*, 2008); and subjects with schizophrenia who were not receiving antipsychotics at the time of death all showed decreased expression for the 10 GABA-related transcripts mentioned above (Hashimoto *et al.*, 2008). Furthermore, the deficits in expression of these GABA-related transcripts is unlikely to be due solely to substances that influence GABA neurotransmission, such as alcohol, benzodiazepines, and valproic acid, because we did not observe a significant difference in expression changes for any transcripts between the subject pairs with or without a comorbid alcohol disorder or those with or without the use of benzodiazepines and/or valproic acid in the schizophrenia subjects at the time of death (Hashimoto *et al.*, 2008).

The within subject pair differences in transcript levels were significantly correlated between GAD67 and SST (r=0.71, P <0.005), GAD67 and NPY (r=0.72, P <0.004), and SST and NPY (r=0.81, P <0.001), suggesting that GAD67 mRNA expression is also decreased in the subset of GABA neurons that express both SST and NPY (Hendry *et al.*, 1984; Kubota *et al.*, 1994). Thus, the presence of SST- and NPY-containing neurons predominantly in layers 2 and 6 (Hendry *et al.*, 1984; Kubota *et al.*, 1994) may account for the deficits in GAD67 mRNA expression in these layers that cannot be explained by the expression deficits in PV-containing neurons.

The idea that the deficit in SST mRNA expression is restricted to a subset of those neurons was supported by *in situ* hybridization studies which revealed that SST mRNA levels were significantly lower in DLPFC layers 2 - superficial 6 of subjects with schizophrenia, but not in layer 1, deep layer 6 or the underlying white matter (Morris *et al.*, 2008). Interestingly, this pattern corresponds to differences in developmental birthdates of subsets of SST neurons. Specifically, the proliferation of early germinal zones over successive rounds of cell division during cortical development gives rise to post-mitotic migratory neurons. The earliest generated cells comprise the preplate which, later in development, is split into the marginal zone (adult layer 1) and the subplate (adult deep layer 6 and superficial white matter) by the later born neurons of the cortical plate (adult layers 2 - superficial 6) (Kostovic and Rakic, 1980; Luskin and Shatz, 1985; Chun and Shatz, 1989; Bayer and Altman, 1990). Thus, it appears that the subpopulation of the early generated preplate neurons that expresses SST (Chun and Shatz, 1989) and resides in layer 1, deep layer 6 and the superficial white matter

are not affected in schizophrenia, whereas the later developing cortical plate neurons that express SST mRNA are affected.

Given that the cortical plate forms during the second trimester of gestation, these findings raise the possibility that the alterations in SST neurons reflect the effect of adverse environmental events during that time frame [*e.g.*, maternal influenza (Brown, 2006)] that have been associated with an increased risk for schizophrenia. However, because early developmental insults appear to be neither necessary nor sufficient in the etiology of schizophrenia (Lewis and Levitt, 2002), other factors must also be contributory. For example, both SST- and PV-containing cortical GABA neurons are affected in schizophrenia, whereas those that contain CR are not. Thus, factors shared by SST and PV neurons but that differ from CR neurons [*e.g.*, place and timing of neuron birth, transcription factors regulating cell fate, etc; see Wonders and Anderson (2006) for review] might also contribute to cell type-specific vulnerability. Of course, other features intrinsic to, or associated with, the connectivity of adult SST and PV cortical neurons might contribute to their greater vulnerability relative to other SST neurons. For example, approximately 50% of SST neurons, and many PV neurons, express trkB (Gorba and Wahle, 1999), the principal receptor of BDNF, whereas CR neurons do not. Interestingly, mice with genetically engineered reductions in the expression of trkB mRNA have significantly lower levels of cortical SST, PV and GAD67 mRNAs, but no change in CR mRNA expression. Given that the expression level of trkB mRNA (Hashimoto *et al.*, 2005; Weickert *et al.*, 2005) is reduced in the DLPFC of subjects with schizophrenia, reduced neurotrophin signaling through the trkB receptor might be an “upstream” event that contributes to reduced expression of SST, PV and GAD67 mRNAs in the illness.

Interneurons that contain both SST and NPY include the Martinotti cells that give rise to axons which project to layer 1 where they synapse on the apical dendrites of pyramidal neurons (Kawaguchi and Kubota, 1997; Reyes *et al.*, 1998; Gibson *et al.*, 1999; Ma *et al.*, 2006). Thus, disturbances in the SST/NPY-containing Martinotti class of GABA neurons could contribute to the dysfunction of DLPFC circuitry associated with working memory impairments in schizophrenia. For example, disturbances in sensory-gating in schizophrenia have been correlated with impaired working memory performance (Silver and Feldman, 2005), consistent with the idea suggesting that the inability to filter distracting stimuli disrupts working memory (Miller and Cohen, 2001). In computational models, GABA neurons that target pyramidal neuron dendrites protect against distracting stimuli by boosting the inhibition on dendrites of nearby pyramidal neurons that are selective for other stimuli (Wang *et al.*, 2004). Similarly, experimental studies have shown that high frequency trains from pyramidal neurons produce facilitating excitatory inputs to Martinotti cells that, by virtue of their synapses onto the dendrites of neighboring pyramidal neurons, cause disynaptic inhibition (Silberberg and Markram, 2007). Together, these findings suggest that Martinotti cells, by mediating the disynaptic inhibition of neighboring pyramidal neurons selective for other stimuli, can filter distracting stimuli during working memory tasks. Consequently, dysfunction of SST/NPY-containing Martinotti cells in schizophrenia could contribute to working memory impairments.

CCK is heavily expressed in GABA neurons that do not contain PV or SST (Lund and Lewis, 1993; Kawaguchi and Kondo, 2002), but that do express the cannabinoid 1 (CB1) receptor. The highly correlated within subject pair expression differences between CCK and GAD67 (r=0.84, P <0.001) suggest a deficit in GABA synthesis in CCK-containing GABA neurons. Interestingly, levels of CB1 receptor mRNA and protein were also reduced in the same subjects with schizophrenia, suggesting that the down regulation of this receptor, whose activation powerfully suppresses GABA release, could partially compensate for a deficit in GABA synthesis (Eggan *et al.*, 2008). The axon terminals of CCK-positive basket neurons converge with those from PV-containing neurons on the perisomatic domain of pyramidal neurons (Kawaguchi and Kondo, 2002). Interestingly, recent studies indicate that CCK enhances the

output of PV-containing basket neurons, while concurrently suppressing GABA release from CCK-containing basket neurons (Foldy *et al.*, 2007; Karson *et al.*, 2008). Thus, alterations in CCK may alter the balance between these two sources of perisomatic inputs to pyramidal neurons (Freund and Katona, 2007) and contribute to alterations in the neural synchrony in the DLPFC that are associated with normal working memory function (Lewis *et al.*, 2005).

The deficits in expression of specific subunits of $GABA_A$ receptors suggest that both phasic and tonic inhibition may be altered in the DLPFC of subjects with schizophrenia. On the other hand, no changes in transcripts for GABAB receptors were observed, although a reduction in cortical $GABA_B$ receptor 1 protein levels in schizophrenia have been reported (Ishikawa *et al.*, 2005). The α1 and γ2 $GABA_A$ subunits co-assemble into receptors that are enriched in postsynaptic sites where they mediate phasic inhibition (Nusser *et al.*, 1998; Mangan *et al.*, 2005). On the other hand, $GABA_A$ receptors containing the δ subunit are selectively localized to extrasynaptic sites (Nusser *et al.*, 1998; Wei *et al.*, 2003; Mangan *et al.*, 2005) where, by virtue of their high affinity for GABA, they mediate the tonic inhibition provided by ambient levels of GABA in extracellular space (Wei *et al.*, 2003; Farrant and Nusser, 2005). Interestingly, the within subject pair expression differences were significantly correlated between α1 and γ2 (r=0.84, P <0.001), α1 and δ (r=0.81, P <0.001), and γ2 and δ (r=0.85, P <0.001) mRNAs (Hashimoto *et al.*, 2008). Given the predominant localization of the α1, γ2, and δ subunits to dendrites (Hendry *et al.*, 1994; Fritschy and Mohler, 1995), the highly correlated expression deficits for these transcripts suggest coordinated downregulation of $GABA_A$ receptors mediating phasic and tonic inhibition in the dendritic domain of DLPFC pyramidal neurons in schizophrenia. In contrast, the differences in tissue levels of these subunit mRNAs were not correlated with any of the presynaptic transcripts that were altered in schizophrenia (Hashimoto *et al.*, 2008), suggesting that distinct processes contribute to these abnormalities. Consistent with this hypothesis, variants in the $GABA_A$ receptor α1 subunit gene have been associated with both schizophrenia and altered expression levels of the α1 subunit mRNA (Petryshen *et al.*, 2005). Furthermore, a targeted deletion of the $GABA_A$ receptor α1 subunit gene in mice resulted in altered cortical expression of other $GABA_A$ receptor subunits, such as increased α2 and decreased γ2 protein levels, as well as decreased levels of SST mRNA (Kralic *et al.*, 2002; Ponomarev *et al.*, 2006). Together, these findings suggest that the deficit in α1 subunit expression could be a causal process for at least some of the GABA-related gene expression changes in the DLPFC of subjects with schizophrenia.

Conclusion

Although the functional significance of these alterations in GABA-related transcript levels depends on the extent to which they are translated into changes at the level of the cognate proteins, these findings inform our understanding of the nature and extent of altered GABA neurotransmission in the DLPFC of subjects with schizophrenia (FIG. 1). The deficits in expression of GAD67, GAT1 and PV mRNAs in PV-containing GABA neurons in the DLPFC of subjects with schizophrenia (Volk *et al.*, 2000;2001;Hashimoto *et al.*, 2003) are associated with lower levels of GAT1 protein in the presynaptic terminals of PV-containing chandelier neurons (Pierri *et al.*, 1999) and the upregulation of $GABA_A$ receptor α2 subunit in the postsynaptic axon initial segments of pyramidal neurons (Volk *et al.*, 2002). Although the CR-containing GABA neurons appear to be unaffected, alterations in GABA neurotransmission do appear to be present in SST/NPY-containing Martinotti cells and CCK-containing basket neurons, which predominately target the distal dendrites and cell bodies of pyramidal neurons, respectively. Furthermore, gene expression deficits for α1 and γ2 $GABA_A$ receptor subunits and for δ and α4 subunits suggest decreased synaptic (phasic) and extrasynaptic (tonic) inhibition, respectively, in pyramidal neuron dendrites. GABA-mediated regulation at the dendritic domain of pyramidal neurons is important for the selection and integration of excitatory inputs from different cortical and subcortical areas, whereas GABA inputs at the

perisomatic domain, including the axon initial segment and cell body, are critical for control of the timing and synchronization of pyramidal neuron firing (Markram *et al.*, 2004;Somogyi and Klausberger, 2005;Freund and Katona, 2007). Therefore, the findings summarized in FIG. 1 suggest altered GABA-mediated regulation of both inputs to and outputs from DLPFC pyramidal neurons in subjects with schizophrenia. These alterations are certain to affect information processing in DLPFC circuitry and thus are likely to be major contributors to the working memory impairments in this illness. Understanding the interactions between, and the pathophysiological consequences of, these alterations in markers of GABA neurotransmission may lead to the identification of new drug targets for improving the cognitive deficits of schizophrenia.

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References

Akbarian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. Brain Res Rev 2006;52:293–304. [PubMed: 16759710]

Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE Jr, Jones EG. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. Arch Gen Psychiatry 1995;52:258–266. [PubMed: 7702443]

Andreasen NC, Rezai R, Alliger R, Swayze VW II, Flaum M, Kirchner P, Cohen G, O'Leary DS. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia: assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Arch Gen Psychiatry 1992;49:943–958. [PubMed: 1360199]

Asada H, Kawamura Y, Maruyama K, Kume H, Ding R, Ji FY, Kanbara N, Kuzume H, Sanbo M, Yagi T, Obata K. Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. Biochem Biophys Res Comm 1996;229:891–895. [PubMed: 8954991]

Asada H, Kawamura Y, Maruyama K, Kume H, Ding R, Kanbara N, Kuzume H, Sanbo M, Yagi T, Obata K. Cleft palate and decreased brain γ-aminobutyric acid in mice lacking the 67-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci USA 1997;94:6496–6499. [PubMed: 9177246]

Baddeley A. Working memory. Science 1992;255:556–559. [PubMed: 1736359]

Barch DM. What can research on schizophrenia tell us about the cognitive neuroscience of working memory? Neuroscience 2006;139:73–84. [PubMed: 16300901]

Barch DM, Sheline YI, Csernansky JG, Snyder AZ. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol Psychiatry 2003;53:376–384. [PubMed: 12614990]

Battaglioli G, Liu H, Martin DL. Kinetic differences between the isoforms of glutamate decarboxylase: implications for the regulation of GABA synthesis. J Neurochem 2003;86:879–887. [PubMed: 12887686]

Bayer SA, Altman J. Development of layer I and the subplate in the rat neocortex. Exp Neurol 1990;107:48–62. [PubMed: 2295319]

Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. Biol Psychiatry 2002;52:708–715. [PubMed: 12372661]

Benes FM, Vincent SL, Marie A, Khan Y. Up-regulation of GABA-A receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. Neuroscience 1996;75:1021–1031. [PubMed: 8938738]

Benes FM, Todtenkopf MS, Logiotatos P, Williams M. Glutamate decarboxylase(65)-immunoreactive terminals in cingulate and prefrontal cortices of schizophrenic and bipolar brain. J Chem Neuroanat 2000;20:259–269. [PubMed: 11207424]

Bird ED, Spokes EGS, Iversen LL. Increased dopamine concentration in limbic areas of brain from patients dying with schizophrenia. Brain 1979;102:347–360. [PubMed: 455044]

Brown AS. Prenatal infection as a risk factor for schizophrenia. Schizophr Bull 2006;32:200–202. [PubMed: 16469941]

Buchsbaum M. The frontal lobes, basal ganglia and temporal lobes as sites for schizophrenia. Schizophr Bull 1990;16:379–389. [PubMed: 2287929]

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am J Psychiatry 2003;160:2209–2215. [PubMed: 14638592]

Cannon TD, Glahn DC, Kim J, Van Erp TG, Karlsgodt K, Cohen MS, Nuechterlein KH, Bava S, Shirinyan D. Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. Arch Gen Psychiatry 2005;62:1071–1080. [PubMed: 16203952]

Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD. Functional hypofrontality and working memory dysfunction in schizophrenia. Am J Psychiatry 1998;155:1285–1287. [PubMed: 9734557]

Chun JJM, Shatz CJ. Interstitial cells of the adult neocortical white matter are the remnant of the early generated subplate neuron population. J Comp Neurol 1989;282:555–569. [PubMed: 2566630]

Condé F, Lund JS, Jacobowitz DM, Baimbridge KG, Lewis DA. Local circuit neurons immunoreactive for calretinin, calbindin D-28k, or parvalbumin in monkey prefrontal cortex: distribution and morphology. J Comp Neurol 1994;341:95–116. [PubMed: 8006226]

Cosway R, Byrne M, Clafferty R, Hodges A, Grant E, Abukmeil SS, Lawrie SM, Miller P, Johnstone EC. Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. Psychol Med 2000;30:1111–1121. [PubMed: 12027047]

Cotter D, Landau S, Beasley C, Stevenson R, Chana G, MacMillan L, Everall I. The density and spatial distribution of GABAergic neurons, labelled using calcium binding proteins, in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia. Biol Psychiatry 2002;51:377–386. [PubMed: 11904132]

Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatry 1999;156:1328–1335. [PubMed: 10484941]

DeFelipe J. Types of neurons, synaptic connections and chemical characteristics of cells immunoreactive for calbindin-D28K, parvalbumin and calretinin in the neocortex. J Chem Neuroanat 1997;14:1–19. [PubMed: 9498163]

DeLima AD, Morrison JH. Ultrastructural analysis of somatostatin-immunoreactive neurons and synapses in the temporal and occipital cortex of the macaque monkey. J Comp Neurol 1989;283:212–227. [PubMed: 2567743]

Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, Bigelow L, Weinberger DR. Relative risk for cognitive impairments in siblings of patients with schizophrenia. Biol Psychiatry 2001;50:98–107. [PubMed: 11527000]

Eggan SM, Hashimoto T, Lewis DA. Reduced cortical cannabinoid 1 receptor mRNA and protein expression in schizophrenia. Arch Gen Psychiatry 2008;65:772–784. [PubMed: 18606950]

Elvevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 2000;14:1–21. [PubMed: 11253953]

Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of $GABA_A$ receptors. Nat Rev Neurosci 2005;6:215–229. [PubMed: 15738957]

Foldy C, Lee SY, Szabadics J, Neu A, Soltesz I. Cell type-specific gating of perisomatic inhibition by cholecystokinin. Nat Neurosci 2007;10:1128–1130. [PubMed: 17676058]

Freund TF, Katona I. Perisomatic inhibition. Neuron 2007;56:33–42. [PubMed: 17920013]

Fritschy JM, Mohler H. $GABA_A$-receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. J Comp Neurol 1995;359:154–194. [PubMed: 8557845]

Gabbott PLA, Bacon SJ. Local circuit neurons in the medial prefrontal cortex (areas 24a,b,c, 25 and 32) in the monkey: II. Quantitative areal and laminar distributions. J Comp Neurol 1996;364:609–636. [PubMed: 8821450]

Gibson JR, Beierlein M, Connors BW. Two networks of electrically coupled inhibitory neurons in neocortex. Nature 1999;402:75–79. [PubMed: 10573419]

Gold JM. Cognitive deficits as treatment targets in schizophrenia. Schizophr Res 2004;72:21–28. [PubMed: 15531404]

Goldman-Rakic, PS. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum, F.; Mountcastle, V., editors. Handbook of Physiology. American Physiological Society; Bethesda, MD: 1987. p. 373-417.

Goldman-Rakic PS. The physiology approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol Psychiatry 1999;46:650–661. [PubMed: 10472417]

Gonzalez-Burgos G, Lewis DA. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. Schizophr Bull 2008;34:944–961. [PubMed: 18586694]

Gorba T, Wahle P. Expression of trkB and trkC but not BDNF mRNA in neurochemically identified interneurons in rat visual cortex *in vivo* and in organotypic cultures. Eur J Neurosci 1999;11:1179–1190. [PubMed: 10103114]

Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–330. [PubMed: 8610818]

Green, MF. Schizophrenia From a Neurocognitive Perspective: Probing the Impenetrable Darkness. Allyn and Bacon; Boston, MA: 1998.

Guidotti A, Auta J, Davis JM, Gerevini VD, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E. Decrease in reelin and glutamic acid decarboxylase67 (GAD_{67}) expression in schizophrenia and bipolar disorder. Arch Gen Psychiatry 2000;57:1061–1069. [PubMed: 11074872]

Gur RC, Gur RE. Hypofrontality in schizophrenia: RIP. Lancet 1995;345:1383–1384. [PubMed: 7760605]

Hanada S, Mita T, Nishino N, Tanaka C. [^{3}H] Muscimol binding sites increased in autopsied brains of chronic schizophrenics. Life Sci 1987;40:239–266. [PubMed: 3025544]

Harvey PD, Howanitz E, Parrella M, White L, Davidson M, Mohs RC, Hoblyn J, Davis KL. Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: a comparison across treatment sites. Am J Psychiatry 1998;155:1080–1086. [PubMed: 9699697]

Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, Sampson AR, Lewis DA. Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J Neurosci 2003;23:6315–6326. [PubMed: 12867516]

Hashimoto T, Bergen SE, Nguyen QL, Xu B, Monteggia LM, Pierri JN, Sun Z, Sampson AR, Lewis DA. Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. J Neurosci 2005;25:372–383. [PubMed: 15647480]

Hashimoto T, Arion D, Unger T, Maldonado-Aviles JG, Morris HM, Volk DW, Mirnics K, Lewis DA. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. Mol Psychiatry 2008;13:147–161. [PubMed: 17471287]

Hendry SHC, Jones EG, Emson PC. Morphology, distribution, and synaptic relations of somatostatin- and neuropeptide Y-immunoreactive neurons in rat and monkey neocortex. J Neurosci 1984;4:2497–2517. [PubMed: 6149273]

Hendry SHC, Huntsman MM, Viñuela A, Mohler H, de Blas AL, Jones EG. $GABA_A$ receptor subunit immunoreactivity in primate visual cortex: distribution in macaques and humans and regulation by visual input in adulthood. J Neurosci 1994;14:2383–2401. [PubMed: 8158275]

Huntsman MM, Tran BV, Potkin SG, Bunney WE, Jones EG. Altered ratios of alternatively spliced long and short γ2 subunit mRNAs of the γ-amino butyrate type A receptor in prefrontal cortex of schizophrenics. Proc Natl Acad Sci USA 1998;95:15066–15071. [PubMed: 9844016]

Hyman SE, Fenton WS. Medicine. What are the right targets for psychopharmacology? Science 2003;299:350–351. [PubMed: 12532001]

Ishikawa M, Mizukami K, Iwakiri M, Asada T. Immunohistochemical and immunoblot analysis of γ-aminobutyric acid B receptor in the prefrontal cortex of subjects with schizophrenia and bipolar disorder. Neurosci Lett 2005;383:272–277. [PubMed: 15955420]

Karson MA, Whittington KC, Alger BE. Cholecystokinin inhibits endocannabinoid-sensitive hippocampal IPSPs and stimulates others. Neuropharmacology 2008;54:117–128. [PubMed: 17689570]

Kawaguchi Y. Physiological subgroups of nonpyramidal cells with specific morphological characteristics in layer II/III of rat frontal cortex. J Neurosci 1995;15:2638–2655. [PubMed: 7722619]

Kawaguchi Y, Kondo S. Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. J Neurocytol 2002;31:277–287. [PubMed: 12815247]

Kawaguchi Y, Kubota Y. Correlation of physiological subgroupings of nonpyramidal cells with parvalbumin- and calbindinD28k-immunoreactive neurons in layer V of rat frontal cortex. J Neurophysiol 1993;70:387–396. [PubMed: 8395585]

Kawaguchi Y, Kubota Y. Physiological and morphological identification of somatostatin- or vasoactive intestinal polypeptide-containing cells among GABAergic cell subtypes in rat frontal cortex. J Neurosci 1996;16:2701–2715. [PubMed: 8786446]

Kawaguchi Y, Kubota Y. GABAergic cell subtypes and their synaptic connections in rat frontal cortex. Cereb Cortex 1997;7:476–486. [PubMed: 9276173]

Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 2005;57:688–691. [PubMed: 15780858]

Kostovic I, Rakic P. Cytology and the time of origin of interstitial neurons in the white matter in infant and adult human and monkey telencephalon. J Neurocytol 1980;9:219–242. [PubMed: 7441294]

Kralic JE, Korpi ER, O'Buckley TK, Homanics GE, Morrow AL. Molecular and pharmacological characterization of $GABA_A$ receptor alpha1 subunit knockout mice. J Pharmacol Exp Ther 2002;302:1037–1045. [PubMed: 12183661]

Krimer LS, Zaitsev AV, Czanner G, Kroner S, Gonzalez-Burgos G, Povysheva NV, Iyengar S, Barrionuevo G, Lewis DA. Cluster analysis-based physiological classification and morphological properties of inhibitory neurons in layers 2-3 of monkey dorsolateral prefrontal cortex. J Neurophysiol 2005;94:3009–3022. [PubMed: 15987765]

Kubota Y, Hattori R, Yui Y. Three distinct subpopulations of GABAergic neurons in rat frontal agranular cortex. Brain Res 1994;649:159–173. [PubMed: 7525007]

Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci 2002;25:409–432. [PubMed: 12052915]

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005;6:312–324. [PubMed: 15803162]

Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci 2008;31:234–242. [PubMed: 18395805]

Lund JS, Lewis DA. Local circuit neurons of developing and mature macaque prefrontal cortex: Golgi and immunocytochemical characteristics. J Comp Neurol 1993;328:282–312. [PubMed: 7678612]

Luskin MB, Shatz CJ. Studies of the earliest generated cells of the cat's visual cortex: cogeneration of the subplate and marginal zones. J Neurosci 1985;5:1062–1075. [PubMed: 3981242]

Ma Y, Hu H, Berrebi AS, Mathers PH, Agmon A. Distinct subtypes of somatostatin-containing neocortical interneurons revealed in transgenic mice. J Neurosci 2006;26:5069–5082. [PubMed: 16687498]

MacDonald AW III, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA, Cohen JD. Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. Am J Psychiatry 2005;162:475–484. [PubMed: 15741464]

Mangan PS, Sun C, Carpenter M, Goodkin HP, Sieghart W, Kapur J. Cultured hippocampal pyramidal neurons express two kinds of $GABA_A$ receptors. Mol Pharmacol 2005;67:775–788. [PubMed: 15613639]

Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res 2003;60:285–298. [PubMed: 12591590]

Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. Interneurons of the neocortical inhibitory system. Nat Rev Neurosci 2004;5:793–807. [PubMed: 15378039]

Mason GF, Martin DL, Martin SB, Manor D, Sibson NR, Patel A, Rothman DL, Behar KL. Decrease in GABA synthesis rate in rat cortex following GABA-transaminase inhibition correlates with the decrease in GAD(67) protein. Brain Res 2001;914:81–91. [PubMed: 11578600]

McBain CJ, Fisahn A. Interneurons unbound. Nat Rev Neurosci 2001;2:11–23. [PubMed: 11253355]

Melchitzky DS, Sesack SR, Lewis DA. Parvalbumin-immunoreactive axon terminals in macaque monkey and human prefrontal cortex: laminar, regional and target specificity of Type I and Type II synapses. J Comp Neurol 1999;408:11–22. [PubMed: 10331577]

Melchitzky DS, Eggan SM, Lewis DA. Synaptic targets of calretinin-containing axon terminals in macaque monkey prefrontal cortex. Neuroscience 2005;130:185–195. [PubMed: 15561434]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202. [PubMed: 11283309]

Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. Neuron 2000;28:53–67. [PubMed: 11086983]

Morris HM, Hashimoto T, Lewis DA. Alterations in somatostatin mRNA expression in the dorsolateral prefrontal cortex of subjects with schizophrenia or schizoaffective disorder. Cereb Cortex 2008;18:1575–1587. [PubMed: 18203698]

Nusser Z, Sieghart W, Somogyi P. Segregation of different $GABA_A$ receptors to synaptic and extrasynaptic membranes of cerebellar granule cells. J Neurosci 1998;18:1693–1703. [PubMed: 9464994]

Ohnuma T, Augood SJ, Arai H, McKenna PJ, Emson PC. Measurement of GABAergic parameters in the prefrontal cortex in schizophrenia: focus on GABA content, $GABA_A$ receptor α-1 subunit messenger RNA and human GABA transporter-1 (HGAT-1) messenger RNA expression. Neuroscience 1999;93:441–448. [PubMed: 10465426]

Patel AB, de Graaf RA, Martin DL, Battaglioli G, Behar KL. Evidence that GAD65 mediates increased GABA synthesis during intense neuronal activity *in vivo*. J Neurochem 2006;97:385–396. [PubMed: 16539672]

Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 2001;158:1105–1113. [PubMed: 11431233]

Petryshen TL, Middleton FA, Tahl AR, Rockwell GN, Purcell S, Aldinger KA, Kirby A, Morley CP, McGann L, Gentile KL, Waggoner SG, Medeiros HM, Carvalho C, Macedo A, Albus M, Maier W, Trixler M, Eichhammer P, Schwab SG, Wildenauer DB, Azevedo MH, Pato MT, Pato CN, Daly MJ, Sklar P. Genetic investigation of chromosome 5q $GABA_A$ receptor subunit genes in schizophrenia. Mol Psychiatry 2005;10:1074–1088. [PubMed: 16172613]

Pierri JN, Chaudry AS, Woo TU, Lewis DA. Alterations in chandelier neuron axon terminals in the prefrontal cortex of schizophrenic subjects. Am J Psychiatry 1999;156:1709–1719. [PubMed: 10553733]

Ponomarev I, Maiya R, Harnett MT, Schafer GL, Ryabinin AE, Blednov YA, Morikawa H, Boehm SL, Homanics GE, Berman AE, Lodowski KH, Bergeson SE, Harris RA. Transcriptional signatures of cellular plasticity in mice lacking the α1 subunit of $GABA_A$ receptors. J Neurosci 2006;26:5673–5683. [PubMed: 16723524]

Rao SG, Williams GV, Goldman-Rakic PS. Destruction and creation of spatial tuning by disinhibition: $GABA_A$ blockade of prefrontal cortical neurons engaged by working memory. J Neurosci 2000;20:485–494. [PubMed: 10627624]

Reyes A, Lujar R, Rozov BN, Somogyi P, Sakman B. Target-cell-specific facilitation and depression in neocortical circuits. Nat Neurosci 1998;1:279–285. [PubMed: 10195160]

Sawaguchi T, Matsumura M, Kubota K. Delayed response deficits produced by local injection of bicuculline into the dorsolateral prefrontal cortex in Japanese macaque monkeys. Exp Brain Res 1989;75:457–469. [PubMed: 2744104]

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 1994;51:124–131. [PubMed: 7905258]

Silberberg G, Markram H. Disynaptic inhibition between neocortical pyramidal cells mediated by Martinotti cells. Neuron 2007;53:735–746. [PubMed: 17329212]

Silver H, Feldman P. Evidence for sustained attention and working memory in schizophrenia sharing a common mechanism. J Neuropsychiatry Clin Neurosci 2005;17:391–398. [PubMed: 16179663]

Silver H, Feldman P, Bilker W, Gur RC. Working memory deficit as a core neuropsychological dysfunction in schizophrenia. Am J Psychiatry 2003;160:1809–1816. [PubMed: 14514495]

Simpson MDC, Slater P, Deakin JFW, Royston MC, Skan WJ. Reduced GABA uptake sites in the temporal lobe in schizophrenia. Neurosci Lett 1989;107:211–215. [PubMed: 2616032]

Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 2004;71:285–295. [PubMed: 15474899]

Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 1999;283:1657–1661. [PubMed: 10073923]

Somogyi P, Klausberger T. Defined types of cortical interneurone structure space and spike timing in the hippocampus. J Physiol 2005;562:9–26. [PubMed: 15539390]

Straub RE, Lipska BK, Egan MF, Goldberg TE, Callicott JH, Mayhew MB, Vakkalanka RK, Kolachana BS, Kleinman JE, Weinberger DR. Allelic variation in GAD1 (GAD67) is associated with schizophrenia and influences cortical function and gene expression. Mol Psychiatry 2007;12:854–869. [PubMed: 17767149]

Tan HY, Choo WC, Fones CS, Chee MW. fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. Am J Psychiatry 2005;162:1849–1858. [PubMed: 16199831]

Taylor SF. Cerebral blood flow activation and functional lesions in schizophrenia. Schizophr Res 1996;19:129–140. [PubMed: 8789911]

Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. Biol Psychiatry 2005;57:252–260. [PubMed: 15691526]

Van Snellenberg JX, Torres IJ, Thornton AE. Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. Neuropsychology 2006;20:497–510. [PubMed: 16938013]

Vawter MP, Crook JM, Hyde TM, Kleinman JE, Weinberger DR, Becker KG, Freed WJ. Microarray analysis of gene expression in the prefrontal cortex in schizophrenia: a preliminary study. Schizophr Res 2002;58:11–20. [PubMed: 12363385]

Volk DW, Austin MC, Pierri JN, Sampson AR, Lewis DA. Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical γ-aminobutyric acid neurons in subjects with schizophrenia. Arch Gen Psychiatry 2000;57:237–245. [PubMed: 10711910]

Volk DW, Austin MC, Pierri JN, Sampson AR, Lewis DA. GABA transporter-1 mRNA in the prefrontal cortex in schizophrenia: decreased expression in a subset of neurons. Am J Psychiatry 2001;158:256–265. [PubMed: 11156808]

Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. Cereb Cortex 2002;12:1063–1070. [PubMed: 12217970]

Wang XJ, Tegner J, Constantinidis C, Goldman-Rakic PS. Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. Proc Natl Acad Sci USA 2004;101:1368–1373. [PubMed: 14742867]

Wei W, Zhang N, Peng Z, Houser CR, Mody I. Perisynaptic localization of delta subunit-containing $GABA_A$ receptors and their activation by GABA spillover in the mouse dentate gyrus. J Neurosci 2003;23:10650–10661. [PubMed: 14627650]

Weickert CS, Ligons DL, Romanczyk T, Ungaro G, Hyde TM, Herman MM, Weinberger DR, Kleinman JE. Reductions in neurotrophin receptor mRNAs in the prefrontal cortex of patients with schizophrenia. Mol Psychiatry 2005;10:637–650. [PubMed: 15940304]

Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 1986;43:114–124. [PubMed: 3947207]

Weinberger DR, Berman KF, Illowsky BP. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a mono-aminergic mechanism. Arch Gen Psychiatry 1988;45:609–615. [PubMed: 3382320]

Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Berman KF, Goldberg TE. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001;50:825–844. [PubMed: 11743939]

Williams SM, Goldman-Rakic PS, Leranth C. The synaptology of parvalbumin-immunoreactive neurons in primate prefrontal cortex. J Comp Neurol 1992;320:353–369. [PubMed: 1613130]

Wonders CP, Anderson SA. The origin and specification of cortical interneurons. Nat Rev Neurosci 2006;7:687–696. [PubMed: 16883309]

Woo TU, Miller JL, Lewis DA. Schizophrenia and the parvalbumin-containing class of cortical local circuit neurons. Am J Psychiatry 1997;154:1013–1015. [PubMed: 9210755]

Zaitsev AV, Gonzalez-Burgos G, Povysheva NV, Kroner S, Lewis DA, Krimer LS. Localization of calcium-binding proteins in physiologically and morphologically characterized interneurons of monkey dorsolateral prefrontal cortex. Cereb Cortex 2005;15:1178–1186. [PubMed: 15590911]

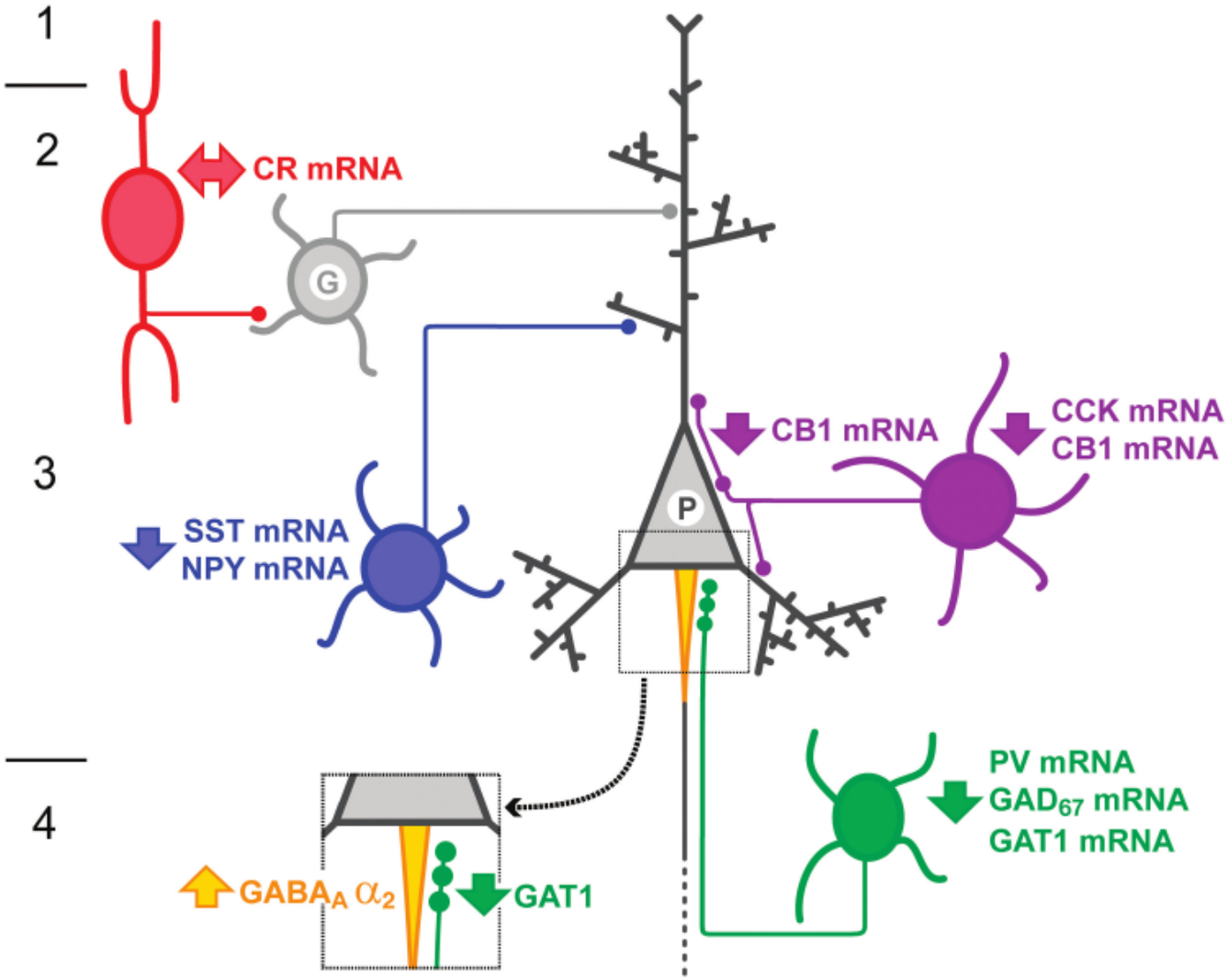

FIGURE 1.

Schematic summary of some alterations in GABA-mediated circuitry in the DLPFC of subjects with schizophrenia. Altered GABA neurotransmission by PV-containing neurons (green) is indicated by gene expression deficits in these neurons and associated changes in their synapses, a decrease in GAT1 expression in their terminals and an upregulation of $GABA_A$ receptor α2 subunit at the axon initial segments of pyramidal neurons (enlarged square). Decreased expression of both SST and NPY mRNAs indicates alterations in SST and/or NPY-containing neurons (blue) that target the distal dendrites of pyramidal neurons. Decreased CCK mRNA levels, and CB1 receptor mRNA and protein levels, indicate an alteration of CCK-containing large basket neurons (purple) that represent a separate source of perisomatic inhibition from PV-containing neurons. Gene expression in CR-containing GABA neurons (red) does not seem to be altered. These changes appear to be accompanied by a downregulation of $GABA_A$ receptor subunits, including the α1 and α2 subunits present in receptors that mediate synaptic (phasic) inhibition and the α4 and δ subunits present in receptors that mediate extrasynaptic (tonic) inhibition. G, generic GABA neuron; P, pyramidal neuron; I-IV, layers of the DLPFC.