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Alterations of Cortical GABA Neurons and Network Oscillations in Schizophrenia

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Abstract

The hypothesis that alterations of cortical inhibitory γ-aminobutyric acid (GABA) neurons are a central element in the pathology of schizophrenia has emerged from a series of postmortem studies. How such abnormalities may contribute to the clinical features of schizophrenia has been substantially informed by a convergence with basic neuroscience studies revealing complex details of GABA neuron function in the healthy brain. Importantly, activity of the parvalbumin-containing class of GABA neurons has been linked to the production of cortical network oscillations. Furthermore, growing knowledge supports the concept that γ band oscillations (30–80 Hz) are an essential mechanism for cortical information transmission and processing. Herein we review recent studies further indicating that inhibition from parvalbumin-positive GABA neurons is necessary to produce γ oscillations in cortical circuits; provide an update on postmortem studies documenting that deficits in the expression of glutamic acid decarboxylase67, which accounts for most GABA synthesis in the cortex, are widely observed in schizophrenia; and describe studies using novel, noninvasive approaches directly assessing potential relations between alterations in GABA, oscillations, and cognitive function in schizophrenia.

Keywords

Neocortex; Synaptic inhibition; Cognitive deficit; Synchronization; GABA; Schizophrenia

Introduction

Schizophrenia is a complex disorder that affects multiple aspects of behavior. Importantly, cognitive dysfunction is the critical determinant of long-term functional outcome for most

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patients [1]. Therefore, understanding the brain mechanisms underlying cognitive function and dysfunction is critical to develop new therapeutic strategies, particularly given that currently approved pharmacologic treatments for schizophrenia are largely ineffective at improving cognition.

Neuronal synchronization in the γ frequency band (~30–80 Hz) maybe critical for the normal flow of neural activity within and between cortical regions and therefore maybe essential to cognitive function [2]. Among other potential mechanisms, neural synchrony is thought to be dependent on γ-aminobutyric acid (GABA)-mediated inhibition. Therefore, GABA neuron dysfunction in schizophrenia may produce cognitive deficits by altering neural synchrony in cortical circuits.

In this review, we provide an update on the following: 1) the role of cortical GABA neurons in the production of neural synchrony, 2) findings of alterations of GABA neurons in the cortex of patients with schizophrenia, and 3) evidence suggesting that schizophrenia is associated with alterations of neural synchrony.

GABA Neurons and Neuronal Synchronization in Cortical Circuits

The critical role of GABA neuron—mediated inhibition in the production of normal synchronized oscillations and their alterations in schizophrenia has been reviewed extensively elsewhere [3••,4•]. Herein we review studiesfurther supporting a functional link between GABA-mediated inhibition and the production of cortical rhythms.

Currently, it is widely accepted that inhibition from the subclass of GABA neurons that express the calcium-binding protein parvalbumin (PV) is essential for synchronization of neural activity [5,6], although the exact mechanisms involving PV neurons are not fully understood. PV neurons furnish strong inhibition onto pyramidal cells and also innervate other GABA neurons, including nearby PV cells. Mutual inhibition between PV neurons is essential to produce γ oscillations in computational network models [5,6]. The importance of inhibition onto PV neurons was addressed using genetically modified mice in which $GABA_A$ receptor ($GABA_AR$)-mediated synaptic inhibition was removed exclusively from PV cells [7]. In these mice, θ (4–8 Hz) rhythms and their coupling to γ oscillations, which is important for cognitive function [8], are strongly altered [7]. Surprisingly, amplitude and frequency of γ oscillations are largely preserved in these mice, suggesting that mutual inhibition between PV neurons is not necessary for rhythmic γ activity [7].

In mathematical models of γ oscillations based on mutual inhibition, the mechanisms providing interneuron excitation are unclear. In alternative models, interneurons are excited by nearby pyramidal cells, which in turn are inhibited in a feedback loop [9]. Excitation of PV neurons via the AMPA subtype of glutamate receptors (AMPARs) actually is strictly necessary to produce normal γ oscillations. For instance, in mice with genetically engineered deletion of AMPAR subunits GluR-A or GluR-D selectively in PV cells, γ rhythms are strongly attenuated [10].

Given that AMPAR-mediated excitation of PV neurons is necessary to produce γ oscillations, an important question is whether N-methyl D-aspartate receptors (NMDARs) are necessary as well. Indeed, NMDAR-mediated PV neuron activation was suggested as a crucial element of the NMDAR hypofunction hypothesis of schizophrenia [11•]. Which properties distinguish AMPAR- from NMDAR-mediated excitation? Compared with AMPAR-, NMDAR-mediated excitation is very slow and long lasting [12,13]. However, inconsistent with a strong NMDAR-mediated excitation, PV neuron excitation is extremely fast [14]. Moreover, glutamate inputs onto PV neurons are fast and have weak NMDAR contribution [15-17•,18]. A predominantly AMPAR-mediated excitation of PV cells may

explain the finding that γ oscillations are abolished by AMPAR antagonists, but not by antagonists of NMDARs [19,20].

In certain genetically modified mice generated recently, NMDARs can be deleted selectively in GABA neurons, including PV cells [21]. NMDAR deletion in GABA neurons of these mice failed to produce significant behavioral effects unless the deletion was induced during very early development, in which case adult mice developed schizophrenia-like behavioral alterations [21]. Interestingly, excitatory inputs onto immature PV neurons have strong NMDAR currents, which get progressively weaker with age until becoming small or absent in adult PV neurons [22]. Similarly, in the cortex of adult humans, only about 30% of PV-positive neurons express NMDAR subunit mRNA [23]. One possibility is that NMDAR deletion induced in adulthood fails to produce effects because NMDAR expression in mature PV cells is normally low [21]. In contrast, NMDAR deletion early in development—when PV neurons have strong NMDAR currents—could disrupt PV cell function persistently into adulthood [21]. The failure of NMDAR deletion from PV neurons in the adult brain to produce significant effects suggests that NMDAR antagonists administered to adults produce schizophrenia-like symptoms by affecting pyramidal cells and/or PV-negative GABA neurons [21]. Potential differences in the effects of NMDAR hypofunction during development versus adulthood are important and must be further assessed, given that the NMDAR hypofunction theory of schizophrenia is mainly based on the effects of NMDAR antagonists in adult volunteers or patients [24].

NMDARs are essential for maturation of excitatory synaptic connections during early development; thus, NMDAR expression in immature PV neurons maybe necessary to establish their functional connectivity with other cells in the network. After the neural network has matured, synaptic NMDARs in PV neurons may decrease to accomplish the fast AMPAR-mediated excitation that is essential to the role of PV neurons in cortical circuits (eg, generating γ oscillations) [5,14]. The formation of interneuron connectivity during early development maybe critical to the emergence of network architectures that enable neuronal synchrony in the adult brain. For example, in developing circuits, certain “hub neurons,” most of which are GABA neurons (possibly including PV-positive cells), display high levels of connectivity with other cells in the network [25]. Such hub GABA neurons can trigger network synchrony following a scale-free topology [25], which maybe essential to optimize synchrony while minimizing wiring and energy use [26]. An interesting question therefore is whether the formation of hub neuron connectivity during development is somehow NMDAR dependent.

PV cell—mediated signaling seems to be strongly modulated by neuregulin-1, a trophic factor important for brain development that is still widely expressed in adulthood and is encoded by a schizophrenia susceptibility gene [27]. Among various neuregulin-1 receptors is the ErbB4 receptor, whose gene also confers schizophrenia susceptibility [27]. ErbB4 is enriched in GABA neurons, particularly in PV-positive cells, and facilitates GABArelease [28-30]. Neuregulin-mediated facilitation of GABA release from PV neurons maybe relevant for the involvement of PV neurons in γ oscillations. Consistent with this idea, neuregulin-1 enhances γ oscillations via an effect that is absent in ErbB4-deficient mice [31]. Further studies are needed to determine whether neuregulin or ErbB4 gene polymorphisms associated with schizophrenia produce alterations of PV neurons and γ oscillations.

PV-positive cells comprise at least two different morphologic subtypes: basket cells innervating the pyramidal cell soma and proximal dendrites, and chandelier neurons synapsing onto the axon initial segment of pyramidal cells. Both PV neuron subtypes are probably affected in schizophrenia [32] and share several functional properties [33]. All PV

neurons synthesize and release GABA, the major inhibitory neurotransmitter; however, whereas basket cells are clearly inhibitory, chandelier neurons surprisingly seem to be excitatory [34]. Supporting such a controversial idea, microapplication of GABA near the axon initial segment of neocortical pyramidal cells is excitatory as well [35]. Moreover, the excitation by chandelier cells is apparent in the human neocortex [36] and thus is not restricted to the rat and mouse cortex. In contrast to these findings, a study of hippocampal GABA neurons showed—using recording techniques that preclude potential methodologic issues sometimes associated with electrophysiologic experiments—that both basket and chandelier neurons are inhibitory [37]. Using similar recording techniques, neocortical chandelier cells still produced GABA-mediated excitation [38]. These data suggest significant hippocampus versus neocortex differences in chandelier neuron properties. Because both hippocampal chandelier and basket neurons participate in θ and γ oscillations [3••], it is important to determine if hippocampal chandelier cells are altered in schizophrenia. Basket cell/GABA-mediated inhibition and chandelier cell/GABA-mediated excitation are actually determined by differences in the distribution of chloride transporters (NKCC1 and KCC2), which control the chloride ion distribution across the membrane [34,35]. These data highlight the importance of chloride transport regulation in pyramidal cells for the normal postsynaptic effects of PV neurons and their alterations in schizophrenia.

Because multiple subtypes of cortical GABA neurons exist in addition to PV cells [3••,4•, 39] a crucial question is whether PV neuron activity is sufficient to produce γ oscillations. Importantly, PV neurons do not have intrinsic pacemaker activity, and in the absence of external excitation, they remain electrically silent. Recently, mice were genetically engineered to express light-sensitive ion channels exclusively in pyramidal cells or PV neurons in order to selectively drive cell activity by means of light flashes [40,41]. Selective activation of PV cells in these mice produced γ band oscillations, whereas inhibiting PV neurons suppressed them [40,41]. Moreover, nonrhythmic stimulation of pyramidal neurons that drive PV cells to produce feedback inhibition generated a γ rhythm [41]. These and other elegant optogenetics experiments (using genetically engineered expression of light-sensitive ion channels) show that PV cell activity, possibly driven by pyramidal cells via AMPARs [10], generates γ oscillations. These results, however, do not mean that PV cell—mediated inhibition is sufficient to produce γ oscillations. Indeed, PV cells innervate other GABA neuron subtypes. Thus, complex effects of PV cell output onto other GABA neuron subtypes maybe involved in γ rhythms [42].

GABA-mediated inhibition may play roles in addition to oscillatory synchronization of neuronal activity. For example, $GABA_AR$- and $GABA_BR$-mediated inhibition are important to maintain and terminate persistent activity [43]. Persistent activity is viewed as the cellular basis of working memory [44,45], a form of memory that is altered in schizophrenia and is essential for cognitive function. Importantly, cortical circuits exhibit the so-called up/down state transitions [46,47]. During up states, pyramidal neurons are depolarized [46,47] by barrages of excitation tightly controlled by inhibition [48]. Interestingly, up states recruit PV neurons [49,50], suggesting that PV cells provide the inhibition crucial for cortical up states. The persistently depolarized up state maybe a model of persistent activity during working memory, suggesting that GABA neuron alterations may contribute to working memory dysfunction in schizophrenia, given the potential involvement of PV neuron—mediated inhibition in controlling the up states. In addition, up/down transitions may play the important role of acting as slow gates for neural activity flow. Therefore, PV neuron alterations in schizophrenia may affect information transmission in the neocortex not only via the faster θ and γ oscillations, but also via slower up/down state transitions.

GABAergic Neuron Dysfunction in Schizophrenia

The hypothesis that GABA signaling is altered in neocortical circuits in schizophrenia is primarily based on findings from postmortem brain studies [32]. In particular, the finding of reduced expression of GAD67 (the 67-kDA isoform of glutamate decarboxylase, a key enzyme in GABA synthesis) continues to rank as one of the most consistently and widely replicated findings in schizophrenia research (Table 1). Moreover, some studies demonstrated decreased expression of GAD67 in PV-positive neurons (Table 1), suggesting that GABA synthesis is reduced specifically—although not exclusively—in the subpopulation of GABA neurons critical to produce γ oscillations. Although these studies show a remarkable uniformity in demonstrating lower mean GAD67 levels in individuals with schizophrenia relative to comparison individuals, the variance of GAD67 levels across schizophrenia patients suggests the possibility of different subtypes of schizophrenia, with a large proportion of patients having low GAD67 expression, but with smaller subgroups characterized by normal—or perhaps even elevated—GAD67 [51].

Interestingly, the deficit in GAD67 mRNA expression in schizophrenia, originally observed in the dorsolateral prefrontal cortex (DLPFC), is not restricted to this cortical area (Table 1). For example, we recently reported lower levels of the GAD67 transcript in the DLPFC, anterior cingulate cortex, primary motor cortex, and primary visual cortex in the same individuals with schizophrenia [52••], suggesting that GABA synthesis is altered in a similar manner across cortical regions that differ markedly in cytoarchitecture, connectivity, and function. Furthermore, reductions in GAD67 mRNA have been found in orbital frontal, superior temporal, and anterior cingulate cortices in other patient cohorts [53-55]. Thus, disturbances in GABA neurotransmission in specific cell types could represent a common pathophysiology for different domains of cortical dysfunction in schizophrenia, raising the possibility that pharmacologic agents with the appropriate specificity for certain GABA-related targets might be effective for a range of clinical features in the illness.

Despite the conserved alterations in GAD67 expression in schizophrenia, the mechanisms leading to GAD67 reduction are poorly understood. Importantly, the pan-cortical alterations in GAD67 are consistent with the presence of one or more common upstream mechanisms that are operative across cortical areas. The idea that altered gene expression in schizophrenia maybe linked to epigenetic regulation mechanisms has received attention recently [56]. This possibility is particularly important for expression of GAD67, whose levels are tightly controlled by neural activity via transcriptional regulation of *GAD1*, the gene encoding GAD67 [57]. Different levels of *GAD1* transcription maybe linked to genetic variability, and polymorphisms in the 5′ region of *GAD1* have been associated with schizophrenia and decreased GAD67 transcription [58]. Interestingly, in the cortex of a subset of schizophrenia patients, methylation of histones (the core proteins of chromatin) near the promoter region of *GAD1* shows a shift from transcription-open to transcription-repressive chromatin structure, which is accompanied by a reduction in GAD67 mRNA in the same individuals [59]. Importantly, changes in histone methylation initiated by transient events produce DNA methylation patterns that cause persistent changes in gene expression [56]. Interestingly, polymorphisms in the 5′ region of the *GAD1* gene that have an influence on chromatin structure are associated with genetic risk of early-onset schizophrenia and early gray matter loss [57]. Given that few studies have assessed chromatin structure in schizophrenia and that histone and DNA methylation show large interindividual heterogeneity, further research is needed to determine how frequently epigenetic mechanisms might contribute to GAD67 alterations in the disease.

Whereas a genetic cause of deficits in GAD67 gene transcription in schizophrenia would suggest that such alterations are a primary deficit, another possibility is that GAD67

alterations are secondary to upstream factors. Recent experiments have suggested that NMDAR hypofunction could produce deficits in GAD67 and PV gene expression that resemble those found in the cortex of patients with schizophrenia [60]. For instance, application of NMDAR antagonists decreases GAD67 and PV expression in cultured neurons [60]. As mentioned, adult PV neurons have weak NMDAR contribution [22], and NMDAR deletion from adult PV neurons does not yield significant effects [21]. Thus, it appears that the effects of NMDAR antagonists on GAD67 and PV expression levels in adult animals probably affect PV neurons indirectly. Moreover, NMDAR antagonists may affect other subtypes of non—PV-positive GABA neurons that express much higher NMDAR levels than PV cells [16,22].

The impact of impaired GABA neurotransmission on information processing in the DLPFC may reveal how a pan-cortical deficit in GAD67 expression could contribute to cortical dysfunction more broadly in schizophrenia. Whereas deficits in GAD67 in schizophrenia have been reported specifically for DLPFC PV-containing neurons [61], PV cells are found across many cortical areas and play a central role in producing γ band oscillations across many cortical regions [5]. In the DLPFC, γ band oscillations are induced and sustained during the delay period of working memory tasks [62], and their power increases in proportion with memory load[63], indicating that the γ band oscillations are associated with the local neuronal processing that is critical to the maintenance and manipulation of information. Indeed, schizophrenia is associated with impaired performance and reduced frontal γ activity in individuals during cognitive tasks [64]. Interestingly, abnormal visual perception accompanied by reduced γ band activity has been reported in occipital cortical areas of individuals with schizophrenia [65]. Furthermore, abnormal γ oscillations observed in individuals with schizophrenia during auditory processing tasks [66] may reflect altered GABA neurotransmission in auditory cortices [55]. Therefore, altered GABA neurotransmission mediated by PV-containing GABA neurons may contribute to the dysfunction of multiple cortical areas by disturbing cortical oscillations in individuals with schizophrenia.

Alterations of Neural Synchrony in Schizophrenia

After the early demonstrations of altered neural synchrony in schizophrenia [64,65], several studies have confirmed and expanded those findings [67]. Interestingly, γ oscillations recently have been linked to working memory function, whereas traditionally, the neural basis of working memory has been associated with the persistent firing of cortical neurons [44,45]. Working memory is a complex system that includes a central executive component plus storage buffers in which information is maintained for a short term [68]. Alterations in specific components of the working memory system may give rise to different types of cognitive deficits in schizophrenia. A recent study confirmed previous findings showing that schizophrenia patients exhibit alterations in γ oscillations during the maintenance phase of working memory [69]. Further studies are needed to elucidate whether γ oscillations are directly involved in information storage in the buffer components of the working memory system.

Although additional research is necessary, some studies suggest that in addition to cognition, altered γ oscillations maybe related to other symptom domains of schizophrenia. For example, although schizophrenia patients overall have reduced γ oscillation power or phase synchronization, they also exhibit a positive correlation between hallucination symptoms rating and auditory cortex γ activity [70]. Importantly, pharmacologically enhanced $GABA_AR$ activity simultaneously improves cognitive performance and frontal γ band power in individuals with schizophrenia [71]. These data support the hypothesis that altered GABA

function in schizophrenia affects cognition by impairing γ oscillations and that γ band power may act as a marker of cognitive deficit and improvement.

Direct demonstration that GABA-mediated inhibition is involved in the production of γ oscillations in healthy humans or schizophrenia patients is challenging. An indirect, noninvasive method to measure GABA activity in human neocortex is magnetic resonance spectroscopy (MRS), which relies on detecting resonance properties of the hydrogen atoms in the GABA molecule exposed to magnetic fields. Combined with electrophysiologic measures of γ oscillations in the same individuals, MRS may help us understand the relations between brain GABA content and neural activity. This approach was recently used to assess bulk GABA concentration in the human cortex. Interestingly, a recent MRS study showed that across healthy individuals, bulk GABA concentration in the visual cortex was positively correlated with γ oscillation strength during visual stimulation [72]. Moreover, interindividual variation in GABA concentration in the visual cortex was correlated with variability of performance in a visual stimulus orientation discrimination task that induces γ oscillations [73].

Given that the bulk cortical GABA concentration is likely to be dependent on GAD67 activity, application of MRS may help clarify the relations among GAD67 levels, γ oscillations, and cognitive performance in schizophrenia patients. One study using MRS did not detect differences between schizophrenia patients and control participants in GABA concentration in the anterior cingulate cortex, whereas GABA concentration was apparently decreased by antipsychotic medications [74]. Another MRS study reported a reduction of bulk GABA concentration in the basal ganglia, but not in the frontal cortex of schizophrenia patients [75]. Finally, an MRS study of schizophrenia patients with relatively low antipsychotic exposure revealed a significant reduction of GABA concentration in the visual cortex that did not co-vary with medication dosage but was correlated with behavioral abnormalities in a visual surround-suppression task thought to depend on GABA-mediated inhibition [76•]. While awaiting independent replication, these preliminary studies highlight the importance of addressing the effects of confounding factors such as medications [77]. It is important to note that postmortem studies in humans and experimental studies in animals have failed to show an effect of antipsychotic medications on GAD67 mRNA levels [77]. In addition, these results underscore the significance of combining neurochemical, electrophysiologic, and behavioral assessment given the large interindividual variability in bulk GABA concentration, γ activity levels, and behavioral performance.

An alternative technique to study GABA activity in the intact human cortex is the so-called “GABA shift” positron emission tomography (PET) method, which is based on the allosteric interactions between benzodiazepine and GABA binding to $GABA_A$Rs [78]. GABA binding produces conformational changes in the $GABA_A$Rs that increase benzodiazepine binding affinity, producing a GABA-induced shift in benzodiazepine binding [78]. Using PET measures of radiolabeled benzodiazepine binding, GABA activity at $GABA_A$Rs can be noninvasively measured in the intact human brain. Indeed, tiagabine, a GABA uptake blocker that increases the extracellular GABA concentration, potentiates binding of the PET benzodiazepine ligand [^{11}C]-flumazenil [78]. Moreover, variability in the magnitude of the GABA shift across individuals is strongly correlated with the power of γ oscillations induced during a task engaging cognitive control [78]. Similar PET studies of patients with schizophrenia may permit assessments of the link between alterations in cortical GABA, γ oscillations, and cognitive dysfunction.

Schizophrenia may have a neurodevelopmental origin, and the onset of psychotic symptoms typically occurs by the end of adolescence. Therefore, understanding the developmental trajectory of neural synchrony through adolescence is crucial. In rats and mice, the

mechanisms producing γ rhythms reach adult-level capacity before adolescence [79]. The preadolescence maturation of γ oscillation mechanisms in rodents maybe explained by the preadolescence maturation of PV cell—mediated inhibition [79,80]. In contrast, GABA-mediated inhibition in the primate cortex is still undergoing maturation during adolescence [32], as further confirmed by recent studies [81,82]. For instance, gephyrin, an important protein for synaptic clustering of $GABA_A$Rs, shows marked changes during adolescence in nonhuman primates [81]. Similarly, in nonhuman primates, the $GABA_A$R subtype predominantly mediating phasic inhibition switches from α2 subunit- to α1 subunit–containing subtype, following a protracted trajectory extending through adolescence [82].

Recent studies began characterizing the developmental trajectory of GABA-related molecules in human cortex. Some parameters (eg, the levels of KCC2 and NKCC1 proteins [the chloride transporters determining excitatory vs inhibitory effects of GABA] and GAD67 mRNA expression) reach adult levels during early human brain development before adolescence [59,83]. In contrast and in agreement with nonhuman primate data, other parameters related to GABA-mediated transmission show protracted development in humans. For instance, mRNA levels for α1 and α2 $GABA_A$R subunits display protracted development in humans, showing differences between adolescence and adulthood [84]. Similar protracted changes are observed for α4 and α5 $GABA_A$R subunits, but not for α3 $GABA_A$R subunits, throughout human adolescence [84].

The data reviewed above suggest that in humans, GABA-mediated inhibition undergoes significant maturational changes throughout a protracted age window that includes adolescence. Because inhibition-based rhythms are a plausible mechanism underlying network oscillations, such findings suggest that maturation of oscillatory activity in human cortex is protracted as well. Recent evidence suggests that major changes in the capacity to produce oscillations take place during late-adolescence and early-adulthood in humans [67]. For instance, oscillations induced during a Gestalt perception task showed a marked age-dependent improvement of γ and θ band activities in adulthood compared with adolescence and childhood [85•]. In addition, long-distance synchronization of θ and γ oscillatory activity increased between adolescence and adulthood [85•]. In a study by another group, γ oscillation power and phase locking, which measures long-range synchronization, increased in adults compared with children [86]. In addition, the auditory state–state oscillatory response to 40-Hz stimuli is enhanced in amplitude between childhood and adulthood, suggesting maturational changes during adolescence [87]. Finally, MRI used to analyze the blood oxygenation level–dependent (BOLD) signal during cognitive tasks revealed significant adolescence-related maturational changes in cortical function [88]. Because the BOLD signal magnitude is tightly correlated with γ oscillation power [89], developmental changes in BOLD signals indirectly support the idea that γ rhythm mechanisms undergo marked changes during human adolescence.

Conclusions

Integration of data from basic studies of cortical function, postmortem findings of pathology, and clinical studies of pathophysiology increases our capacity to understand potential links between measurable alterations in cortical circuits and cortical dysfunction in schizophrenia. Novel techniques using tools from mathematics, physics, chemistry, molecular biology, genetics, and basic neuroscience provide better ways to formulate and test novel hypotheses regarding the schizophrenia disease process. The particular case of alterations in GABA neuron function, γ oscillations, and cognition maybe an informative example of the power of such an approach. Since the original report of GAD67 deficits, use of such an integrative approach has strengthened the hypothesis of alterations in GABA neurons in schizophrenia. A challenge for future studies will be to determine the causes and

developmental nature of the GABA neuron dysfunction, as this knowledge maybe critical for the identification of biomarkers that predict disease risk and for the development of preemptive therapeutic interventions. Finally, it is important to perform integrative studies measuring, in the same individuals, GABA neuron deficits and other types of alterations associated with schizophrenia, such as changes in pyramidal cells and glutamate transmission. Such studies may help reveal the cascade of pathogenetic mechanisms that lead to the signs of cortical dysfunction frequently observed in individuals with schizophrenia.

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Table 1

Studies reporting decreased cortical GAD67 expression

Study	GAD67	Cortical area	Method	Findings	Brain bank (cohort size)
Akbarian et al. [90]	mRNA	DLPFC (BA9)	In situ hybridization	30%–50% decrease in number of expressing cells across layers I–VI	University of California (CON: 10, SCH: 10)
Impagnatiello et al. [55]	Protein	STG (BA22)	Western blot analysis	70% decrease	National Neurological Research Specimen Bank; Harvard Brain Tissue Resource Center (CON: 8, SCH: 8)
Volk et al. [91]	mRNA	DLPFC (BA9)	In situ hybridization	25%–35% decrease in number of expressing cells across layers III–V; normal expression levels in labeled cells	University of Pittsburgh (CON: 10, SCH: 10)
Guidotti et al. [92]	mRNA; protein	DLPFC (BA9)	Quantitative PCR; Western blot analysis	50% and 68% decrease in protein and mRNA levels, respectively	Stanley Foundation Brain Bank (CON: 15, SCH: 15 for protein, CON6, SCH:6 for mRNA)
Mimics et al. [93]	mRNA	DLPFC (BA9)	DNA microarray	20%–70% decrease in mRNA levels across subject pairs	University of Pittsburgh (CON: 6, SCH: 6)
Vawter et al. [94]	mRNA	DLPFC (BA9/46)	DNA microarray	Decreased mRNA levels	National Institute of Mental Health (CON: 15, SCH: 15)
Woo et al. [54]	mRNA	ACC (BA24)	In situ hybridization	53% and 23% decrease in number of expressing cells in layers II and V, respectively	Harvard Brain Tissue Resource Center (CON: 17, SCH: 17)
Hashimoto et al. [95]	mRNA	DLPFC (BA9)	In situ hybridization	24% and 28% decrease in mRNA levels in 2 separate cohorts	University of Pittsburgh (CON: 27, SCH: 27)
Straub et al. [58]	mRNA; protein	DLPFC	Real time PCR; Western blot analysis	16% decrease in mRNA levels; no difference in protein levels	National Institute of Mental Health (CON: 67, SCH: 32 for mRNA; CON: 27, SCH: 26 for protein)
Huang et al. [59]	mRNA	DLPFC (BA10)	Real time PCR	Significant decrease only in females	University of California; Maryland Psychiatric Research Center (CON: 12, SCH: 12 for female; CON: 24, SCH: 24 for male)
Woo et al. [96]	mRNA	DLPFC (BA9)	In situ hybridization	27%–36% decrease in number of expressing cells across layers II–V	Harvard Brain Tissue Resource Center (CON: 20, SCH: 20)
Hashimoto et al. [97]	mRNA	DLPFC (BA9)	DNA microarray; Real time PCR	25% decrease by DNA microarray; 12% decrease by real time PCR	University of Pittsburgh (CON: 14, SCH: 14)
Hashimoto et al. [52••]	mRNA	DLPFC (BA9); ACC (BA24); M1 (BA4); V1 (BA17)	Real time PCR	28%, 21%, 28%, and 32% decrease in BA9, BA24, BA4, and BA17, respectively	University of Pittsburgh (CON: 12, SCH: 12)
Thompson et al. [53]	mRNA	OFC (BA45); ACC (BA24); STG (BA22)	In situ hybridization	26%–30% decrease across layers II–V of BA45; 22% decrease in layer V of BA24; 22% decrease in layer IV of BA22	Stanley Foundation Brain Bank (CON: 15, SCH: 14)
Duncan et al. [84]	mRNA	DLPFC (BA9/46)	Real time PCR	17% decrease	New South Wales Tissue Resource Centre (CON: 37, SCH:37)

ACC anterior cingulate cortex; *BA* Brodmann area; *CON* Non-psychiatry control subjects; *DLPFC* dorsolateral prefrontal cortex; *GAD67* g lutamic acid decarboxylase67; *M1* primary motor cortex; *OFC* orbitofrontal cortex; *PCR* polymerase chain reaction; *SCH* subjects diagnosed with schizophrenia or schizoaffective disorder; *STG* superior temporal gyrus; *V1* primary visual cortex