

Cortical interneurons in schizophrenia – cause or effect?

Matija Vid Prkačin, Ivan Banovac, Zdravko Petanjek, Ana Hladnik

Department of Anatomy and Clinical Anatomy, University of Zagreb School of Medicine, Zagreb, Croatia

The first two authors contributed equally.

GABAergic cortical interneurons are important components of cortical microcircuits. Their alterations are associated with a number of neurological and psychiatric disorders, and are thought to be especially important in the pathogenesis of schizophrenia. Here, we reviewed neuro-anatomical and histological studies that analyzed different populations of cortical interneurons in postmortem human tissue from patients with schizophrenia and adequately matched controls. The data strongly suggests that in schizophrenia only selective interneuron populations are affected, with alterations of somatostatin and parvalbumin neurons being the most convincing. The most prominent changes are found in the prefrontal cortex, which is consistent with the impairment of higher cognitive functions characteristic of schizophrenia. In contrast, calretinin neurons, the most numerous interneuron population in primates, seem to be largely unaffected. The selective alterations of cortical interneurons are in line with the neurodevelopmental model and the multiple-hit hypothesis of schizophrenia. Nevertheless, a large number of data on interneurons in schizophrenia is still inconclusive, with different studies yielding opposing findings. Furthermore, no studies found a clear link between interneuron alterations and clinical outcomes. Future research should focus on the causes of changes in the cortical microcircuitry in order to identify potential therapeutic targets.

Received: June 17, 2022

Accepted: February 15, 2023

Correspondence to:

Ivan Banovac
Department of Anatomy and
Clinical Anatomy
University of Zagreb School of
Medicine
Šalata 11
10 000 Zagreb, Croatia
ivan.banovac@mef.hr

Schizophrenia is a psychiatric disorder that affects up to 1% of the population and is characterized by the dysregulation of cognitive, emotional, and behavioral functions (1,2). The clinical manifestation of schizophrenia is usually categorized into three groups of symptoms: positive, negative, and cognitive. Positive symptoms are experienced during psychotic episodes and include hallucinations, delusions, and speech disorders, while negative symptoms include apathy, flattened affect, avolition, and anhedonia. Cognitive symptoms typically manifest as deficits in memory, attention, and reasoning. They are often present in the prodromal stage, long before the manifestation of the core positive and negative symptoms (2). Among these three groups of symptoms, positive symptoms best respond to pharmacotherapy, while negative and cognitive symptoms are more resistant to treatment and are the main cause of decreased quality of life in schizophrenia (3).

Schizophrenia is diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) (4) or the International Classification of Diseases (ICD) (5). The most recent versions of these diagnostic handbooks currently in use are the DSM-5 and ICD-10, with the ICD-11 being proposed to replace ICD-10 in the near future (6).

The etiology and pathogenesis of schizophrenia are still unclear, though it is generally agreed that the clinical manifestation of schizophrenia necessitates a combination of environmental and genetic factors. There are several prevailing hypotheses on the origin of schizophrenia, yet none of these completely explain all the observed clinical manifestations. Nevertheless, most of them are not mutually exclusive, which leaves open the possibility of multiple hypotheses eventually explaining the mechanisms underlying the pathogenesis of schizophrenia (2,7).

The potential role of GABAergic cortical neurons in the pathophysiology of schizophrenia is of particular interest because schizophrenia is often associated with dysfunction of cortical microcircuits (8,9). Understanding the alterations of different populations of GABAergic cortical neurons in schizophrenia could provide important insight into the clinical presentation and treatment of this disorder.

Here, we give a comprehensive overview of the possible roles of GABAergic cortical neurons in schizophrenia. In particular, we focused on molecular studies done on human brain tissue and accentuated the strength and conclusiveness of the findings, which was not done in previous reviews on this topic. We also evaluated the different

hypotheses on its etiology and pathogenesis in relation to the dysfunction of GABAergic neurons.

NEUROANATOMICAL BACKGROUND OF SCHIZOPHRENIA

Research on the neuroanatomical background of schizophrenia is vast; however, the exact regions and functional circuits affected are still somewhat contentious. The most consistent finding in postmortem and *in vivo* studies is a relatively generalized reduction in brain volume, predominantly attributed to a reduction in gray matter of the cerebral cortex (10,11). Nevertheless, the overall thinning of the cerebral cortex does not adequately explain the typical clinical manifestations of schizophrenia, and evidence points to more subtle subcellular abnormalities being the main driving force behind the cognitive disturbances (9,12-16). Furthermore, even though the extent to which the white matter is affected varies between studies, white matter abnormalities in schizophrenia are still frequently reported. Most studies point to disrupted white matter integrity and demyelination. Nevertheless, the exact impact of white matter lesions on the pathogenesis and overall clinical presentation of schizophrenia is still being studied (17-21). Overall, the gross anatomical changes in schizophrenia are largely non-specific and are likely merely a consequence of underlying microcircuitry alterations.

Despite the lack of specificity regarding gross morphological changes in schizophrenia, majority of studies suggest that the most affected regions of the brain are the prefrontal cortex (PFC), temporal lobe, and basal nuclei.

The most intriguing of these is the PFC. The PFC is generally divided into two distinct functional parts – the lateral PFC (LPFC) and the ventromedial (vmPFC) or orbitomedial PFC (omPFC). The term vmPFC is sometimes used partially or completely synonymously with the term orbitofrontal cortex (OFC). The LPFC is further divided into the dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex. The LPFC is crucial for the integration of higher cognitive functions (executive functions), such as decision making and working memory, while the vmPFC is involved in the control of emotions and motivation (22). The PFC receives rich dopaminergic innervation via the mesocortical pathway, which originates in the ventral tegmental area (VTA) of the mesencephalon (Figure 1) (23). The overall effect of dopamine on prefrontal cortical neurons is predominantly inhibitory. However, it modulates the activ-

ity of cortical neurons in the PFC through at least three major modes of action (9). The first is via direct innervation of pyramidal neurons, which enables dopaminergic regulation of cortico-thalamic, cortico-striatal, and cortico-cortical projections from the PFC. The second is via non-synaptic dopamine neurotransmission, while the third is via the innervation of local circuit non-pyramidal neurons (GABAergic interneurons). This last and particularly significant mode of action enables indirect regulation of PFC projection pathways via feed-forward inhibition. Alterations in the dopaminergic innervation of the PFC via the mesocortical pathway are thought to be important in the pathophysiology of schizophrenia. The changes in the LPFC have been connected to cognitive (DLPFC) and negative (VLPFC) symptoms in schizophrenia (24). Interestingly, dysconnectivity between the cerebellum and the DLPFC has been associated with negative symptom severity (25). Furthermore, the thinning of the left medial OFC was associated with the severity of negative symptoms (26), while vmPFC dysfunction was more strongly associated with positive symptoms (24). In addition, the hypoactivity of the anterior cingulate cortex (ACC), which is often considered a functional extension of the vmPFC, was associated with the presence of negative symptoms (27-29). Alterations to von Economo neurons, a highly specialized class of projection neurons located in the ACC, have also been described (30-32).

Besides the mesocortical pathway, the mesolimbic pathway is as well affected in schizophrenia. This pathway also originates in the VTA; however, its synaptic targets are located in the ventral striatum (part of the basal nuclei), which includes the nucleus accumbens and olfactory tubercle (Figure 1). In contrast to the mesocortical pathway, which is involved in the regulation of executive functions, the mesolimbic pathway is involved in aversion-related and reward-related cognition (positive reinforcement, pleasure response to stimuli, and incentive salience) (23). The ventral striatum has been associated with both positive and negative symptoms in schizophrenia (24).

The medial portion of the temporal lobe contains the hippocampus, which is usually significantly reduced in size in schizophrenia. The hippocampus and its adjacent structures are involved in short-term memory consolidation, and their dysfunction in schizophrenia can explain poor memory retrieval and some of the positive symptoms. Another important part of the temporal lobe affected in schizophrenia is the superior temporal gyrus, which is involved in language comprehension, auditory processing, and self-monitoring. Its cortico-cortical projections form part of the temporal-frontal-parietal network involved in language production and interpretation. Cortical thinning in the superior temporal gyrus is associated with the severity of positive symptoms, particularly thought disturbance.

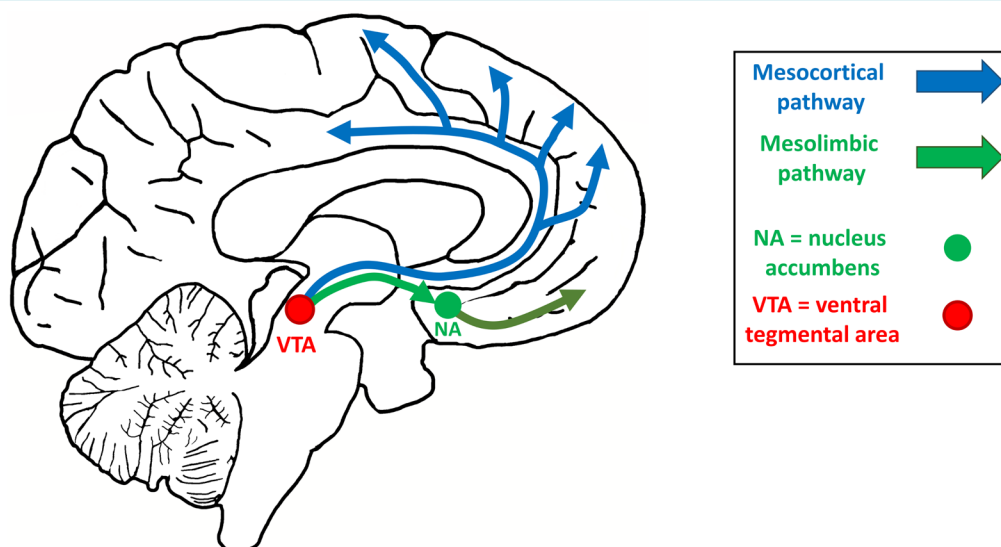


FIGURE 1. Dopaminergic pathways altered in schizophrenia – mesocortical pathway (blue) and mesolimbic pathway (light green). The origin of both pathways – the ventral tegmental area is shown as a red circle, while the light green circle represents the nucleus accumbens (NA), which is part of the ventral striatum. The dark green arrow represents projections from the NA.

es and auditory hallucinations (33). However, some studies showed a less convincing association between the superior temporal gyrus and positive symptoms (24).

In general, reduced blood flow in the PFC and striatum observed on functional MRI is particularly common in patients with prominent negative and cognitive symptoms. Such patients typically experience a prolonged prodromal period, characterized by inadequate social functioning, before the onset of positive (psychotic) symptoms (23).

Overall, numerous studies investigated the neuroanatomical abnormalities in schizophrenia and their relation to the specific symptoms (24,25,27-29,33). An overview of these findings is shown in Table 1. Most of the available data refer to neuroimaging correlation studies, which typically do not determine whether the relationships are causal to the disorder, or whether they are compensatory processes or secondary phenomena.

ETIOLOGY AND PATHOGENESIS OF SCHIZOPHRENIA

The hypotheses explaining the etiology and pathogenesis of schizophrenia can be grouped into two categories – the hypotheses involving altered levels of different neurotransmitters (dopamine, GABA, and glutamate dysfunction) and the hypotheses involving reduced cortical synaptic connectivity.

Among the hypotheses related to neurotransmitter dysfunction, the most prevalent is the dopamine hypothesis. This hypothesis suggests that the main cause of psychotic symptoms in schizophrenia is excessive dopamine D2 receptor activation. It is supported by the significant efficacy

of D2-like-receptor antagonists in the treatment of psychotic symptoms. This hypothesis also has a strong neuroanatomical basis, since the PFC, cingulate cortex, and medial temporal cortex, which are all extensively affected in schizophrenia, receive particularly strong dopaminergic innervation (2).

The next most prominent hypothesis is the one involving glutamate dysfunction. This hypothesis explains the etiology of both positive and negative symptoms of schizophrenia through the dysfunction of N-methyl-D-aspartate (NMDA) glutamate receptors. It is supported by ketamine (an NMDA receptor blocker) causing schizophrenia-like symptoms in pharmacological models of schizophrenia. Most models suggest a hypofunction of NMDA receptors, which could explain some of the negative and cognitive symptoms. Interestingly, the expression of the NR2D subtype of NMDA receptors in schizophrenia is increased. NR2D receptors in schizophrenia are characterized by hyperexcitability, probably as a compensatory response to reduced cortical activity. This particularly affects the stimulatory input of cortical GABAergic interneurons, thus impacting feedback inhibition in cortical circuits. Such a dysfunction of NMDA receptors is particularly prevalent in the PFC (2).

The GABA hypothesis suggests that schizophrenia occurs due to alterations in the GABAergic cortical networks. Possible mechanisms include altered GABA synthesis and reuptake. Once again, such dysfunctions are most prominent in the PFC. Newer models attempted to integrate the GABA hypothesis with NMDA hypofunction (2). These models explain the altered cortical activity in schizophrenia by a disbalance between GABAergic and glutamatergic activity. Such a disbalance could cause instability

TABLE 1. Overview of the affected anatomical regions in schizophrenia and their relation to the clinical presentation of the disorder. The level of association with certain groups of symptoms is shown in parentheses (data extrapolated from 24,25, 27-29,33)

Anatomical region affected in schizophrenia	Connection to clinical presentation of schizophrenia
Dorsolateral prefrontal cortex	cognitive symptoms (moderate association)
Ventrolateral prefrontal cortex	negative symptoms (moderate association)
Ventromedial prefrontal cortex	positive symptoms (moderate association) negative symptoms (inconclusive)*
Ventral striatum (nucleus accumbens)	negative symptoms (moderate association) positive symptoms (weak association)
Hippocampus	positive symptoms (weak association)
Amygdala	positive symptoms (weak association)
Anterior cingulate cortex	negative symptoms (inconclusive)†
Superior temporal gyrus	positive symptoms (inconclusive)*
Cerebellum	negative symptoms (inconclusive)†

*only some studies showed clear association, while others did not show clear association.

†the number of studies demonstrating a clear association was small.

within cortical microcircuits and lead to impaired cortical functioning, consistent with the negative and cognitive symptoms (2).

According to the disconnection hypothesis, rather than by a disbalance of particular neurotransmitters, the pathogenesis of schizophrenia can be explained primarily by reduced or dysfunctional synaptic connectivity between different cortical areas. These changes in synaptic connectivity could disproportionately affect the mesocortical pathway involving the PFC. Synaptic dysfunction impacts both local circuit neurons (typically GABAergic interneurons) and projections neurons (typically glutamatergic pyramidal neurons), with changes in microcircuits as well as in cortico-cortical and cortico-subcortical networks (34,35). Cortical connectivity could be greatly affected by structural or functional alterations to specific neuron classes. The disconnection hypothesis is also particularly interesting because it is in line with the neurodevelopmental model and the two-hit hypothesis on the pathogenesis of schizophrenia (2).

The neurodevelopmental model of schizophrenia proposes that the first pathological events in the brain occur long before the onset of the symptoms (7,36-39). Numerous studies demonstrated a correlation between perinatal events (eg, infection in pregnancy, placental insufficiency) and the occurrence of schizophrenia later in life. In this model, at least two hits (noxae) are necessary for the

clinical manifestation of schizophrenia. The first hit occurs during the early development of the brain, either due to genetic or prenatal environmental factors. The second hit occurs during postnatal brain development. The examples of such adverse events include infectious agents, social factors (eg, social defeat – related to the negative experience of being excluded from a majority group; and social cognition – people's perception of themselves and other individuals), and substance abuse (36). In the two-hit model, the clinical presentation of schizophrenia becomes apparent only after the second hit occurs. Certain hits may occur only during certain neurodevelopmental windows. These hits can affect the migration and maturation of neurons in critical regions of the brain, and their effects become apparent when the development of associated functions is most pronounced (Figure 2). The neurodevelopmental model does not exclude the possibility of more than two hits occurring – this is usually referred to as the multiple-hit hypothesis (36).

CORTICAL INTERNEURONS IN SCHIZOPHRENIA

Initially, research on neuropathology in schizophrenia mainly focused on cortical pyramidal neurons. The changes to pyramidal neurons were subtle, and included reduced arborization and synaptic connectivity. There was also a reduced number of specific membrane receptors, with GABA receptors being among the most affected. The latter alterations suggested that the pathological chang-

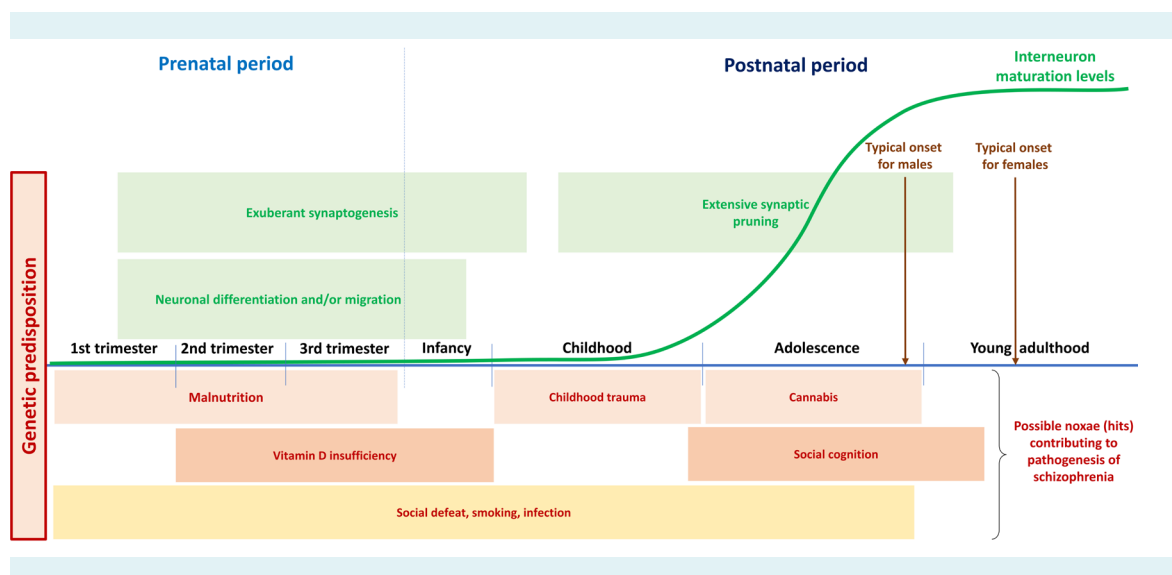


FIGURE 2. The multiple-hit neurodevelopmental model of schizophrenia. The x-axis represents the different prenatal and postnatal life periods during which certain hits (shown below the axis) can affect normal developmental processes (shown above the axis).

es in pyramidal neurons might be related to the dysfunction of GABAergic cortical neurons (cortical interneurons). Therefore, research interest has recently shifted to cortical interneurons, which regulate pyramidal neuron activity in cortical microcircuits.

There are numerous studies on cortical interneurons and their alterations in schizophrenia, in both animals and humans. We reviewed the data from neuroanatomical and histological studies that analyzed different populations of cortical interneurons in postmortem human tissue from patients with schizophrenia and adequately matched controls. We focused on the studies using the following methodologies: immunohistochemistry, RNA *in situ* hybridization, and real-time polymerase chain reaction. Research revealed that even the alterations of cortical interneurons were relatively subtle and affected only certain interneuron populations. However, there is a large number of contradicting studies, and certain changes in cortical microcircuitry are less supported than others. Many of these discrepancies could be attributed to differences in methodology, the use of animal models, prolonged use of pharmacotherapy, as well as differences in the postmortem delay of the analyzed brain. Furthermore, the predominance of different types of symptoms in schizophrenia may be related to alterations in different interneuron populations.

The three most consistent findings among all of these studies are a general decrease in *GAD1* (glutamate decarboxylase; GAD67) mRNA expression, a decrease in *SST* (somatostatin) mRNA expression, and a decrease in parvalbumin (PV) expression and/or PV⁺ neuron density (Table 2 and Figure 3).

Glutamate decarboxylase

Many studies found consistent alterations in *GAD1* mRNA expression in schizophrenia. *GAD1* encodes for the GAD67 protein, which is located primarily in the neuronal cell body and synthesizes GABA for numerous metabolic purposes, including neuroprotection and oxidative stress regulation (40,41). Many studies, using various techniques on both animal models and postmortem human tissue, consistently found significantly decreased *GAD1* mRNA expression in the PFC in schizophrenia (42-58). A similar decrease in *GAD1* expression was also found in other cortical areas, such as the visual cortex, hippocampus, ACC, motor cortex, and cerebellum (45,59-62). Some studies suggested that the overall reduction in *GAD1* mRNA expression in schizophrenia might be predominantly due to a selective reduction in a certain subset of cortical interneurons, rather than due to a generalized reduction affecting all interneuron populations (8).

TABLE 2. Changes in specific GABAergic interneuron populations in schizophrenia

Interneuron population	Alteration in schizophrenia (method used)	Brain region analyzed	Relevant studies
Somatostatin	decreased expression of <i>SST</i> mRNA (ISH) reduced number of SOM ⁺ neurons (IHC)	DLPFC subiculum entorhinal cortex hippocampus	Nakatani et al 2006, Hashimoto et al 2008a, Morris et al 2008, Konradi et al 2011, Wang et al 2011
Parvalbumin	decreased expression of PV protein (IHC) and/or reduced number of PV ⁺ neurons (IHC)	DLPFC subiculum entorhinal cortex inferior colliculus hippocampus	Beasley and Reynolds 1997, Konradi et al 2011, Wang et al 2011, Chung et al 2016, Kilonzo et al 2020, Kalus et al 1997, Shepard et al 2019, Woo et al 1997
Calbindin	inconclusive (IHC, ISH, RT-PCR)	DLPFC temporal cortex striatum subiculum entorhinal cortex	Daviss and Lewis 1995, Benes et al 1998, Holt et al 1999, Iritani et al 1999, Takahashi et al 2000, Chance et al 2005, Fung et al 2010, Wang et al 2011
Calretinin	inconclusive (IHC, RT-PCR)	DLPFC striatum	Daviss and Lewis 1995, Woo et al 1997, Hashimoto et al 2003, Adorjan et al 2020
Cholecystokinin	decreased expression of <i>CCK</i> mRNA (ISH, RT-PCR)	DLPFC	Hashimoto et al 2008a, Fung et al 2010
Neuropeptide Y	inconclusive (IHC, RT-PCR)	DLPFC	Ikeda et al 2004, Hashimoto et al 2008a, Fung et al 2010
Nitric oxide synthase	reduced number of NOS ⁺ neurons (IHC)	striatum	Fritzen et al 2007
Reelin	decreased expression of <i>RELN</i> mRNA (RT-PCR)	DLPFC	Guidotti et al 2000

*Abbreviations: *SST* – somatostatin mRNA; SOM – somatostatin protein; CCK – cholecystokinin; NOS – nitric oxide synthase; *RELN* – reelin mRNA; ISH – *in situ* hybridization; IHC – immunohistochemistry; RT-PCR – reverse transcription polymerase chain reaction; DLPFC – dorsolateral prefrontal cortex.

Interestingly, *GAD2* mRNA expression in schizophrenia appears to be largely unaltered or only slightly decreased (42,45,58). *GAD2* encodes for the GAD65 protein, which is located in the axon terminals and is primarily involved in GABA synthesis for neurotransmission (40,41).

Since both the *GAD1* and *GAD2* genes are important for the production of GABA, this raises the question why only *GAD1* expression is altered. One explanation might be that *GAD2* is less expressed in healthy brain tissue compared with *GAD1*. This means that it could be more difficult to detect subtler changes in *GAD2* expression. Another explanation is the fact that GAD67 (the product of *GAD1*) is predominantly located in the soma and involved in metabolic production of GABA, while GAD65 (the product of *GAD2*) is located in the axon terminal and is involved in GABA synthesis for neurotransmission. This might suggest that in schizophrenia the neuroprotective role of GABA is more affected than GABA transmission. This is also in line with the selective loss of certain interneuron populations, such as SOM⁺ and PV⁺ cells, which seems to occur in this disorder.

Besides the described alterations to GABAergic markers, the expression of certain subtypes of GABA receptors, lo-

cated predominantly on pyramidal neurons, also appears to be altered in schizophrenia (Figure 3) (8).

Somatostatin and calbindin

Besides *GAD1* expression, there is additional convincing evidence for the alterations of *SST* mRNA expression in schizophrenia. Multiple studies demonstrate a significant decrease in *SST* expression in the PFC and hippocampus in schizophrenia (42,63–66). There is also evidence of a reduced number or density of somatostatin (SOM⁺) cells (63,66).

Unlike that on SOM, research on calbindin (CB) in schizophrenia yielded inconclusive results, with different authors finding increased, decreased, or unchanged levels of CB protein or mRNA (66–73). Several studies demonstrated a reduction in *SST* expression, but did not demonstrate a reduction in CB expression (66,73,74).

This discrepancy between SOM and CB alteration in schizophrenia is particularly interesting. In the human PFC, SOM and CB are expressed in highly overlapping interneuron populations – up to 70% of CB⁺ interneurons co-express SOM and up to 50% of SOM⁺ interneurons co-express CB

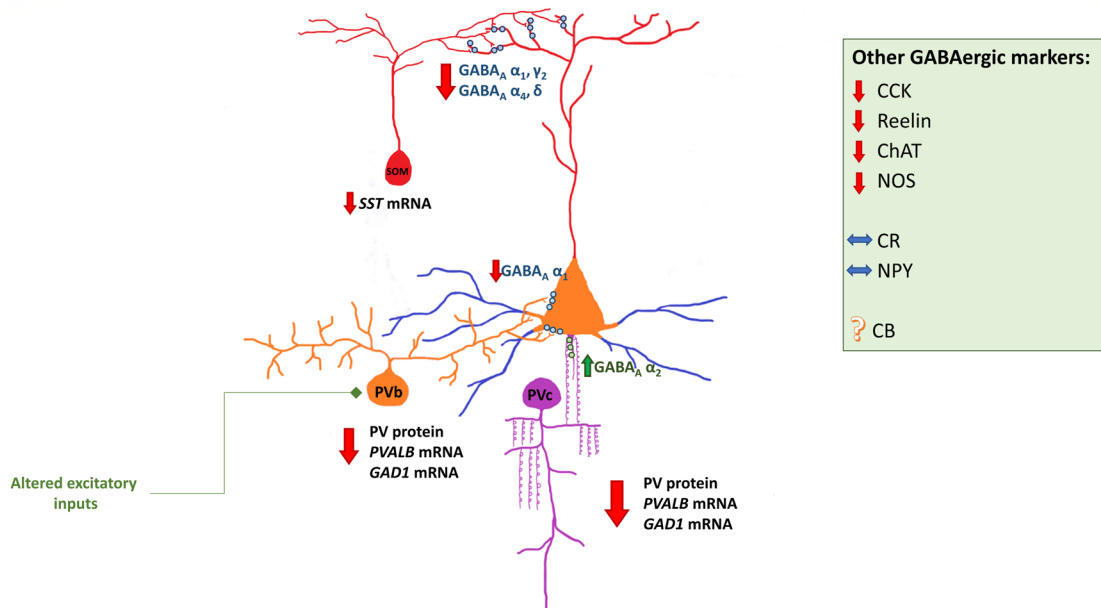


FIGURE 3. The alterations of cortical interneurons in schizophrenia. The synaptic targets of different interneuron types are shown on the pyramidal neuron in the center. Somatostatin-positive Martinotti cells (SOM) target the pyramidal neurons' apical dendrites, parvalbumin-positive basket cells (PVb) target the somata, while the parvalbumin-positive chandelier cells (PVC) target the axon initial segments. Alterations (or lack thereof) of other common GABAergic markers are shown in the framed box on the right: cholecystokinin (CCK), reelin, choline acetyltransferase (ChAT), nitric oxide synthase (NOS), calretinin (CR), neuropeptide Y (NPY), and calbindin (CB).

(75). Therefore, the discrepancies in the expression of SOM and CB in schizophrenia point to a very selective change in the non-overlapping SOM and CB interneuron subpopulations. This could be especially notable because SOM and CB are predominantly co-expressed by interneurons in the supragranular cortical layers (layers II and III). The non-overlapping subpopulations are located predominantly in the infragranular layers (layers V and VI) and may have different synaptic targets with involvement in different cortical microcircuits (75). Nevertheless, it is also possible that SOM as a neuromodulator is differently affected in schizophrenia than CB as a calcium-binding protein.

Parvalbumin

Even though PV⁺ neurons have probably been the most studied interneuron population in schizophrenia, there is still no consensus on how exactly PV⁺ cells are altered in this disorder.

Most research suggests a decrease in PV protein or *PVALB* mRNA levels (47,63,66,76-78). However, some animal models and some human studies found the levels of PV protein to be elevated (79,80). A smaller number of studies revealed no significant alterations in PV⁺ cell density (47). Some studies claimed that lower PV levels in schizophrenia reflected only a decrease in PV expression in a subset of PV⁺ neurons and not an actual deficit in PV⁺ neuron numbers (76,81-84). Though these opposing claims could be explained by methodological and regional differences between studies, it is difficult to determine whether this is truly the case. Possibly, different cohorts exhibited different changes to the PV⁺ interneuron population, some resulting in cell loss and others resulting in decreased PV expression. The overall findings could also be influenced by the severity and type of symptoms, as well as the pharmacotherapy the patients were exposed to during the course of their lives.

Some studies demonstrated that a reduction in PV⁺ neurons also confirmed a reduction in *Wisteria floribunda* agglutinin (WFA⁺) perineuronal nets (PNNs) in schizophrenia (83), which are predominantly related to a certain subpopulation of PV⁺ neurons (85). Such findings suggested that PV⁺ neuron loss in schizophrenia could be rather selective, targeting only specific neuronal subpopulations (86). However, in the amygdala and the entorhinal cortex, a reduction in the number of PNNs was not accompanied by a reduction in PV⁺ cell density (83). WFA⁺ PNNs are also found around certain pyramidal neurons – this means that reduc-

tions in the number of WFA⁺ PNNs and PV⁺ cells are not necessarily always related to each other.

Calretinin

Unlike the alternations in SOM⁺ and PV⁺ interneuron populations, most research found no significant alterations in the CR⁺ cortical interneuron population in schizophrenia (47,69,81,87). However, some studies found a reduction in CR⁺ neurons in subcortical structures, such as the striatum (88). Together, CR, PV, and SOM likely mark the vast majority of GABAergic cortical neurons, at least in the human PFC (89). Out of these three large non-overlapping populations, CR⁺ neurons are the most numerous in the primate brain (90). It is, therefore, intriguing that this is the only interneuron population that is largely unaffected in schizophrenia. Furthermore, CR⁺ neurons are relatively unaltered in most other neuropsychiatric or neurodegenerative disorders, such as Alzheimer's disease and depression (91). CR is a calcium-binding protein that protects neurons from calcium cytotoxicity, and this neuroprotective role might provide CR⁺ neurons with a unique resistance to various noxae (92). Nevertheless, this would still not explain why other neuron populations expressing different types of calcium-binding protein, particularly PV, are significantly affected in schizophrenia and other disorders. Another explanation is that CR⁺ neurons, as a vital component of cortical microcircuits in the human brain, are significantly altered only in rare and/or extremely severe disorders.

Other interneuron markers

Significant findings regarding other interneuron markers include reduced expression of *CCK* mRNA (cholecystokinin) (42,73), decreased expression of *RELN* mRNA (reelin) (45), and a reduced number of nitric oxide synthase (NOS⁺) neurons (93). Studies on neuropeptide Y were less conclusive and demonstrated no changes or a very subtle decrease in its expression or cell number (42,73,94).

DIFFERENT DEVELOPMENTAL ORIGINS OF INTERNEURON POPULATIONS AFFECTED IN SCHIZOPHRENIA COULD BE IN LINE WITH THE NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

The differences in alterations between different interneuron populations could also be explained by the distinct developmental origin of CR⁺ neurons compared with SOM⁺ and PV⁺ neurons (95). Whereas CR⁺ neurons originate from the caudal ganglionic eminence and

the dorsal proliferative zones (in primates), SOM⁺ and PV⁺ neurons originate from the medial ganglionic eminence (MGE) and preoptic area (POA) (89). If interneuron alterations in schizophrenia are caused by an early hit during interneuron development, this could mean that pathological changes primarily occur in the MGE and POA. However, interneuron alterations could also be caused by a later hit occurring during adolescence, when most interneuron maturation occurs. If this is the case, PV⁺ and SOM⁺ neurons might simply be more vulnerable to the pathological changes occurring in schizophrenia or to the specific hits typically occurring in this life period (eg, cannabis abuse). Therefore, both an early and a late hit possibility could be in line with the neurodevelopmental model of schizophrenia and the multiple-hit hypothesis. Moreover, multiple hits to specific interneuron populations at different life stages are not mutually exclusive.

CONCLUSIONS

In conclusion, specific populations of GABAergic cortical interneurons are selectively affected in schizophrenia. Changes in the somatostatin interneuron population are the most substantiated in the literature, followed by alteration of parvalbumin neurons. Calretinin neurons seem to be largely unaltered, at least in the cerebral cortex. The changes in selective interneuron populations are most pronounced in specific cortical regions, particularly the PFC, where they likely have highly specific effects on the cortical microcircuitry. Nevertheless, the question remains whether the described changes in schizophrenia are part of the underlying pathophysiological mechanism that contributes to the clinical manifestation of the disorder, or whether they are a consequence of other underlying mechanisms. Future research should focus on determining the exact causes of these changes in the cortical microcircuitry in order to identify potential therapeutic targets. Such research could be especially beneficial if we want to better understand the pathophysiology and treatment of negative and cognitive symptoms.

Funding: This work was supported by the Croatian Science Foundation Grants No. IP-2019-04-3182 (Brain Extracellular Matrix in Development and in Perinatal Hypoxia, PI: Nataša Jovanov Milošević) and No. 5943 (Microcircuitry of Higher Cognitive Functions, PI: Zdravko Petanjek), and co-financed by the Scientific Centre of Excellence for Basic, Clinical, and Translational Neuroscience (project "Experimental and Clinical Research of Hypoxic-Ischemic Damage in Perinatal and Adult Brain," GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

Ethical approval Not required.

Declaration of authorship MVP and IB conceived and designed the study; MVP and IB acquired the data; all authors analyzed and interpreted the data; MVP and IB drafted the manuscript; all authors

critically revised the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

Competing interests ZP is a member of the Managerial Board of the *Croatian Medical Journal*. To ensure that any possible conflict of interest relevant to the journal has been addressed, this article was reviewed according to best practice guidelines of international editorial organizations. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

- Häfner H, der Heiden W. Epidemiology of schizophrenia. *Can J Psychiatry*. 1997;42:139-51. [Medline:9067063](#) [doi:10.1177/070674379704200204](#)
- Valton V, Romaniuk L, Douglas Steele J, Lawrie S, Seriès P. Comprehensive review: Computational modelling of schizophrenia. *Neurosci Biobehav Rev*. 2017;83:631-46. [Medline:28867653](#) [doi:10.1016/j.neubiorev.2017.08.022](#)
- Spark DL, Fornito A, Langmead CJ, Stewart GD. Beyond antipsychotics: a twenty-first century update for preclinical development of schizophrenia therapeutics. *Transl Psychiatry*. 2022;12:147. [Medline:35393394](#) [doi:10.1038/s41398-022-01904-2](#)
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington D.C.: American Psychiatric Association; 2013. xlv, 947
- World Health Organization. International statistical classification of diseases and related health problems. 10th ed. Geneva, Switzerland: World Health Organization; 2011. 3 volumes.
- Gaebel W, Zielasek J, Reed GM. Mental and behavioural disorders in the ICD-11: concepts, methodologies, and current status. *Psychiatr Pol*. 2017;51:169-95. [Medline:28581530](#) [doi:10.12740/PP/69660](#)
- Birnbaum R, Weinberger DR. Genetic insights into the neurodevelopmental origins of schizophrenia. *Nat Rev Neurosci*. 2017;18:727-40. [Medline:29070826](#) [doi:10.1038/nrn.2017.125](#)
- Dienel SJ, Lewis DA. Alterations in cortical interneurons and cognitive function in schizophrenia. *Neurobiol Dis*. 2019;131:104208. [Medline:29936230](#) [doi:10.1016/j.nbd.2018.06.020](#)
- Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr Bull*. 1997;23:437-58. [Medline:9327508](#) [doi:10.1093/schbul/23.3.437](#)
- Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, et al. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol Psychiatry*. 2008;64:774-81. [Medline:18486104](#) [doi:10.1016/j.biopsych.2008.03.031](#)
- Bortolon C, Macgregor A, Capdevielle D, Raffard S. Apathy in schizophrenia: A review of neuropsychological and neuroanatomical studies. *Neuropsychologia*. 2018;118(Pt B):22-33.

- 12 Braff DL, Swerdlow NR. Neuroanatomy of schizophrenia. *Schizophr Bull.* 1997;23:509-12. [Medline:9327513](#) [doi:10.1093/schbul/23.3.509](#)
- 13 Broadbelt K, Byne W, Jones LB. Evidence for a decrease in basilar dendrites of pyramidal cells in schizophrenic medial prefrontal cortex. *Schizophr Res.* 2002;58:75-81. [Medline:12363393](#) [doi:10.1016/S0920-9964\(02\)00201-3](#)
- 14 Banovac I, Sedmak D, Rojnić Kuzman M, Hladnik A, Petanjek Z. Axon morphology of rapid Golgi-stained pyramidal neurons in the prefrontal cortex in schizophrenia. *Croat Med J.* 2020;61:354-65. [Medline:32881434](#) [doi:10.3325/cmj.2020.61.354](#)
- 15 Fortea L, Albajes-Eizaguirre A, Yao Y-W, Soler E, Verdolini N, Hauson AO, et al. Focusing on Comorbidity-a novel meta-analytic approach and protocol to disentangle the specific neuroanatomy of co-occurring mental disorders. *Front Psychiatry.* 2021;12:807839. [Medline:35115973](#) [doi:10.3389/fpsy.2021.807839](#)
- 16 Kasai K, Iwanami A, Yamasue H, Kuroki N, Nakagome K, Fukuda M. Neuroanatomy and neurophysiology in schizophrenia. *Neurosci Res.* 2002;43:93-110. [Medline:12067745](#) [doi:10.1016/S0168-0102\(02\)00023-8](#)
- 17 Lee D-K, Lee H, Park K, Joh E, Kim C-E, Ryu S. Common gray and white matter abnormalities in schizophrenia and bipolar disorder. *PLoS One.* 2020;15:e0232826. [Medline:32379845](#) [doi:10.1371/journal.pone.0232826](#)
- 18 Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, et al. White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Arch Gen Psychiatry.* 2003;60:443-56. [Medline:12742865](#) [doi:10.1001/archpsyc.60.5.443](#)
- 19 Kubicki M, McCarley RW, Shenton ME. Evidence for white matter abnormalities in schizophrenia. *Curr Opin Psychiatry.* 2005;18:121-34. [Medline:16639164](#) [doi:10.1097/00001504-200503000-00004](#)
- 20 Cetin-Karayumak S, Di Biase MA, Chunga N, Reid B, Somes N, Lyall AE, et al. White matter abnormalities across the lifespan of schizophrenia: a harmonized multi-site diffusion MRI study. *Mol Psychiatry.* 2020;25:3208-19. [Medline:31511636](#) [doi:10.1038/s41380-019-0509-y](#)
- 21 Erkol C, Cohen T, Chouinard V-A, Lewandowski KE, Du F, Öngür D. White matter measures and cognition in schizophrenia. *Front Psychiatry.* 2020;11:603. [Medline:32765308](#) [doi:10.3389/fpsy.2020.00603](#)
- 22 Fuster JM. The prefrontal cortex. Morgan Kaufmann series in representation and reasoning. Amsterdam: Elsevier; 2015. 1 online resource.
- 23 Kandel ER. Principles of neural science. 5th ed. New York: McGraw-Hill; 2013. 1, 1709.
- 24 Goghari VM, Sponheim SR, MacDonald AW. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. *Neurosci Biobehav Rev.* 2010;34:468-86. [Medline:19772872](#) [doi:10.1016/j.neubiorev.2009.09.004](#)
- 25 Brady RO, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, et al. Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. *Am J Psychiatry.* 2019;176:512-20. [Medline:30696271](#) [doi:10.1176/appi.ajp.2018.18040429](#)
- 26 Walton E, Hibar DP, van Erp TGM, Potkin SG, Roiz-Santiañez R, Crespo-Facorro B, et al. Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium. *Psychol Med.* 2018;48:82-94. [Medline:28545597](#) [doi:10.1017/S0033291717001283](#)
- 27 Bersani FS, Minichino A, Fojanesi M, Gallo M, Maglio G, Valeriani G, et al. Cingulate cortex in schizophrenia: its relation with negative symptoms and psychotic onset. A review study. *Eur Rev Med Pharmacol Sci.* 2014;18:3354-67. [Medline:25491609](#)
- 28 Nelson BD, Bjorkquist OA, Olsen EK, Herbener ES. Schizophrenia symptom and functional correlates of anterior cingulate cortex activation to emotion stimuli: An fMRI investigation. *Psychiatry Res.* 2015;234:285-91. [Medline:26596521](#) [doi:10.1016/j.psychres.2015.11.001](#)
- 29 Cui L-B, Liu J, Wang L-X, Li C, Xi Y-B, Guo F, et al. Anterior cingulate cortex-related connectivity in first-episode schizophrenia: a spectral dynamic causal modeling study with functional magnetic resonance imaging. *Front Hum Neurosci.* 2015;9:589. [Medline:26578933](#) [doi:10.3389/fnhum.2015.00589](#)
- 30 Brüne M, Schöbel A, Karau R, Benali A, Faustmann PM, Juckel G, et al. Von Economo neuron density in the anterior cingulate cortex is reduced in early onset schizophrenia. *Acta Neuropathol.* 2010;119:771-8. [Medline:20309567](#) [doi:10.1007/s00401-010-0673-2](#)
- 31 Banovac I, Sedmak D, Džaja D, Jalšovec D, Jovanov Milošević N, Rašin MR, et al. Somato-dendritic morphology and axon origin site specify von Economo neurons as a subclass of modified pyramidal neurons in the human anterior cingulate cortex. *J Anat.* 2019;235:651-69. [Medline:31435943](#) [doi:10.1111/joa.13068](#)
- 32 Banovac I, Sedmak D, Judaš M, Petanjek Z. Von Economo neurons – primate-specific or commonplace in the mammalian brain? *Front Neural Circuits.* 2021;15. [Medline:34539353](#) [doi:10.3389/fncir.2021.714611](#)
- 33 Walton E, Hibar DP, van Erp TGM, Potkin SG, Roiz-Santiañez R, Crespo-Facorro B, et al. Positive symptoms associate with cortical thinning in the superior temporal gyrus via the ENIGMA Schizophrenia consortium. *Acta Psychiatr Scand.* 2017;135:439-47. [Medline:28369804](#) [doi:10.1111/acps.12718](#)
- 34 Petanjek Z, Judaš M, Šimic G, Rasin MR, Uylings HBM, Rakic P, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci U S A.* 2011;108:13281-6. [Medline:21788513](#) [doi:10.1073/pnas.1105108108](#)
- 35 Petanjek Z, Sedmak D, Džaja D, Hladnik A, Rašin MR, Jovanov-Milosevic N. The Protracted maturation of associative layer iiic pyramidal neurons in the human prefrontal cortex during childhood: a major role in cognitive development and

- selective alteration in autism. *Front Psychiatry*. 2019;10:122. [Medline:30923504 doi:10.3389/fpsy.2019.00122](#)
- 36 Davis J, Eyre H, Jacka FN, Dodd S, Dean O, McEwen S, et al. A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. *Neurosci Biobehav Rev*. 2016;65:185-94. [Medline:27073049 doi:10.1016/j.neubiorev.2016.03.017](#)
 - 37 Benoit LJ, Canetta S, Kellendonk C. Thalamocortical Development: a neurodevelopmental framework for schizophrenia. *Biol Psychiatry*. 2022. [Medline:35550792 doi:10.1016/j.biopsych.2022.03.004](#)
 - 38 Westacott LJ, Wilkinson LS. Complement Dependent synaptic reorganisation during critical periods of brain development and risk for psychiatric disorder. *Front Neurosci*. 2022;16:840266. [Medline:35600620 doi:10.3389/fnins.2022.840266](#)
 - 39 Petanjek Z, Kostović I. Epigenetic regulation of fetal brain development and neurocognitive outcome. *Proc Natl Acad Sci U S A*. 2012;109:11062-3. [Medline:22753478 doi:10.1073/pnas.1208085109](#)
 - 40 Soghomonian J-J, Martin DL. Two isoforms of glutamate decarboxylase: why? *Trends Pharmacol Sci*. 1998;19:500-5. [Medline:9871412 doi:10.1016/S0165-6147\(98\)01270-X](#)
 - 41 Lariviere K, MacEachern L, Greco V, Majchrzak G, Chiu S, Drouin G, et al. GAD(65) and GAD(67) isoforms of the glutamic acid decarboxylase gene originated before the divergence of cartilaginous fishes. *Mol Biol Evol*. 2002;19:2325-9. [Medline:12446824 doi:10.1093/oxfordjournals.molbev.a004057](#)
 - 42 Hashimoto T, Arion D, Unger T, Maldonado-Avilés JG, Morris HM, Volk DW, et al. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry*. 2008;13:147-61. [Medline:17471287 doi:10.1038/sj.mp.4002011](#)
 - 43 Woo T-UW, Kim AM, Viscidi E. Disease-specific alterations in glutamatergic neurotransmission on inhibitory interneurons in the prefrontal cortex in schizophrenia. *Brain Res*. 2008;1218:267-77. [Medline:18534564 doi:10.1016/j.brainres.2008.03.092](#)
 - 44 Woo T-UW, Shrestha K, Armstrong C, Minns MM, Walsh JP, Benes FM. Differential alterations of kainate receptor subunits in inhibitory interneurons in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Schizophr Res*. 2007;96:46-61. [Medline:17698324 doi:10.1016/j.schres.2007.06.023](#)
 - 45 Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry*. 2000;57:1061-9. [Medline:11074872 doi:10.1001/archpsyc.57.11.1061](#)
 - 46 Stansfield KH, Ruby KN, Soares BD, McGlothlan JL, Liu X, Guilarte TR. Early-life lead exposure recapitulates the selective loss of parvalbumin-positive GABAergic interneurons and subcortical dopamine system hyperactivity present in schizophrenia. *Transl Psychiatry*. 2015;5:e522. [Medline:25756805 doi:10.1038/tp.2014.147](#)
 - 47 Hashimoto T, Volk DW, Eggen SM, Mirnics K, Pierri JN, Sun Z, et al. Gene Expression Deficits in a Subclass of GABA Neurons in the Prefrontal Cortex of Subjects with Schizophrenia. *J Neurosci*. 2003;23:6315-26. [Medline:12867516 doi:10.1523/JNEUROSCI.23-15-06315.2003](#)
 - 48 Curley AA, Arion D, Volk DW, Asafu-Adjei JK, Sampson AR, Fish KN, et al. Cortical deficits of glutamic acid decarboxylase 67 expression in schizophrenia: clinical, protein, and cell type-specific features. *Am J Psychiatry*. 2011;168:921-9. [Medline:21632647 doi:10.1176/appi.ajp.2011.11010052](#)
 - 49 Gonzalez-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. *Curr Psychiatry Rep*. 2010;12:335-44. [Medline:20556669 doi:10.1007/s11920-010-0124-8](#)
 - 50 Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE, et al. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch Gen Psychiatry*. 1995;52:258-66. [Medline:7702443 doi:10.1001/archpsyc.1995.03950160008002](#)
 - 51 Volk DW, Austin MC, Pierri JN, Sampson AR, Lewis DA. Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Arch Gen Psychiatry*. 2000;57:237-45. [Medline:10711910 doi:10.1001/archpsyc.57.3.237](#)
 - 52 Benes F, Vincent S, Marie A, Khan Y. Up-regulation of GABAA receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. *Neuroscience*. 1996;75:1021-31. [Medline:8938738 doi:10.1016/0306-4522\(96\)00328-4](#)
 - 53 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. [Medline:11086983 doi:10.1016/S0896-6273\(00\)00085-4](#)
 - 54 Hashimoto T, Bergen SE, Nguyen QL, Xu B, Monteggia LM, Pierri JN, et al. Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. *J Neurosci*. 2005;25:372-83. [Medline:15647480 doi:10.1523/JNEUROSCI.4035-04.2005](#)
 - 55 Straub RE, Lipska BK, Egan MF, Goldberg TE, Callicott JH, Mayhew MB, et al. Allelic variation in GAD1 (GAD67) is associated with schizophrenia and influences cortical function and gene expression. *Mol Psychiatry*. 2007;12:854-69. [Medline:17767149 doi:10.1038/sj.mp.4001988](#)
 - 56 Mellios N, Huang H-S, Baker SP, Galdzicka M, Ginns E, Akbarian S. Molecular determinants of dysregulated GABAergic gene expression in the prefrontal cortex of subjects with schizophrenia. *Biol Psychiatry*. 2009;65:1006-14. [Medline:19121517 doi:10.1016/j.biopsych.2008.11.019](#)
 - 57 Duncan CE, Webster MJ, Rothmond DA, Bahn S, Elashoff M,

- Shannon Weickert C. Prefrontal GABA(A) receptor alpha-subunit expression in normal postnatal human development and schizophrenia. *J Psychiatr Res.* 2010;44:673-81. [Medline:20100621](#) [doi:10.1016/j.jpsychires.2009.12.007](#)
- 58 Dracheva S, Elhakem SL, McGurk SR, Davis KL, Haroutunian V. GAD67 and GAD65 mRNA and protein expression in cerebrocortical regions of elderly patients with schizophrenia. *J Neurosci Res.* 2004;76:581-92. [Medline:15114630](#) [doi:10.1002/jnr.20122](#)
- 59 Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry.* 2008;165:479-89. [Medline:18281411](#) [doi:10.1176/appi.ajp.2007.07081223](#)
- 60 Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, et al. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc Natl Acad Sci U S A.* 1998;95:15718-23. [Medline:9861036](#) [doi:10.1073/pnas.95.26.15718](#)
- 61 Thompson M, Weickert CS, Wyatt E, Webster MJ. Decreased glutamic acid decarboxylase(67) mRNA expression in multiple brain areas of patients with schizophrenia and mood disorders. *J Psychiatr Res.* 2009;43:970-7. [Medline:19321177](#) [doi:10.1016/j.jpsychires.2009.02.005](#)
- 62 Woo T-UW, Walsh JP, Benes FM. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Arch Gen Psychiatry.* 2004;61:649-57. [Medline:15237077](#) [doi:10.1001/archpsyc.61.7.649](#)
- 63 Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H, et al. Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res.* 2011;131:165-73. [Medline:21745723](#) [doi:10.1016/j.schres.2011.06.007](#)
- 64 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;18:1575-87. [Medline:18203698](#) [doi:10.1093/cercor/bhm186](#)
- 65 Nakatani N, Hattori E, Ohnishi T, Dean B, Iwayama Y, Matsumoto I, et al. Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. *Hum Mol Genet.* 2006;15:1949-62. [Medline:16687443](#) [doi:10.1093/hmg/ddl118](#)
- 66 Wang AY, Lohmann KM, Yang CK, Zimmerman EI, Pantazopoulos H, Herring N, et al. Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathol.* 2011;122:615-26. [Medline:21968533](#) [doi:10.1007/s00401-011-0881-4](#)
- 67 Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry.* 1998;44:88-97. [Medline:9646890](#) [doi:10.1016/S0006-3223\(98\)00138-3](#)
- 68 Chance SA, Walker M, Crow TJ. Reduced density of calbindin-immunoreactive interneurons in the planum temporale in schizophrenia. *Brain Res.* 2005;1046:32-7. [Medline:15927548](#) [doi:10.1016/j.brainres.2005.03.045](#)
- 69 Daviss SR, Lewis DA. Local circuit neurons of the prefrontal cortex in schizophrenia: selective increase in the density of calbindin-immunoreactive neurons. *Psychiatry Res.* 1995;59:81-96. [Medline:8771223](#) [doi:10.1016/0165-1781\(95\)02720-3](#)
- 70 Holt DJ, Herman MM, Hyde TM, Kleinman JE, Sinton CM, German DC, et al. Evidence for a deficit in cholinergic interneurons in the striatum in schizophrenia. *Neuroscience.* 1999;94:21-31. [Medline:10613493](#) [doi:10.1016/S0306-4522\(99\)00279-1](#)
- 71 Iritani S, Kuroki N, Keda K, Kazamatsuri H. Calbindin immunoreactivity in the hippocampal formation and neocortex of schizophrenics. *Prog Neuropsychopharmacol Biol Psychiatry.* 1999;23:409-21. [Medline:10378226](#) [doi:10.1016/S0278-5846\(99\)00005-6](#)
- 72 Takahashi M, Shirakawa O, Toyooka K, Kitamura N, Hashimoto T, Maeda K, et al. Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. *Mol Psychiatry.* 2000;5:293-300. [Medline:10889532](#) [doi:10.1038/sj.mp.4000718](#)
- 73 Fung SJ, Webster MJ, Sivagnanasundaram S, Duncan C, Elashoff M, Weickert CS. Expression of interneuron markers in the dorsolateral prefrontal cortex of the developing human and in schizophrenia. *Am J Psychiatry.* 2010;167:1479-88. [Medline:21041246](#) [doi:10.1176/appi.ajp.2010.09060784](#)
- 74 Fung SJ, Fillman SG, Webster MJ, Shannon Weickert C. Schizophrenia and bipolar disorder show both common and distinct changes in cortical interneuron markers. *Schizophr Res.* 2014;155:26-30. [Medline:24674775](#) [doi:10.1016/j.schres.2014.02.021](#)
- 75 Banovac I, Sedmak D, Esclapez M, Petanjek Z. The distinct characteristics of somatostatin neurons in the human brain. *Mol Neurobiol.* 2022;59:4953-65. [Medline:35665897](#) [doi: 10.1007/s12035-022-02892-6](#)
- 76 Chung DW, Fish KN, Lewis DA. Pathological basis for deficient excitatory drive to cortical parvalbumin interneurons in schizophrenia. *Am J Psychiatry.* 2016;173:1131-9. [Medline:27444795](#) [doi:10.1176/appi.ajp.2016.16010025](#)
- 77 Kilonzo VW, Sweet RA, Glausier JR, Pitts MW. Deficits in glutamic acid decarboxylase 67 immunoreactivity, parvalbumin interneurons, and perineuronal nets in the inferior colliculus of subjects with schizophrenia. *Schizophr Bull.* 2020. [Medline:32681171](#) [doi:10.1093/schbul/sbaa082](#)
- 78 Beasley CL, Reynolds GP. Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. *Schizophr Res.* 1997;24:349-55. [Medline:9134596](#) [doi:10.1016/S0920-](#)

- 9964(96)00122-3
- 79 Shepard R, Heslin K, Hagerdorn P, Coutellier L. Downregulation of Npas4 in parvalbumin interneurons and cognitive deficits after neonatal NMDA receptor blockade: relevance for schizophrenia. *Transl Psychiatry*. 2019;9:99. [Medline:30792384](#) [doi:10.1038/s41398-019-0436-3](#)
 - 80 Kalus P, Senitz D, Beckmann H. Altered distribution of parvalbumin-immunoreactive local circuit neurons in the anterior cingulate cortex of schizophrenic patients. *Psychiatry Res Neuroimaging*. 1997;75:49-59. [Medline:9287373](#) [doi:10.1016/S0925-4927\(97\)00020-6](#)
 - 81 Woo TU, Miller JL, Lewis DA. Schizophrenia and the parvalbumin-containing class of cortical local circuit neurons. *Am J Psychiatry*. 1997;154:1013-5. [Medline:9210755](#) [doi:10.1176/ajp.154.7.1013](#)
 - 82 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;52:708-15. [Medline:12372661](#) [doi:10.1016/S0006-3223\(02\)01360-4](#)
 - 83 Pantazopoulos H, Woo T-UW, Lim MP, Lange N, Berretta S. Extracellular matrix-glia abnormalities in the amygdala and entorhinal cortex of subjects diagnosed with schizophrenia. *Arch Gen Psychiatry*. 2010;67:155-66. [Medline:20124115](#) [doi:10.1001/archgenpsychiatry.2009.196](#)
 - 84 Tooney PA, Chahl LA. Neurons expressing calcium-binding proteins in the prefrontal cortex in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:273-8. [Medline:14751422](#) [doi:10.1016/j.pnpbp.2003.10.004](#)
 - 85 Trnski S, Nikolić B, Ilic K, Drlje M, Bobic-Rasonja M, Darmopil S, et al. The Signature of moderate perinatal hypoxia on cortical organization and behavior: altered PNN-parvalbumin interneuron connectivity of the cingulate circuitries. *Front Cell Dev Biol*. 2022;10:810980. [Medline:35295859](#) [doi:10.3389/fcell.2022.810980](#)
 - 86 Berretta S, Pantazopoulos H, Markota M, Brown C, Batzianouli ET. Losing the sugar coating: potential impact of perineuronal net abnormalities on interneurons in schizophrenia. *Schizophr Res*. 2015;167:18-27. [Medline:25601362](#) [doi:10.1016/j.schres.2014.12.040](#)
 - 87 Barinka F, Druga R. Calretinin expression in the mammalian neocortex: a review. *Physiol Res*. 2010;59:665-77. [Medline:20406030](#) [doi:10.33549/physiolres.931930](#)
 - 88 Adorjan I, Sun B, Feher V, Tyler T, Veres D, Chance SA, et al. Evidence for decreased density of calretinin-immunopositive neurons in the caudate nucleus in patients with schizophrenia. *Front Neuroanat*. 2020;14:581685. [Medline:33281566](#) [doi:10.3389/fnana.2020.581685](#)
 - 89 Hladnik A, Džaja D, Darmopil S, Jovanov-Milošević N, Petanjek Z. Spatio-temporal extension in site of origin for cortical calretinin neurons in primates. *Front Neuroanat*. 2014;8:50. [Medline:25018702](#) [doi:10.3389/fnana.2014.00050](#)
 - 90 Džaja D, Hladnik A, Bičanić I, Baković M, Petanjek Z. Neocortical calretinin neurons in primates: increase in proportion and microcircuitry structure. *Front Neuroanat*. 2014;8:103. [Medline:25309344](#)
 - 91 Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: gaba and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*. 2019;102:75-90. [Medline:30946828](#) [doi:10.1016/j.neuron.2019.03.013](#)
 - 92 Krawczyk A, Szalak R, Jaworska-Adamu J. Immunocytochemical analysis of calretinin in the frontal cortex of chinchilla. *Bull Vet Inst Pulawy*. 2012;56:103-7. [doi:10.2478/v10213-012-0019-z](#)
 - 93 Fritzen S, Lauer M, Schmitt A, Töpner T, Strobel A, Lesch K-P, et al. NO synthase-positive striatal interneurons are decreased in schizophrenia. *Eur Neuropsychopharmacol*. 2007;17:595-9. [Medline:17267181](#) [doi:10.1016/j.euroneuro.2006.12.004](#)
 - 94 Ikeda K, Ikeda K, Iritani S, Ueno H, Niizato K. Distribution of neuropeptide Y interneurons in the dorsal prefrontal cortex of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:379-83. [Medline:14751436](#) [doi:10.1016/j.pnpbp.2003.11.008](#)
 - 95 Inan M, Petros TJ, Anderson SA. Losing your inhibition: linking cortical GABAergic interneurons to schizophrenia. *Neurobiol Dis*. 2013;53:36-48. [Medline:23201207](#) [doi:10.1016/j.nbd.2012.11.013](#)