Inhibitory control of the excitatory/inhibitory balance in psychiatric disorders [version 1; peer review: 2 approved]

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Abstract
Neuronal networks consist of different types of neurons that all play their own role in order to maintain proper network function. The two main types of neurons segregate in excitatory and inhibitory neurons, which together regulate the flow of information through the network. It has been proposed that changes in the relative strength in these two opposing forces underlie the symptoms observed in psychiatric disorders, including autism and schizophrenia. Here, we review the role of alterations to the function of the inhibitory system as a cause of psychiatric disorders. First, we explore both patient and post-mortem evidence of inhibitory deficiency. We then discuss the function of different interneuron subtypes in the network and focus on the central role of a specific class of inhibitory neurons, parvalbumin-positive interneurons. Finally, we discuss genes known to be affected in different disorders and the effects that mutations in these genes have on the inhibitory system in cortex and hippocampus. We conclude that alterations to the inhibitory system are consistently identified in animal models of psychiatric disorders and, more specifically, that mutations affecting the function of parvalbumin-positive interneurons seem to play a central role in the symptoms observed in these disorders.

Keywords
psychiatric disorders, PV basket cells, PV interneurons, chandelier cells

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**Introduction**

Psychiatric disorders, including autism, schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD) and depression, affect millions of people and are a major socio-economic burden\(^1\). The identification of underlying genetic defects and risk factors is becoming increasingly efficient because of genome-wide interrogation methodologies, yet owing to the complex multifactorial origin of most cases, a conclusive molecular diagnosis is made for only a minority of patients. Therefore, the underlying causes for these conditions are poorly understood, and often treatment is still based on symptomology\(^1\). In 2003, Rubenstein and Merzenich proposed autism spectrum disorders (ASDs) to be caused by an increase in the ratio between excitation and inhibition, called the E/I balance\(^2\). Since then, this hypothesis has been substantiated by a vast number of studies and also has been implicated in other psychiatric disorders such as schizophrenia\(^3\), consistent with their partially overlapping phenotypes\(^4\). Recently, the focus has shifted to changes to the inhibitory side of the E/I balance\(^5,6\), in particular to one class of inhibitory neurons, parvalbumin (PV)-positive interneurons\(^7\). In this review, we focus on the role of the inhibitory system in psychiatric disorders and explore the changes to the inhibitory systems in different disorders. We then discuss the role and function of PV interneurons and highlight the changes to this specific class of interneurons in the various psychiatric disorders.

**Evidence for inhibitory dysfunction in psychiatric disorders**

Since Rubenstein and Merzenich postulated their hypothesis of a reduced E/I balance in ASDs, there has been an increasing amount of evidence for disrupted inhibitory control in psychiatric disorders. This evidence comes from post-mortem studies and studies of patient phenotypes.

Firstly, post-mortem studies on patient brains have revealed consistent changes to the inhibitory system in various disorders. Studies of autistic brains revealed reduced expression of the gamma-aminobutyric acid (GABA) synthesizing enzymes GAD65 and GAD67, as well as various GABA receptor subunits, in parietal cortex and cerebellum\(^8,9\). In schizophrenia, reductions of interneuron markers have been found in the prefrontal cortex\(^10,11\), in particular to one class of inhibitory neurons, parvalbumin (PV)-positive interneurons\(^12\). In this review, we focus on the role of the inhibitory system in psychiatric disorders and explore the changes to the inhibitory systems in different disorders. We then discuss the role and function of PV interneurons and highlight the changes to this specific class of interneurons in the various psychiatric disorders.

**The central role of parvalbumin-positive interneurons in E/I balance**

Cortical and hippocampal synaptic inhibition is mediated by inhibitory interneurons, most of which use GABA as their neurotransmitter. While interneurons make up around 20% of the total neuronal population, they are highly diverse\(^13\). For example, children with autism show a reduced gamma frequency modulation to a visual task\(^14\), whereas in ADHD, increased power and synchrony were observed\(^15\). Together, post-mortem and patient studies point to an important role for altered inhibitory function in various psychiatric disorders and indicate a vital role for inhibition in the maintenance of the E/I balance in the healthy brain.

**Another recurrent phenotypic change is the altered power of gamma oscillations, as measured with electroencephalography or magnetoencephalography in humans, indicating changes in neuronal synchrony\(^13\). Gamma oscillations are important for integration of information in neuronal circuits and have been linked to various functions, including attention\(^16\) and memory\(^17\). It was shown that PV-positive interneurons\(^18\), specifically PV-positive basket cells (see below), play an important role in these oscillations\(^19,20,21\).

Though studied mainly in schizophrenia, changes in gamma oscillations have been observed in other psychiatric disorders, including autism, ADHD and bipolar disorder\(^22,23\). For example, children with autism show a reduced gamma frequency modulation to a visual task\(^24\), whereas in ADHD, increased power and synchrony were observed\(^25,26\). Together, post-mortem and patient studies point to an important role for altered inhibitory function in various psychiatric disorders and indicate a vital role for inhibition in the maintenance of the E/I balance in the healthy brain.

The prevalence of epilepsy can be as high as 80% in Rett syndrome\(^27\), a monogenic form of autism caused by mutation in the MeCP2 gene\(^28\). It is currently unclear whether schizophrenia is a risk factor for epilepsy. A limited number of studies have been dedicated to this question, and contradicting results have been reported\(^29,30\). However, patients with epilepsy show an increased risk of schizophrenia or schizophrenia-like psychosis\(^31\). Likewise, patients with epilepsy show an increased risk for ADHD\(^32,33\).

Cortical interneurons can be segregated in three non-overlapping groups by means of specific markers: PV, somatostatin (SOM) and the serotonin receptor 3a (5HT3aR), accounting for 40%, 30% and 30% of the total interneuron population, respectively\(^34\). 5HT3aR-positive cells mainly originate from the caudal ganglionic eminence and are further divided as vasoactive intestinal peptide (VIP)-positive and VIP-negative interneurons\(^35\). VIP-positive interneurons mainly inhibit other interneurons and play an important role in disinhibition of the local circuit\(^36\), where they receive excitatory input from other cortical areas\(^37,38\). VIP cells mainly inhibit SOM
cells but also target PV interneurons and are involved in the regulation of the behavioural state of the network. Recent studies have suggested a direct inhibition by VIP interneurons of pyramidal cells in cortex. Despite the prominent, mainly disinhibitory, function of VIP cells in the network, only a limited number of studies have implicated VIP cells to be involved in psychiatric disorders.

SOM interneurons are a diverse class of interneurons originating from the medial ganglionic eminence (MGE). These interneurons target non-SOM interneurons as well as the dendritic domain of pyramidal neurons, including dendritic spines. SOM interneurons regulate the integration of local excitatory input and have been shown to regulate synaptic plasticity via the control of dendritic calcium spikes in pyramidal neurons, affecting learning tasks. Increasing evidence implicates SOM interneurons in psychiatric disorders. Disinhibition of SOM interneurons leads to an antidepressive–like phenotype in mice, and reduced levels of SOM in cerebral spinal fluid have been linked to major depression and mood disorders. In addition, a recent article shows a role for SOM interneurons in gamma oscillations in the visual cortex, hinting towards a possible role for SOM interneurons in the changes in gamma oscillations observed in psychiatric disorders.

PV interneurons are MGE-derived and are electrophysiologically identified by their fast-spiking phenotype. Although PV interneurons make up only a small part of the entire neuronal population, these interneurons are strongly implicated in psychiatric disorders and have been shown to play an important role in the regulations of the E/I balance. PV interneurons are involved in gamma oscillations (see above), and various mutations in disease-linked genes affect PV interneuron function (discussed below) (Table 1). Different subtypes of PV interneurons are distinguished: basket cells, chandelier cells, bistratified cells, and, in hippocampus, oriens-alveus-lacunosum-moleculare cells. The perisomatic location of these axon terminals allows PV basket cells to have a strong control over the excitability of pyramidal neurons. Among other cortical inputs, PV basket cells receive the same excitatory input as their pyramidal cell targets, wiring the basket cell into a feed-forward circuit: excitatory input will excite both the PV basket cell and the pyramidal neuron, followed by the PV basket cell inhibiting the pyramidal neuron. The delay between the excitatory and inhibitory input onto the pyramidal cell creates a coincidence detection window, in which excitatory input can summate to elicit an action potential in the pyramidal cell. If inhibitory input arrives at the pyramidal cell before an action potential is evoked, the somatic targeted GABA action will prevent action potential initiation. So PV basket cells allow action potential initiation in pyramidal neurons only if the excitatory information is time-locked and of sufficient strength.

In order to mediate fast inhibition, PV basket cells are optimized for fast signalling. Action potentials are initiated at the AIS and propagate at high velocities through the axon, which is enriched for the fast sodium channel. Synaptically, calcium inflow is mediated by fast P/Q-type calcium channels, which are located directly adjacent to the release site. The post-synaptic site, on the pyramidal neuron, contains the fast GABAAα1 receptor subunit. These fast properties ensure an optimal speed of PV basket cell signalling and tightly regulate coincidence detection windows of pyramidal neurons.

**Chandelier cells**

Chandelier cells, or axo-axonic cells, are a group of interneurons that target the AIS of pyramidal neurons. These cells form vertically oriented clusters of axon terminals, called cartridges, giving them a chandelier-like appearance. A single pyramidal cell receives contacts from multiple chandelier cells, forming an average of 3 to 5 boutons each depending on the brain region and age. The synapses are enriched for the GABA transporter 1 (GAT1) and pre-synaptically express the high-affinity GABA transporter subunit and pre-synaptically express the high-affinity GABA transporter subunit, suggesting a role in preventing excessive excitatory activity in the network for these interneurons.

Since their discovery, there has been a debate about the actions of chandelier cells (reviewed by Wang and colleagues). Some studies using brain slice recordings showed a depolarizing action and even excitatory action for these interneurons, whereas others report an inhibitory action. However, chandelier cell membrane potential fluctuations resembling in vivo patterns appear strongly inhibitory, and recordings in vivo also suggest an inhibitory role for these interneurons.

Whereas patient studies of schizophrenia patients consistently identify both a reduction in the number or length of chandelier cell cartridges as well as the misregulation of proteins associated with chandelier cell synapses, mouse research on this interneuron class is hampered by the absence of a strategy to specifically target these interneurons. As a result, a limited number of studies focus on chandelier cells but instead report on PV interneurons in general, or PV basket cells, which provide a more accessible target of study because of their relative abundance (Figure 1). Nonetheless, chandelier cells are considered to play an important role in psychiatric disorders, and the development of strategies to specifically target this interneuron subtype would be an important step towards understanding the role of these interneurons.

Targeting the perisomatic region (basket cells) or AIS (chandelier cells) gives these interneurons strong control over pyramidal cell excitability, and regulation of the synaptic strength of these interneurons is important for normal function of the network.
| Aspect | Gene | Syndrome/Disorder | Model | Investigated region | Phenotype | Reference |
|--------|------|------------------|-------|---------------------|-----------|-----------|
| Input  | Erbb4| SZ               | PV interneuron KO | Hippocampus | Reduced excitatory input to PV basket cells and chandelier cells | 120       |
|        | Nrg1 | SZ               | NRG1 treatment of dissociated cortical cultures | Cortical (cultures) | Increased excitatory synapse number onto interneurons | 121       |
|        | Fmr1 | Fragile X syndrome; ASD | Fmr1 KO mouse | Cortex | Reduced local excitatory input onto FS interneurons | 122       |
|        | DISC1| SZ, ASD, depressive disorder, BD | PV-specific shRNA KD in vivo | Cortex | Increased excitatory input onto PV interneurons | 123       |
|        | Nlgn3| ASD              | PV interneuron KO | Hippocampus | Decreased NMDAR responses, increased glutamate release onto PV interneurons | 124       |
|        | MeCP2| Rett syndrome; ASD | PV interneuron KO | Cortex | Reduced local excitatory input onto PV interneurons | 125       |
| Intrinsic | MeCP2| Rett syndrome; ASD | PV interneuron KO | Cortex | Increased intrinsic excitability of PV interneurons | 125       |
|        | Dysbindin | SZ | Dysbindin KO mouse | Cortex | Reduced excitability of FS interneurons | 126       |
|        | Scn1a| Dravet syndrome; ASD | Scn1a KO mouse | Hippocampus | Impaired action potential kinetics in interneurons | 127       |
|        | Shank3| ASD, SZ | Shank3-B KO mouse | Cortex, Striatum | Reduced activity of PV interneurons | 22        |
| Output | Erbb4| SZ               | PV interneuron KO | Hippocampus | Reduced cartridges from chandelier cells onto pyramidal neurons | 120       |
|        | Nrg1 | SZ               | Overexpression in pyramidal neurons | Cortex | Increased basket cell and chandelier cell boutons onto pyramidal neurons | 128       |
|        | Tsc1 | Tuberous sclerosis; ASD | Sparse Tsc1 deletion in CA1 pyramidal neurons | Hippocampus | Reduced inhibitory synaptic strength onto pyramidal neurons | 129       |
|        | Ube3a| Angelman syndrome; ASD | Maternal loss of Ube3a mouse | Cortex | Reduced inhibitory drive from FS and non-FS interneurons onto pyramidal neurons | 130       |
|        | Shank3| ASD, SZ | Shank3-exon9 KO mice | Cortex | Reduced inhibitory input onto pyramidal neurons | 131       |
|        |       |                 | Shank3-exon9 KO mice | Hippocampus | Increased inhibitory input onto pyramidal neurons | 131       |
|        | Git1 | ADHD             | Git1 KO mouse | Hippocampus | Reduced inhibitory inputs onto pyramidal neurons | 132       |
|        | Cdh13| ADHD             | Cdh13 KO mouse | Hippocampus | Increased number of inhibitory synapses onto pyramidal neurons | 133       |
|        | Nlgn2| ASD              | Nlgn2 KO mouse | Cortex | Reduced inhibitory drive onto pyramidal neurons from FS interneurons | 134       |
|        | Nlgn3| ASD              | Nlgn3 R451C mouse | Hippocampus | Reduced inhibitory drive from PV basket cells onto pyramidal neurons | 136       |
|        | Cntnap2| ASD | shRNA KD in dissociated cortical cultures | Cortical (cultures) | Reduced inhibitory drive onto pyramidal neurons | 137       |

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; FS, fast-spiking; KD, knockdown; KO, knockout; PV, parvalbumin-positive; shRNA, short hairpin RNA; SZ, schizophrenia.
example, Xue and colleagues have shown that pyramidal neurons receive an amount of synaptic inhibition that is proportional to the amount of synaptic excitation they receive, maintaining the E/I balance on the pyramidal cell. Manipulation of pyramidal cell activity leads to a compensatory change in inhibitory drive onto these cells, specifically from PV interneurons. In addition, PV interneuron activity is reduced during learning and increased during fear conditioning, and an experimental increase of PV interneuron activity leads to impaired learning. Apart from synaptic connections, basket cells and chandelier cells connect via electrical connections, called gap junctions. This electrical coupling synchronizes the interneurons, which in turn allows them to synchronize the network (for example, in gamma oscillations).

Together, these studies indicate that control of the E/I balance by PV interneurons is important for normal network function and that PV interneuron-mediated inhibition can be regulated upon alterations in the network state. Changes in PV interneuron-mediated inhibition would shift the E/I balance and lead to a disruption in network function. Indeed, various parameters affecting inhibitory function of PV cells are consistently found to be altered in psychiatric disorders. In the next section, we focus on studies on animal models of these conditions and discuss how different changes affecting PV cell activity lead to a shift of the E/I balance (Table 1).

**Altered PV interneuron activity is caused by changes to different subcellular aspects**

Alterations to the inhibitory drive, affecting the E/I balance, can arise in different ways. Reduced excitatory input onto interneurons, reduced intrinsic excitability of interneurons, and a reduction in inhibitory synapse number or strength onto pyramidal cells all result in a shift of the E/I balance towards excitation. Indeed, patient and animal studies of psychiatric disorders consistently report changes affecting inhibitory function. A complicating factor in the interpretation of these results comes from the dynamic ability of neuronal networks to adapt to changes, known as homeostatic plasticity. Homeostatic plasticity is the ability of neurons to maintain their levels of excitability within a narrow range and is a constantly active feedback process. For example, classic experiments have shown that blocking of action potentials leads to a strengthening of excitatory and a weakening of inhibitory synapses. Apart from their synaptic input, neurons can regulate their intrinsic excitability, which is observed both in excitatory and inhibitory neurons in culture and in vivo. This means that genetic mutations affecting a specific neuronal property in a specific cell type can trigger homeostatic processes affecting other properties or cell types. In this way, mutations affecting both inhibitory or excitatory cells could ultimately affect inhibitory function. It is therefore difficult to distinguish the direct effect of a gene related to a psychiatric disorder from the network adaptation it causes.

Nonetheless, changes to the function of PV interneurons, either direct or indirect, are consistently observed in psychiatric disorders affecting input, output and intrinsic properties, which all lead to an altered inhibitory action of these cells onto their targets (Figure 1).

**Changes to the input onto PV interneurons**

Excitatory inputs onto neurons drive their excitability. Depending on the brain region, PV interneurons receive various types of
excitatory input\textsuperscript{45}, and the amount of excitatory inputs onto PV interneurons is dynamically regulated by behaviour\textsuperscript{45}. Changes in the amount of excitation onto PV interneurons, altering their activity, have been reported in mouse models of various psychiatric disorders.

The tyrosine kinase receptor ErbB4 has been identified as a risk gene for schizophrenia in genome-wide association studies (GWAS)\textsuperscript{140,150}. In the adult mouse, expression of ErbB4 is restricted to interneurons\textsuperscript{128,151} and localizes to both the axon terminals\textsuperscript{128,152} and post-synaptic densities\textsuperscript{128,151}. Selective removal of ErbB4 from PV interneurons causes a reduction in excitatory synapses formed onto both PV basket cells and chandelier cells as well as a reduced number of PV synapses formed on pyramidal neurons\textsuperscript{20,121}. This reduced input and output connectivity of PV interneurons is indicative of a reduced inhibitory drive onto pyramidal neurons. As a result of this reduced inhibition of the pyramidal neurons, these neurons become more active, as was seen from the increased frequency of excitatory inputs to both pyramidal neurons and PV interneurons\textsuperscript{20}. Consequently, recording of the local field potential in vivo revealed a hyperactive network and increased gamma oscillations\textsuperscript{120}. Single-nucleotide polymorphisms in neuregulin 1 (NRG1), a ligand of ErbB4, have been implicated in schizophrenia\textsuperscript{51} and bipolar disorder\textsuperscript{52,153}. Treatment of neuronal cultures with NRG1, activating ErbB4, leads to an increase in excitatory synapses formed onto interneurons\textsuperscript{31}. Together, these data show that ErbB4 signalling plays an important role in the regulation of excitatory synapse number onto PV interneurons and that disruption of this system leads to a shift of the E/I balance towards excitation\textsuperscript{20}.

Also, studies on animal models of ASD have reported postsynaptic changes on PV interneurons. Fragile X syndrome is caused by reduced or absent levels of the RNA-binding protein FMRP, leading to intellectual disability and, in about half of the affected males, ASD\textsuperscript{154,155}. While changes to long-term depression on excitatory inputs have been reported\textsuperscript{154,155}, changes to the intrinsic properties of PV interneurons have consistently been identified\textsuperscript{150,160}. Fmr1 knockout (KO) mice show a reduced expression of GABAA receptor subunits\textsuperscript{161} as well as a reduction in the number of PV interneurons\textsuperscript{162}. In addition, these mice show a marked reduction in local, but not thalamic, excitatory input onto fast-spiking interneurons in layer 4 of the somatosensory cortex, while both the connectivity of fast-spiking interneurons onto pyramidal neurons and excitatory inputs onto pyramidal neurons were unaltered\textsuperscript{122}. Consistently, the resulting reduced inhibitory drive from fast-spiking interneurons was accompanied by reduced synchrony of gamma oscillations\textsuperscript{122}. These changes point towards an altered E/I balance towards excitation in fragile X syndrome\textsuperscript{162}.

Mutations in another gene linked to autism, the transcriptional modulator methyl-CpG-binding protein 2 (MECP2), the causative gene for Rett syndrome\textsuperscript{17}, show a similar phenotype. Selective removal of MeCP2 from PV cells leads to a specific reduction of local excitatory input, but not thalamocortical input, onto these cells in layer 4 of the visual cortex at postnatal day (P) 30\textsuperscript{125}. In addition, experimentally evoked PV interneuron input onto pyramidal cells was unaltered\textsuperscript{125}. Calcium imaging revealed that these synaptic changes lead to a reduced visually evoked, but not spontaneous, activity of PV interneurons\textsuperscript{125}. Paired recordings at P15 revealed an increased inhibition from PV interneurons through an earlier maturation in MeCP2 KO mice\textsuperscript{166}, and this earlier maturation might influence network development through interference with the normal critical period\textsuperscript{164,165}, leading to the changes observed at later ages. This notion is consistent with the recent idea that developmental changes might play an important role in the development of psychiatric symptoms later in life\textsuperscript{166}. The exact contribution of PV interneurons to the phenotypes observed in Rett syndrome is still unclear. While a general interneuron removal of MeCP2 does recapitulate most Rett syndrome phenotypes\textsuperscript{167}, studies removing MeCP2 specifically from PV interneurons have been able to replicate only some of these phenotypes\textsuperscript{168} or none at all\textsuperscript{125}. Of note, selective removal of MeCP2 from SOM interneurons also recapitulates part of the Rett syndrome phenotypes\textsuperscript{166}, and selective removal of MeCP2 from either PV interneurons or SOM interneurons has been reported to cause circuit-wide deficits in information processing\textsuperscript{166}. From these studies, a picture is emerging in which excitatory inputs onto PV interneurons are found to be altered in different psychiatric disorders, leading to a reduced activity of these neurons and thereby tilting the E/I balance towards excitation.

### Changes to the intrinsic properties of PV interneurons

The intrinsic properties of neurons are important in translating input into output. Altering these properties allows the neurons to regulate their excitability\textsuperscript{170,171}, through which they play an important role in the maintenance of the E/I balance\textsuperscript{45}. Whereas some of these changes might be causative to psychiatric disorders, others are believed to be compensatory. For example, selective deletion of MeCP2 from PV interneurons leads to an increased membrane potential, as well as a hyperpolarized action potential threshold in these cells at P30\textsuperscript{125}, but only a slight hyperpolarization of the membrane potential at P15\textsuperscript{164}. These changes increase the cell’s excitability and are most likely compensatory for the reduced excitatory synaptic input described above\textsuperscript{125} but could still act towards deficits in information processing observed in these animals\textsuperscript{166}.

Family-based association data have identified dysbindin (DTNBP1) as a susceptibility gene for schizophrenia\textsuperscript{172}, whose dominant circuit impact is impaired inhibition\textsuperscript{173}. Dysbindin KO mice show a reduced number of PV interneurons in hippocampal CA1\textsuperscript{173,174}, and transcriptome changes of various proteins involved in the regulation of intrinsic properties\textsuperscript{175}. Recordings from PV interneurons in dysbindin KO mice show a reduction in action potential frequency resulting in a reduced inhibitory drive\textsuperscript{176}. Interestingly, dopamine D2-receptor expression is increased in these mice, and application of the D2-receptor antagonist quinpirole increases PV interneuron action potential frequency more in dysbindin KO mice than in wild-type mice, suggesting that the changes in action potential frequency are compensatory\textsuperscript{126}.

Intrinsic changes can also be the primary cause of psychiatric disorders. Single-gene mutations in SCN1A, encoding the sodium channel Na\textsubscript{v}1.1\textalpha subunit, give rise to Dravet syndrome, a rare genetic epileptic encephalopathy. Patients with Dravet syndrome suffer from epilepsy and have an increased risk for autism\textsuperscript{175,176}.
Na\(_{\text{v}1.1}\) is enriched in the AIS of inhibitory neurons\(^{177}\), primarily of PV interneurons\(^{2}\), where axon potentials are initiated\(^{175}\). Interneurons from Scn1a heterozygous and KO mice show reduced firing frequencies to current injections as well as a reduced action potential amplitude and an increased action potential width, indicating a reduced inhibitory control over downstream targets\(^{197}\). Removal of Scn1a specifically from forebrain interneurons\(^{29}\) or PV interneurons specifically\(^{80}\) recapitulates phenotypes found in patients. In addition, increasing GABA signalling by application of the positive allosteric GABA\(_{A}\) receptor modulator clonazepam was sufficient to rescue the abnormal social behaviour in Scn1a\(^{-/-}\) mice\(^{80}\). These data show that loss of SCN1A primarily affects interneurons and that the consequently reduced inhibitory drive plays an important role in Dravet syndrome.

Recently, a new hypothesis has been proposed in the field of schizophrenia, focussing on the myelination of PV interneurons as a point of pathological convergence\(^{182}\). As discussed above, PV cells play a central role in schizophrenia. Myelination abnormalities, including white matter abnormalities\(^{183}\), reduced numbers of oligodendrocytes\(^{84}\) and post-mortem gene expression analysis\(^{185}\), have been identified in schizophrenia. Myelination of PV interneurons has been observed in rats\(^{186}\), mice\(^{187}\) and post-mortem in humans\(^{188}\). Myelination is important for fast action potential propagation\(^{198}\) and deficits in the myelination of PV interneurons are proposed to disrupt inhibitory network function\(^{82}\). However, this appealing hypothesis remains to be experimentally tested.

**Changes to synapses formed by PV interneurons**

Changes to PV synapses are abundantly studied and identified in various conditions. Post-mortem studies of schizophrenia patients consistently identify changes to the cartridges formed by chandelier cells, showing a decrease in pre-synaptic GAT1 expression\(^{116,117}\) and an increase in the expression of post-synaptic GABA\(_{A}\) receptor\(^{118}\). These changes would lead to an increased inhibitory drive from chandelier cells and are believed to be compensatory for a reduced activity of these cells, as indicated by reduced levels of GAD67 in PV cells\(^{199}\). In addition, a recent study shows a reduction in the density of a specific type a carbidopa-positive carbidopa, in schizophrenia\(^{184}\).

Besides changes in the input to PV interneurons, mutations in ErbB4 also lead to a reduction in synapses formed by PV interneurons on pyramidal neurons, specifically from chandelier cells\(^{30,32}\). In addition, overexpression of Nrg1, the ligand for ErbB4, in pyramidal neurons increases bouton density on both the AIS and the soma of pyramidal neurons. The increase in bouton density on the AIS originates from chandelier cells since only these cells target the AIS. The origin of the increase in perisomatic bouton density is not clear since a recent report has shown that synapses formed by cholecystokinin (CCK) basket cells require ErbB4 function to form perisomatic synapses\(^{191}\). Future research should unveil whether the increase in perisomatic boutons density arises from PV or CCK basket cells.

Tuberous sclerosis is a disorder whose symptoms include epilepsy and autism\(^{92}\). Loss-of-function mutations in the mammalian target of rapamycin (mTOR)-negative regulators TSC1 or TSC2 underlie this condition\(^{93}\). Slice recordings from TSC1 KO neurons revealed a reduced inhibitory drive onto CA1 pyramidal neurons, while excitatory input was unaltered\(^{198}\). TSC1 KO neurons were created by sparsely targeting neurons in a conditional TSC1 KO mouse with a pre-expressing adeno-associated virus\(^{197}\). The finding that sparse KO of TSC1 leads to a similar phenotype as in neurons from full KO animals indicates that these results are cell-autonomous rather than compensatory\(^{115}\).

Angelman syndrome, caused by loss-of-function mutations or deletion of E3 ubiquitin ligase UBE3A\(^{199}\), is characterized by epilepsy and autism\(^{155,196}\). Mouse models for Angelman syndrome recapitulate human phenotypes\(^{197}\) and initially were found to show a reduced excitatory drive onto pyramidal neurons\(^{198}\). However, inhibitory input was also found to be decreased, caused by defects in synaptic vesicle cycling\(^ {199}\). It was hypothesized that the reduced inhibition could outweigh the reduced excitation, leading to the epilepsy and autism phenotypes observed\(^ {190,199}\). Consistent with this idea, a recent study using in vivo whole cell recordings shows that pyramidal neurons in Ube3a KO mice display decreased orientation selectivity\(^ {200}\), indicative of reduced inhibition\(^ {201,202}\). However, these mice also show increased excitability of pyramidal neurons, which is non-cell-autonomous, suggesting that pyramidal neurons homeostatically increase their excitability because of a relative decrease of excitation\(^ {200}\). While it is unclear whether reduced inhibition or reduced excitation has a stronger impact on pyramidal neurons in Angelman syndrome, the change in their relative contribution, resulting in an altered E/I balance, seems to play a pivotal role in this condition.

Single SHANK3 mutations, at the level of point mutations or microdeletions, have been identified in patients with ASD\(^ {201}\). In the human genome, there are three SHANK genes (SHANK1-3), which all code for scaffold proteins located at the postsynaptic density of excitatory synapses, of which SHANK3 is best studied\(^ {203-206}\). Because of this localisation, most studies have focussed on excitatory synapses, where Shank3-deficient mice show reduced cortico-striatal connectivity\(^ {207}\), impaired long-term potentiation\(^ {208}\) and reduced GluA1 expression\(^ {209}\). Recent studies, however, indicate that the inhibitory system is also affected. Shank3 mutant mice lacking exon 9 show reduced inhibitory input onto layer 2/3 pyramidal neurons but an increase of these events in CA1 pyramidal neurons\(^ {192}\). In addition, PV levels are reduced in Shank1 KO and Shank3b KO mice, indicating reduced activity\(^ {202}\).

Presynaptic neurexins and their postsynaptic partners neuroligins are a large class of cell-adhesion molecules that have been shown to play important roles in synaptic specificity\(^ {210}\). Overexpression or knockdown of neuroligins leads to an increase or decrease in synapse number, respectively\(^ {211}\). Neuroligins are expressed at specific synapses: neuroligin 1 (NLGN1) is mainly expressed at excitatory synapses\(^ {12}\). NLGN2 is expressed at inhibitory synapses\(^ {13}\). NLGN3 is expressed at both inhibitory and excitatory synapses\(^ {214}\) and NLGN4 is expressed at glycinergic synapses\(^ {215}\). Mutations and deletions affecting human NLGN3, including a gain-of-function mutation, and NLGN4 de novo mutations have been found in Swedish families and have been associated with autism\(^ {116}\). Nlg3 deletion in mice leads to increased inhibitory transmission onto pyramidal neurons\(^ {37}\), specifically from CCK-positive interneurons because of an increased tonic endocannabinoid
signalling, whereas PV interneuron connectivity is unaffected\textsuperscript{136}. A recent study, however, has shown that conditional deletion of \textit{Ngn3} from PV interneurons alters AMPA/NMDA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/N-methyl-d-aspartate) ratio of excitatory input onto these cells and causes reduced gamma oscillations\textsuperscript{124}. In addition to the loss of \textit{NLGN3}, a gain-of-function amino acid substitution (R451C) in \textit{NLGN3} is associated with autism\textsuperscript{106}. Mice carrying this mutation show a strong reduction in inhibitory drive from PV interneurons while increasing the inhibitory drive from CCK cells\textsuperscript{119}.

\textit{Nlgn4} KO mice show a reduced number of perisomatic inhibitory synapses in hippocampus and a concomitant reduction in inhibitory input\textsuperscript{218}. In addition, a reduced power of evoked gamma oscillations in acute slices was observed\textsuperscript{218}. Different mutations in \textit{NLGN2} have been linked to autism\textsuperscript{219} and schizophrenia\textsuperscript{220}. Deletion of \textit{Nlgn2} has been shown to specifically reduce the amount of perisomatic synapses on pyramidal neurons in hippocampus\textsuperscript{135} and reduce inhibitory transmission from PV interneurons but not SOM interneurons\textsuperscript{134}.

Neurexins are less well studied in the context of psychiatric disorders. There are three neurexin genes, each coding for an \textalpha- and \textbeta-neurexin. Mutations in neurexin (Nrxn1) have been associated with autism\textsuperscript{137} and schizophrenia\textsuperscript{220}. Nrxn1 KO mice do not show changes in inhibitory drive but do show a reduced excitatory drive onto CA1 pyramidal neurons\textsuperscript{224}. However, mice carrying mutations in Nrxn1 beta show a reduced frequency of both inhibitory and excitatory input onto cortical pyramidal neurons\textsuperscript{225} suggestive of a reduced number of synaptic contacts. These studies show that neuroligin and neurexin mutations that are linked to autism affect the inhibitory system, including perisomatic-targeting interneurons.

In addition to changes in the number and strength of inhibitory synapses, changes are found in the modulation of inhibitory synaptic transmission. Metabotropic GABA\textsubscript{A} receptors, GABA\textsubscript{A} receptors, are expressed both pre- and postsynaptically in GABAergic synapses\textsuperscript{244}. Postsynaptic GABA\textsubscript{A} receptors activate potassium channels that hyperpolarize the postsynaptic cell\textsuperscript{231}. Presynaptic GABA\textsubscript{A} receptors, in addition, can reduce calcium influx and reduce neurotransmitter release\textsuperscript{236,237}. A reduction of GABA\textsubscript{A} subunit expression has been observed in post-mortem studies of patients with schizophrenia\textsuperscript{238,239}, patients with bipolar disorder\textsuperscript{240} and patients with major depression\textsuperscript{241} as well as animal models for schizophrenia\textsuperscript{242–244}. However, more research is required to identify the exact role for GABA\textsubscript{A} receptors in psychiatric disorders.

In summary, changes to the inhibitory drive of PV interneurons can be caused by changes affecting the input, output or intrinsic properties of PV interneurons, and animal models of various psychiatric disorders all show alterations to one or more of these aspects, tilting the E/I balance.

**Conclusions**

Psychiatric disorders are a diverse group of disorders, but changes to the inhibitory system seem to be a point of convergence. Impairment of normal inhibitory function can arise from input to, output from, or intrinsic properties of inhibitory neurons. Altered inhibitory activity or drive leads to changes in signal processing, which in turn is believed to underlie the phenotypic changes observed in the various psychiatric disorders. PV-positive interneurons play a pivotal role in these conditions, possibly through their strong inhibitory effect on pyramidal cell activity due to the axonal or perisomatic targeting of their axons in combination with the nature of their functions in the network.

Changes to either excitation or inhibition will change the ratio between these two types of input, leading to a change in the E/I balance. The examples described above indicate that various psychiatric disorders occur following changes to the input, output or intrinsic properties of specific interneurons, PV interneurons, leading to an altered activity of these neurons. It seems from the studies discussed that specific changes in the E/I balance lead to a disruption of specific function(s) in the network that affect signal processing in a specific way to result in a specific psychiatric phenotype. This might explain why different disorders present different phenotypes, in both patients and animal studies. For example, changes in chandelier cell cartridges seem to be more prominent in schizophrenia. However, other factors are likely to contribute to the development of a specific disorder. Apart from the affected PV cell type, the direction of the altered activity (increased/decreased E/I balance) might be an important factor. Another interesting aspect might be the changes in interneuron-interneuron connectivity, which could lead to altered signal integration and network activity. Some genes have been associated with multiple psychiatric disorders, indicating that a mutation does not in all cases lead to a specific condition. Individual difference in compensatory plasticity could subtly affect network development, steering the developing network towards a specific disorder. It should be noted that while homeostatic changes might compensate a specific alteration, this compensation might disrupt other pathways.

Studies of ADHD rodent models have mainly focussed on the dopamine system and excitatory synapses\textsuperscript{258}. However, recent studies identify changes to inhibitory connectivity. \textg protein-coupled receptor kinase interacting protein 1 (Giti) has been identified by a GWAS as a risk gene for ADHD\textsuperscript{235}, but recent studies challenge this claim\textsuperscript{227,228}. \textit{Git1} KO mice show ADHDLike phenotypes, including hyperactivity\textsuperscript{222}. While excitatory input to CA1 pyramidal neurons remains unaltered, the frequency of inhibitory inputs is reduced, suggesting a reduction of inhibitory synaptic contacts\textsuperscript{135}, consistent with previous studies showing a role for \textit{Git1} in inhibitory synapses\textsuperscript{229}. In addition, PV expression was reduced while other interneuron markers remained unaltered\textsuperscript{132}.

Another ADHD-linked gene identified by GWASs, cadherin 13 (\textit{CdH13})\textsuperscript{230–233}, is exclusively expressed in inhibitory neurons\textsuperscript{135}. \textit{CdH13} KO mice show an increase in inhibitory synaptic contacts onto CA1 pyramidal neurons, while excitatory inputs remained unaltered\textsuperscript{131}. This increase in inhibitory synaptic contacts could underlie the increase in gamma oscillations observed in ADHD patients discussed before\textsuperscript{245–247}. \textit{CdH13} KO mice show a reduced number of interneurons at embryonic day 18.5\textsuperscript{218} but not at P21\textsuperscript{135}. Experiments are needed to test whether the changes in interneuron number have a role in the aetiology of ADHD.
While the above-mentioned factors potentially all play a role in the development of specific psychiatric disorders, more research is needed to identify how specific alterations to PV interneurons affect network processing and behaviour.

The notion that psychiatric disorders are caused by changes to the inhibitory drive from PV interneurons means that a restoration of this drive could improve patient symptoms. An interesting possibility is the 'hijack' these pathways and manipulate the neuron’s activity in a way to compensate for the altered inhibitory drive. Homeostatic mechanisms function to keep neurons in an optimal state, but their capacity of counteracting the changes to the inhibitory system would be limited. Further research might thus further increase our understanding of both the diseased and the healthy brain and hopefully lead to treatment or alleviation of the symptoms for those suffering from these conditions.

Competing interests

The authors declare that they have no competing interests.

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References

1. Gore FM, Bloem PJ, Patton GC, et al.: Global burden of disease in young people aged 10–24 years: a systematic analysis. Lancet. 2011; 377(9783): 2093–102. PubMed Abstract | Publisher Full Text
2. Lee FS, Heimer H, Giedd JN, et al.: Mental health. Adolescent mental health—opportunity and obligation. Science. 2014; 346(6209): 547–9. PubMed Abstract | Publisher Full Text | Free Full Text
3. Elsabbagh M, Divan G, Koh YJ, et al.: Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012; 5(3): 160–79. PubMed Abstract | Publisher Full Text | Free Full Text
4. Remington G, Fournier G, Ferreira G, et al.: Perceptual and functional impairments in schizophrenia: an update. J Psychiatr Pract. 2016; 22(2): 133–50. PubMed Abstract | Publisher Full Text | Free Full Text
5. Doyle CA, McDougle CJ. Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. Dialogues Clin Neurosci. 2012; 14(3): 263–79. PubMed Abstract | Free Full Text
6. van Os J, Kapur S: Schizophrenia. Lancet. 2009; 374(9690): 635–45. PubMed Abstract | Publisher Full Text
7. Rubenstein JL, Merzenich MM: Model of autism: increased ratio of excitation/inhibition in key neural systems. Games Brain Behav. 2003; 2(5): 255–67. PubMed Abstract | Publisher Full Text | F1000 Recommendation
8. Gao R, Peretz P: Common mechanisms of excitation and inhibitory imbalance in schizophrenia and autistic spectrum disorders. Curr Mol Med. 2015; 15(2): 146–67. PubMed Abstract | Publisher Full Text | F1000 Recommendation
9. Canitano R, Pallagrosi M: Autism Spectrum Disorders and Schizophrenia Spectrum Disorders: Excitation/Inhibition Imbalance and Developmental Trajectories. Front Psychiatry. 2017; 8: 69. PubMed Abstract | Publisher Full Text | Free Full Text
10. Marin O: Interneuron dysfunction in psychiatric disorders. Nat Rev Neurosci. 2012; 13(2): 107–20. PubMed Abstract | Publisher Full Text | F1000 Recommendation
11. Lewis DA, Hashimoto T, Volk DW: Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005; 6(4): 312–24. PubMed Abstract | Publisher Full Text | F1000 Recommendation
12. Lewis DA, Curley AA, Glaser JR, et al.: Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 2012; 35(1): 57–67. PubMed Abstract | Publisher Full Text | F1000 Recommendation
13. Fatemi SH, Reutiman TJ, Folsom TD, et al.: GABA<sub>A</sub>-receptor downregulation in brains of subjects with autism. J Autism Dev Disord. 2009; 39(2): 223–30. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
14. Fatemi SH, Hall AR, Stary JM, et al.: Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. Biol Psychiatry. 2002; 52(8): 805–10. PubMed Abstract | Publisher Full Text
15. Beasley CL, Reynolds GP: Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. Schizophr Res. 1997; 24(3): 349–55. PubMed Abstract | Publisher Full Text
16. Beasley CL, Zhang ZJ, Patton L, et al.: Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. Biol Psychiatry. 2002; 52(7): 708–15. PubMed Abstract | Publisher Full Text
17. Sakai T, Oshima A, Nozaki Y, et al.: Changes in density of calcium-binding-protein-immunoreactive GABAergic neurons in prefrontal cortex in schizophrenia and bipolar disorder. Neuropathology. 2008; 28(2): 143–50. PubMed Abstract | Publisher Full Text
18. Selemion LD, Zecovic N: Schizophrenia: an insight from a tale of two critical periods for prefrontal cortical development. Transl Psychiatry. 2015; 5: e623. PubMed Abstract | Publisher Full Text | Free Full Text
19. Hashimoto T, Volk DW, Eggen SM, et al.: Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J Neurosci. 2003; 23(15): 6315–26. PubMed Abstract
20. Enwright JF, Sanapala S, Foglio A, et al.: Reduced Labeling of Parvalbumin Neurons and Perineuronal Nets in the Dorsolateral Prefrontal Cortex of Subjects with Schizophrenia. Neuropsychopharmacology. 2016; 41(9): 2206–14. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
21. Filice F, Vöröketl KL, Sungur AO, et al.: Reduction in parvalbumin expression in the temporal region of the brain in schizophrenia and Alzheimer disease. Neuropsychologia. 2016; 87: 132–40. PubMed Abstract | Publisher Full Text | Free Full Text
22. Donato F, Rompani SB, Caroni P: Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. Nature. 2013; 504(7479): 272–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation
23. Philpot BD, Lin JH, Brnjes PC: Activity-dependent regulation of calcium-binding proteins in the developing rat olfactory bulb. J Comp Neurol. 1997; 387(1): 12–26. PubMed Abstract | Publisher Full Text
25. Gonzalez-Burgos G, Lewis DA: Activity-Dependent Bidirectional Regulation of GAD Expression in a Homeostatic Fashion Is Mediated by BDNF-Dependent and Independent Pathways. PLoS One. 2015; 10(8): e0134296. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

26. Fung SJ, Fillman SG, Webster MJ, et al.: Schizophrenia and bipolar disorder show both common and distinct changes in cortical interneuron markers. Schizophr Res. 2014; 155(1–3): 26–30. Published Abstract | Publisher Full Text

27. Reppas TA, Seguela A, Canetti L, et al.: Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. Mol Psychiatry. 2009; 14(2): 175–89. Published Abstract | Publisher Full Text

28. Luscher B, Shen Q, Sahir N: The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry. 2011; 16(4): 383–406. Published Abstract | Publisher Full Text | Free Full Text

29. Guidotti A, Auta J, Davis JM, et al.: Decrease in relin and glutamic acid decarboxylase 67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Arch Gen Psychiatry. 2000; 57(11): 1061–9. Published Abstract | Publisher Full Text

30. Fukuta Y, Fukata M: Epilepsy and synaptic proteins. Curr Opin Neurobiol. 2017: 1–8. Published Abstract | Publisher Full Text

31. Treiman DM: GABAergic mechanisms in epilepsy. Epilepsia. 2001; 42(Suppl 3): 8–12. Published Abstract | Publisher Full Text

32. Symonds C: Excitation and inhibition in epilepsy. Proc R Soc Med. 1959; 52(6): 385–402. Published Abstract | Publisher Full Text | Free Full Text

33. Wong M: Too much inhibition leads to excitation in absence epilepsy. Epilepsia Curr. 2010; 10(3): 131–2. Published Abstract | Publisher Full Text | Free Full Text

34. Bolton PF, Carcarni-Rathlev I, Hutton J, et al.: Epilepsy in autism: features and correlates. Br J Psychiatry. 2011; 198(4): 289–94. Published Abstract | Publisher Full Text | Free Full Text

35. Tuchman R, Moshe SL, Rapin I: Convulsing toward the pathophysiology of autism. Brain Dev. 2009; 31(2): 95–103. Published Abstract | Publisher Full Text

36. Jan L, Nagarajan L, de Klerk N, et al.: Predictors of seizure onset in Rett syndrome. J Pediatr. 2006; 149(4): 542–7. Published Abstract | Publisher Full Text

37. Amir RE, Van den Veyver IB, Wan M, et al.: Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999; 23(2): 185–8. Published Abstract | Publisher Full Text

38. Gelisse P, Samiiyan JC, Genton P: Is schizophrenia a risk factor for epilepsy or acute symptomatic seizures? Epilepsia. 1998; 40(11): 1566–71. Published Abstract | Publisher Full Text

39. Mäkikyrö T, Karvonen JT, Hakko H, et al.: Autism spectrum disorders and the cerebral cortex. J Affect Disord. 2011; 133(3): 115–27. Published Abstract | Publisher Full Text

40. Cardin JA, Cardin M, Meletis K, et al.: Driven fast-spiking cells induces gamma rhythm and controls sensory responses. Nature. 2009; 459(7247): 663–7. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

41. Sohal VS, Zhang F, Yihar O, et al.: Parvalbuim neurons and gamma rhythms enhance cortical circuit performance. Nature. 2009; 459(7247): 698–702. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

42. Shin YW, O'Donnell BF, Youn S, et al.: Gamma oscillation in schizophrenia. Psychiatry Investig. 2011; 8(4): 288–96. Published Abstract | Publisher Full Text | Free Full Text

43. Chen CM, Stanford AD, Mao X, et al.: GABA level, gamma oscillation, and working memory performance in schizophrenia. Neuroimage Clin. 2014; 4: 531–9. Published Abstract | Publisher Full Text | Free Full Text

44. Farzan F, Barr MS, Levinson AJ, et al.: Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. Brain. 2010; 133(Pt 5): 1505–14. Published Abstract | Publisher Full Text | Free Full Text

45. Gordon E, Williams L, Haig AR, et al.: Symptom profile and “gamma” processing in schizophrenia. Cogn Neuropsychiatry. 2001; 6(1): 7–19. Published Full Text

46. Baldeweg T, Spence S, Hirsch SR, et al.: Gamma-band electroencephalographic oscillations in a patient with somatic hallucinations. Lancet. 1998; 352(9128): 620–1. Published Abstract | Publisher Full Text

47. Landau ID, Egger R, Dercksen VJ, et al.: The Impact of Structural Heterogeneity on Excitation-Inhibition Balance in Cortical Networks. Neuron. 2016; 92(5): 1106–21. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

48. Vierling-Claassen D, Siekmeyer P, Stufflebeam S, et al.: Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. J Neuropsychol. 2008; 9(2): 2656–71. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

49. Uhlhaas PJ, Singer W: Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci. 2010; 11(2): 100–13. Published Abstract | Publisher Full Text | Free Full Text

50. Rojas DC, Maharaj K, Teale P, et al.: Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. BMC Psychiatry. 2008; 8: 66. Published Abstract | Publisher Full Text | Free Full Text

51. Rojas DC, Wilson LB: γ-band abnormalities as markers of autism spectrum disorders. Biomark Med. 2014; 8(3): 353–68. Published Abstract | Publisher Full Text | Free Full Text

52. Lenz D, Krauel K, Schadow J, et al.: Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children. Brain Res. 2008; 1235: 117–32. Published Abstract | Publisher Full Text

53. Kamida A, Shimabashyki O, Oguri M, et al.: EEG Power Spectrum Analysis in Children with ADHD. Yonago Acta Med. 2016; 59(2): 169–73. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

54. Karch S, Segmüller F, Hantschl I, et al.: Increased γ oscillations during voluntary selection processes in adult patients with attention deficit/hyperactivity disorder. J Psychiatr Res. 2012; 46(11): 1515–23. Published Abstract | Publisher Full Text | Free Full Text

55. Yordanova J, Banaschewski T, Kivel V, et al.: Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder−evidence from event-related gamma oscillations. Clin Neurophysiol. 2001; 112(6): 1096–108. Published Abstract | Publisher Full Text

56. Özdemir A, Güntekin B, Atağın I, et al.: Reduced long distance gamma (28–48 Hz) coherence in euthymic patients with bipolar disorders. J Affect Disord. 2011; 132(3): 325–32. Published Abstract | Publisher Full Text | Free Full Text

57. Stroganova TA, Butorina AV, Sysnova OV, et al.: Altered modulation of gamma oscillation frequency by speed of visual motion in children with autism spectrum disorders. J Neurodev Disord. 2015; 7(1): 21. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

58. Pettit Interneuron Nomenclature Group, Ascoli GA, Alonso-Nanclares L, et al.: Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci. 2008; 9(7): 557–68. Published Abstract | Publisher Full Text | Free Full Text

59. DeFelipe J, López-Cruz PL, Benavides-Piccione R, et al.: New Insights into the classification and nomenclature of cortical GABAergic interneurons. Nat Rev Neurosci. 2013; 14(3): 202–16. Published Abstract | Publisher Full Text | Free Full Text

60. Kepecs A, Fishel G: Interneuron cell types are fit to function. Nature. 2014; 508(7483): 318–26. Published Abstract | Publisher Full Text | Free Full Text

61. Rudy B, Fishel G, Lee S, et al.: Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. Dev Neurosci. 2011; 33(1): 45–61. Published Abstract | Publisher Full Text | Free Full Text

62. Pi H, Hangya B, Kvetnisa D, et al.: Cortical interneurons that specialize in...
...control. Nature. 2013; 603(7477): 521–4.

70. Lee S, Kruglikov I, Huang ZJ, et al.: A disinhibitory circuit mediates motor integration in the somatosensory cortex. Nat Neurosci. 2013; 16(11): 1662–70.

71. Fu V, Tucciaroni JM, Espinosa JS, et al.: A cortical circuit for gain control by behavioral state. Cell. 2014; 156(6): 1139–52.

72. Pfelffer DK, Xue M, He M, et al.: Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. Nat Neurosci. 2013; 16(8): 1068–76.

73. Jackson J, Ayzenshtat I, Karnani MM, et al.: VIP+ interneurons control neocortical activity across brain states. J Neurophysiol. 2016; 115(6): 3008–17.

74. Balesta-Brito R, Vinck M, Ferguson KA, et al.: Developmental Dysfunction of VIP Interneurons Impairs Cortical Circuits. Neuron. 2017; 95(4): 884–896.e9.

75. Garcia-Junco-Clemente P, Isrra T, Tring E, et al.: An inhibitory pull-push circuit in frontal cortex. Nat Neurosci. 2017; 20(3): 389–92.

76. Vacic V, McCarthy S, Mahotra D, et al.: Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. Nature. 2011; 471(7341): 495–503.

77. Chiu CQ, Lu G, Morse TM, et al.: Compartamentalization of GABAergic inhibition by dendritic spines. Science. 2013; 340(6133): 759–62.

78. Gentet LJ, Kremer Y, Taniguchi H, et al.: Unique functional properties of somatostatin-expressing GABAergic neurons in mouse barrel cortex. Nat Neurosci. 2012; 15(4): 607–12.

79. Scheyltjes I, Arkons L: The Current Status of Somatostatin-Interneurons in Inhibitory Control of Brain Function and Plasticity. Neur Plast. 2016; 2016: 8723623.

80. Veit J, Haskim R, Jadi MP, et al.: Cortical gamma band synchronization through somatostatin interneurons. Nat Neurosci. 2017; 20(7): 851–9.

81. Bezaire MJ, Soltesz I: Somatostatin-expressing GABAergic neurons in mouse barrel cortex. J Neurophysiol. 2008; 99(4): 536–45.

82. Nusser Z, Sieghart W, Benke D, et al.: Differential synaptic localization of two major gamma-amino-butyric acid type A receptor alpha subunits on hippocampal pyramidal cells. Proc Natl Acad Sci USA. 1996; 93(21): 11939–44.

83. Buticchi S, Blázquez-Llorca L, Merchán-Pérez A, et al.: Densitmetric analysis of somatostatin-ergic interneurons in the mouse hippocampus. J Comp Neurol. 2005; 485(3): 385–400.

84. Baldrige-Siegfried W, Benci K, et al.: Disinhibition of somatostatin+ VIP+ interneurons control pyramidal neurons in monkey prefrontal cortex. J Comp Neurol. 2015; 523(1): 143–60.

85. Nyiri G, Freund TF, Somogyi P: Input-dependent synaptic targeting of alpha- subunit-containing GABA receptors in synapses of hippocampal pyramidal cells of the rat. Eur J Neurosci. 2011; 33(6): 428–42.

86. Nusser Z, Blázquez-Llorca L, Merchán-Pérez A, et al.: GABAergic interneurons control disinhibitory control. Nature. 2013; 27(5): 3567–73.

87. Inan M, Blázquez-Llorca L, Merchán-Pérez A, et al.: Dense and overlapping innervation of pyramidal neurons by chandelier cells. J Neurosci. 2013; 33(5): 1907–14.

88. Wang Y, Zhang P, Wyeki DR: Chandelier Cells in Functional and Dysfunctional Neural Circuits. Front Neural Circuits. 2016; 10: 33.

89. Inda MC, Defelipe J, Múrιoz A: The distribution of chandelier cell axon terminals that express the GABA plasma membrane transporter GAT-1 in the human neocortex. Cereb Cortex. 2007; 17(9): 2060–71.

90. Cruz DA, Egan SM, Lewis DA: Postnatal development of pre- and postsynaptic GABA markers at chandelier cell connections with pyramidal neurons in monkey prefrontal cortex. J Comp Neurol. 2005; 485(3): 385–400.

91. Shaywitz BA, Shaywitz SE, Pugh K, et al.: Literacy achievement in children with specific language impairment: a 20-year longitudinal follow-up study. Science. 2009; 325(5940): 975–80.

92. Watanabe T, Okada M, Oshima Y, et al.: Dissociable properties of chandelier cells and basket cells in the neocortex. J Neurophysiol. 2007; 98(2): 949–66.
terminals in the prefrontal cortex of schizophrenic subjects. Am J Psychiatry. 1999; 156(11): 1709–19. PubMed Abstract

116. Schleimer SB, Hinton T, Dixon G, et al.: GABA transporters GAT-1 and GAT-3 in the human dorsal prefrontal cortex in schizophrenia. Neuropsychobiology. 2004; 50(3): 226–30. PubMed Abstract | Publisher Full Text

117. Volk D, Austin M, Pieri J, et al.: GABA transporter-1 mRNA in the prefrontal cortex in schizophrenia: decreased expression in a subset of neurons. Am J Psychiatry. 2001; 158(2): 256–65. PubMed Abstract | Publisher Full Text

118. Volk DW, Pieri JH, Fritzsch JM, et al.: Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. Cereb Cortex. 2002; 12(10): 1063–70. PubMed Abstract

119. Howard A, Tamas G, Soltesz I: Lighting the chandelier: new vistas for axo-axonic cells. Trends Neurosci. 2005; 28(6): 310–6. PubMed Abstract | Publisher Full Text

120. Del Pino I, García-Frigola C, Dehorter N, et al.: Neuronal assembly at perisomatic inhibitory synapses through gephyrin and collybistin. Neuron. 2012; 72(9): 1225–64. PubMed Abstract | Publisher Full Text

121. Ting AK, Chen Y, Wen L, et al.: Role of dysbindin in dopamine receptor modulation of excitation on cortical pyramidal neurons. J Neurophysiol. 2016; 116(1): 264–76. PubMed Abstract | Publisher Full Text

122. Gipson JR, Bartley AF, Hays SA, et al.: Imbalance of neocortical excitation and inhibition and altered UP states reflect network hyperexcitability in the mouse model of fragile X syndrome. J Neurophysiol. 2008; 100(5): 2615–26. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

123. Seshadri S, Faust T, Ishizuka K, et al.: Interneuronal DISC1 regulates NRG1- ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. Nat Commun. 2015; 6: 10118. PubMed Abstract | Publisher Full Text | Free Full Text

124. Polepalli JS, Wu H, Goswami D, et al.: Modulation of excitation on parvalbumin interneurons by neuriligin-3 regulates the hippocampal network. Nat Neurosci. 2017; 20(2): 219–29. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

125. He L, Liu N, Cheng TL, et al.: Conditional deletion of Mopp2 in parvalbumin-expressing GABAergic cells results in the absence of critical period plasticity. Nat Commun. 2014; 5(1): 5036. PubMed Abstract | Publisher Full Text | F1000 Recommendation

126. JY, Yang F, Papaleo F, et al.: Role of dysbindin in dopamine receptor trafficking and cortical GABA function. Proc Natl Acad Sci U S A. 2009; 106(46): 19593–8. PubMed Abstract | Publisher Full Text | Free Full Text

127. Yu FH, Mantegazza M, Westenbroek RE, et al.: Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci. 2006; 9(9): 1142–9. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

128. Fazzan P, Patemam AV, Valiente M, et al.: Control of cortical GABA circuitry development by Nr1l1 and ErbB4 signalling. Nature. 2010; 464(7293): 1376–80. PubMed Abstract | Publisher Full Text | F1000 Recommendation

129. Bateup HS, Johnson CA, Denefro CL, et al.: Excitatory/inhibitory synaptic imbalance leads to hippocampal hyperexcitability in mouse models of tuberous sclerosis. Neurosci. 2013; 178(3): 510–22. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

130. Wallace ML, Burette AC, Weinberg RJ, et al.: Maternal loss of Ube3a produces an excitatory/inhibitory imbalance through neuron type-specific synaptic defects. Neurosci. 2012; 74(5): 793–800. PubMed Abstract | Publisher Full Text | Free Full Text

131. Lee J, Chung C, Ha S, et al.: Shank3-mutant mice lacking exon 9 show altered excitation/inhibition balance, enhanced rearing, and spatial memory deficit. Front Cell Neurosci. 2015; 9: 94. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

132. Won H, Mah W, Kim E, et al.: GIT1 is associated with ADHD in humans and ADHD-like behaviors in mice. Nat Med. 2011; 17(5): 566–72. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

133. Rivero O, Selten MM, Sich S, et al.: Catherin-13, a risk gene for ADHD and comorbid disorders, impacts GABAergic function in hippocampus and cognition. Transl Psychiatry. 2015; 5: e655. PubMed Abstract | Publisher Full Text | Free Full Text

134. Gibson JR, Huber KM, Südhof TC: Neuroligin-2 deletion selectively decreases inhibitory synaptic transmission originating from fast-spiking but not from somatostatin-positive interneurons. J Neurosci. 2009; 29(44): 13883–97. PubMed Abstract | Publisher Full Text | Free Full Text

135. Pouloupolous A, Amrami G, Meyer G, et al.: Neuroligin 2 drives postsynaptic assembly at perisomatic inhibitory synapses through gephyrin and collybistin. Neuropsychiatr Genet. 2009; 24(2): 82–89. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

136. Földy C, Malenka RC, Südhof TC: Autism-associated neurilgin-3 mutations commonly disrupt tonic endocannabinoid signaling. Neuron. 2013; 78(3): 498–509. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

137. Anderson GR, Galfin T, Xu W, et al.: Candidate autism gene screen identifies a missense G1R714C mutation in GASP2R1 in dendritic arborization and spine development. Proc Natl Acad Sci U S A. 2012; 109(4): 18125–5. PubMed Abstract | Publisher Full Text | Free Full Text

138. Xue M, Atalah BV, Scanziani M: Equalizing excitation-inhibition ratios across visual cortical neurons. Nature. 2014; 511(751): 596–600. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

139. Tamás G, Buhl EH, Lörincz A, et al.: Proximally targeted GABAergic synapses and gap junctions synchronize cortical interneurons. Nat Neurosci. 2000; 3(4): 365–70. PubMed Abstract | Publisher Full Text

140. Bartos M, Vida I, Jonas P: Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci. 2007; 8(1): 45–56. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

141. Traub RD, Kopell N, Bibbig A, et al.: Gap junctions between interneuron dendrites can enhance synchrony of gamma oscillations in distributed networks. J Neurosci. 2001; 21(23): 9478–86. PubMed Abstract | F1000 Recommendation

142. Mullins C, Fishel G, Tsien RW: Unifying Views of Autism Spectrum Disorders: A Consideration of Autoregulatory Feedback Loops. Neurosci. 2018; 89(9): 1131–56. PubMed Abstract | Publisher Full Text | F1000 Recommendation

143. Turrigiano GG, Leslie KR, Desai NS, et al.: Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature. 1998; 391(6670): 852–6. PubMed Abstract | Publisher Full Text | Free Full Text

144. Desai NS, Rutherford LC, Turrigiano GG: Plasticity in the intrinsic excitability of cortical pyramidal neurons. Nat Neurosci. 1999; 2(6): 515–20. PubMed Abstract | Publisher Full Text | Free Full Text

145. Bartley AF, Huang ZJ, Huber KM, et al.: Differential activity-dependent, homeostatic plasticity of two neocortical inhibitory circuits. J Neurophysiol. 2008; 100(4): 1983–94. PubMed Abstract | Publisher Full Text | Free Full Text

146. Echegoyen J, Neu A, Graber KD, et al.: Homeostatic plasticity studied using in vivo hippocampal activity-blockade: synaptic scaling, intrinsic plasticity and age-dependence. PLoS One. 2007; 2(8): e700. PubMed Abstract | Publisher Full Text | Free Full Text

147. Norton N, Moskivina V, Morris DW, et al.: Evidence that interaction between neuregulin 1 and its receptor erbB4 increases susceptibility to schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2006; 141B(1): 96–101. PubMed Abstract | Publisher Full Text | Free Full Text

148. Silberberg G, Davarai A, Pinkas-Krämers R, et al.: The involvement of ErbB4 with schizophrenia: association and expression studies. Am J Med Genet B Neuropsychiatr Genet. 2006; 141B(2): 142–5. PubMed Abstract | Publisher Full Text | Free Full Text

149. Prata DP, Breen G, Osborne S, et al.: An association study of the neuregulin 1 gene, bipolar affective disorder and psychosis. Psychiatr Genet. 2009; 19(3): 113–6. PubMed Abstract | Publisher Full Text

150. Verkerk AJ, Pieretti M, Sutcliffe JS, et al.: Candidate autism gene screen identifies a missense G1R714C mutation in GASP2R1 in dendritic arborization and spine development. Proc Natl Acad Sci U S A. 2012; 109(4): 18125–5. PubMed Abstract | Publisher Full Text | Free Full Text

151. Kaufmann WE, Cortell R, Kau AS, et al.: Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. Am J Med Genet A. 2004; 129A(3): 225–31. PubMed Abstract | Publisher Full Text | Free Full Text
1. The mGluR theory of fragile X mental retardation. Neuron. 2004; 27(7): 379–70. 

2. Kole MH, Huber KM, Warren ST: The mGluR theory of fragile X mental retardation. Trends Neurosci. 2004; 27(7): 379–70. 

3. Paluszewicz SM, Martin BS, Huntsman MM: Fragile X syndrome: the GABAergic system and circuit dysfunction. Dev Neurosci. 2011; 33(9): 349–64. 

4. Cea-Del Rio CA, Huntsman MM: The contribution of inhibitory interneurons to circuit dysfunction in Fragile X Syndrome. Front Cell Neurosci. 2014; 8: 245. 

5. D'Hulst C, De Geest N, Reeve SP, Cea-Del Rio CA, Huntsman MM: Loss of MeCP2 in Parvalbumin-and Basket Cells Disrupts Spatial Information Coding. J Neurosci. 2017; 37(22): 5854–66. 

6. Gatto CL, Broadie K: Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. Front Synaptic Neurosci. 2010; 2: 4. 

7. Keinan K, Wang BS, Lu J, et al.: MeCP2 regulates the timing of critical period plasticity that shapes functional connectivity in primary visual cortex. Proc Natl Acad Sci U S A. 2015; 112(24): E4782–91. 

8. Hensel TK: Critical period plasticity in local cortical circuits. Nat Rev Neurosci. 2005; 6(11): 877–88. 

9. Marin O: Developmental and critical period windows for the treatment of psychiatric disorders. Nat Med. 2016; 22(11): 1229–38. 

10. Chao HT, Chen H, Samaco RC, et al.: Dysfunction in GABA signalling mediates autism-like stereotypes and Rett syndrome phenotypes. Nature. 2010; 469(7321): 263. 

11. Itô-Ishida A, Ue K, Chen H, et al.: Loss of MeCP2 in Parvalbumin-and Somatostatin-Expressing Neurons in Mice Leads to Distinct Rett Syndrome-like Phenotypes. Neuron. 2015; 88(4): 651–63. 

12. Banerjee A, Rikhye RV, Breton-Provencher V, et al.: Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome. Proc Natl Acad Sci U S A. 2016; 113(46): E7287–E7296. 

13. Dehoret N, Maito N, Marin O, et al.: Tuning neural circuits by turning the interneuron knob. Curr Opin Neurobiol. 2017; 42: 144–51. 

14. Beck H, Yaar Y: Plasticity of intrinsic neuronal properties in CNS disorders. Nat Rev Neurosci. 2008; 9(6): 357–69. 

15. Straub RE, Jiang Y, MacLean CJ, et al.: Genetic variation in the sp22.3 gene DTNBP1, the human ortholog of the mouse dynein gene, is associated with schizophrenia. Am J Hum Genet. 2002; 71(2): 337–48. 

16. Carlson GC, Talbot K, Hatien TB, et al.: Dysbindin-1 mutant mice implicate reduced fast-phasic inhibition as a final common mechanism in schizophrenia. Proc Natl Acad Sci U S A. 2011; 108(3): E962–70. 

17. Lariumore J, Zatiche SA, Arnold M, et al.: Dysbindin Deficiency Modifies the Expression of GABA Neuron and Ion Permeation Transcripts in the Developing Hippocampus. Front Genet. 2017; 8: 28. 

18. O’Roak BJ, Deriziotis P, Lee C, et al.: Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011; 43(6): 585–9. 

19. Van Wart A, Trimmer JS, Matthews G: Polarized distribution of ion channels within microdomains of the axon initial segment. J Comp Neurol. 2007; 500(2): 339–52. 

20. Kole MH, Stuart GJ: Signal processing in the axon initial segment. Neuron. 2012; 75(2): 235–47. 

21. Cheah CS, Yu FH, Westenbroek RE, et al.: Specific deletion of Na1.1 sodium channels in inhibitory interneurons causes seizures and premature death in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A. 2012; 109(36): 14646–51. 

22. Dutton SB, Makinson CD, Papale LA, et al.: Preferential inactivation of Scn1a in parvalbumin interneurons increases seizure susceptibility. Neurobiol Dis. 2013; 49: 211–20. 

23. Han S, Tai C, Westenbroek RE, et al.: Autistic-like behaviour in Scn1a+ mice and rescue by enhanced GABA-meditated neurotransmission. Nature. 2012; 489(7416): 385–90. 

24. Stedehouder J, Kushner SA: Myelination of parvalbumin interneurons: a parsimonious locus of pathophysiological convergence in schizophrenia. Mol Psychiatry. 2017; 22(1): 4–11. 

25. White T, Magnotta VA, Bockholt HJ, et al.: Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. Schizophr Bull. 2011; 37(1): 222–32. 

26. Usanov NA, Vostrikov VM, Ovchyskaya DD, et al.: Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res. 2004; 67(2–3): 269–75. 

27. Hanak Y, Walker JR, Li C, et al.: Loss-of-function expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A. 2001; 98(7): 4746–51. 

28. Kazounarou H, Kosala T, Hentz CR, et al.: Immunocytochemical study of GABAergic neurons containing the calcium-binding protein parvalbumin in the rat hippocampus. Exp Brain Res. 1988; 72(2): 347–62. 

29. Nave KA, Werner HB: Myelination of the nervous system: mechanisms and functions. Annu Rev Cell Dev Biol. 2014; 30: 503–33. 

30. Lewis DA: The chandelier neuron in schizophrenia. Dev Neurobiol. 2011; 71(1): 118–27. 

31. Del Pino I, Brotons-Mas JR, Marques-Smith A, et al.: Abnormal wiring of CC-K+ basket cells disrupts spatial information coding. Nat Neurosci. 2017; 20(6): 784–92. 

32. Prather P, de Vries PJ: Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol. 2004; 19(10): 666–74. 

33. Jones AC, Shyamsundar MM, Thomas MW, et al.: Comprehensive mutation analysis of TSC1 and TSC2 and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet. 1999; 65(6): 1305–15. 

34. Rougeulle C, Glatt H, Lalonde M: The Angelman syndrome candidate gene, UBE3A/E6-AP, is impaired in brain. Nat Genet. 1997; 17(1): 14–5. 

35. Williams CA, Beaudet AL, Clayton-Smith J, et al.: Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A. 2006; 140(3): 413–8. 

36. Thibert RL, Conant KD, Braun EK, et al.: Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options. Epilepsia. 2009; 50(1): 2369–76. 

37. Shinno K, Riday TT, Condon KA, et al.: Ube3a is required for experience-dependent maturation of the neocortex. Nat Neurosci. 2009; 12(6): 777–83. 

38. Judson MC, Wallace ML, Sidorenko MS, et al.: GABAergic Neuron-Specific Loss of Ube3a Causes Angelman Syndrome-Like EEG Abnormalities and Enhances Seizure Susceptibility. Neurology. 2016; 90(1): 56–69. 

39. Wallace ML, van Woerden GM, Elgersma Y, et al.: Neurochemical analysis of Ube3a−/− basket cells and the excitatory/inhibitory signaling imbalance in Angelman syndrome. Proc Natl Acad Sci U S A. 2016; 113(14): 3796–801. 

40. Rasus BM, Bishop KS, Bostock TW, et al.: The Angelman syndrome candidate gene, UBE3A, is necessary for normal learning and memory in mice. J Neurosci. 2002; 22(26): 11983–97. 

41. Rasus BM, Bishop KS, Bostock TW, et al.: The Angelman syndrome candidate gene, UBE3A, is necessary for normal learning and memory in mice. J Neurosci. 2002; 22(26): 11983–97. 

42. Rasus BM, Bishop KS, Bostock TW, et al.: The Angelman syndrome candidate gene, UBE3A, is necessary for normal learning and memory in mice. J Neurosci. 2002; 22(26): 11983–97.
cortical inhibitory networks in vivo. Nature. 2012; 488(7411): 343–8.

203. Leblond CS, Nava C, Polge A, et al.: Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. PLoS Genet. 2014; 10(9): e1004580.

204. Monteiro P, Feng G: SHANK proteins: roles at the synapse and in autism spectrum disorder. Nat Rev Neurosci. 2017; 18(3): 147–57.

205. Naisbitt S, Kim E, Tu JC, et al.: Shank, a novel family of postsynaptic density proteins that binds to the NMDA receptor/PSD-95/GKAP complex and cortactin. Neuron. 1999; 23(3): 569–82.

206. Tao-Cheng J, Yang Y, Reese TS, et al.: Differential distribution of Shank and GKP at the postsynaptic density. PLoS One. 2015; 10(3): e0118750.

207. Bozgati O, Sakurada T, Papapetrou E, et al.: Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. Mol Autism. 2010; 1(1): 15.

208. Wang X, McCoy PA, Rodriguez RN, et al.: Synaptic dysfunction and abnormal behaviors in mice lacking major isoforms of Shank3. Hum Mol Genet. 2011; 20(5): 1003–10.

209. Scourf TC: Neurelink and neurexins link synaptic function to cognitive disease. Nature. 2008; 455(7215): 903–11.

210. Chih B, Engelmann H, Schellfie P: Control of excitory and inhibitory synapse formation by neureligins. Science. 2005; 307(5713): 1324–8.

211. Südhof TC: Neurexins and neurexins link synaptic function to cognitive disease. Nature. 2008; 455(7215): 903–11.

212. Vanroose F, Jamam S, Bisse N: Neurilin 2 is exclusively localized to inhibitory synapses. Eur J Cell Biol. 2004; 83(9): 449–56.

213. Budnick EC, Schellfie P: Neurilin-3 is a neuronal adhesion protein at GABAergic and glutamatergic synapses. Eur J Neurosci. 2007; 26(7): 1738–48.

214. Hoon M, Soykan T, Falkenberg B, et al.: Neurilin-4 is localized to glycinergic postsynapses and regulates inhibition in the retina. Proc Natl Acad Sci U S A. 1999; 96(3): 1100–5.

215. Vanroose F, Jamam S, Bisse N: Neurilin 2 is exclusively localized to inhibitory synapses. Eur J Cell Biol. 2004; 83(9): 449–56.

216. Budnick EC, Schellfie P: Neurilin-3 is a neuronal adhesion protein at GABAergic and glutamatergic synapses. Eur J Neurosci. 2007; 26(7): 1738–48.

217. Jamam S, Quach H, Betancur C, et al.: Mutations of the X-linked genes encoding neurilins NLGN3 and NLGN4 are associated with autism. Nat Genet. 2003; 34(3): 27–9.

218. Tabuchi K, Blundell J, Etherton MR, et al.: A neurilin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science. 2007; 318(5847): 71–6.

219. Hammer M, Krueger-Burg D, Tuffy LP, et al.: Perturbed Hippocampal Synaptic Inhibition and γ-Oscillations in a Neurilin-4 Knockout Mouse Model of Autism. Cell Rep. 2015; 13(3): 516–23.

220. Parente DJ, Garriga C, Baskin B, et al.: Neurilin 2 nonsense variant associated with anxiety, autism, intellectual disability, hyperphagia, and obesity. Am J Med Genet A. 2017; 173(1): 213–6.

221. Sun C, Cheng MC, Qin R, et al.: Identification and functional characterization of rare mutations of the neurilin-2 gene (NLGN2) associated with schizophrenia. Hum Mol Genet. 2011; 20(15): 3042–51.

222. Kim HG, Kishikawa S, Higgins AW, et al.: Disruption of neurilin 1 associated with autism spectrum disorder. Am J Hum Genet. 2008; 82(1): 199–207.

223. Kirov G, Gumsarian D, Chen W, et al.: Comparative genome hybridization suggests a role for NRXN1 and APBA2 in schizophrenia. Hum Mol Genet. 2008; 17(3): 458–65.

224. Etherton MR, Blass CA, Powell CM, et al.: Mouse neurilin-1alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. Proc Natl Acad Sci U S A. 2009; 106(42): 17988–18003.

225. Rabaneda LG, Robles-Lanuza E, Nieto-Gonzalez JL, et al.: Neurexin dysfunction in adult neurons results in autistic-like behavior in mice. Cell Rep. 2014; 8(2): 338–46.

226. de la Peña JB, Dela Peña I, Custodio RJ, et al.: Exploring the Validity of Proposed Transgenic Animal Models of Attention-Deficit Hyperactivity Disorder (ADHD), Mol Neurobiol. 2017; 1–16.

227. Salatino-Oliveira A, Genro JP, Chazarra R, et al.: Association study of GI1T gene with attention-deficit hyperactivity disorder in Brazilian children and adolescents. Genes Brain Behav. 2017; 11(7): 864–8.

228. Klein M, van der Voet M, Harich B, et al.: Converging evidence does not support GI1T as an ADHD risk gene. Am J Med Genet B Neuropsychiatr Genet. 2015; 168B(6): 492–507.

229. Smith KR, Davenport EC, Wei J, et al.: GI1T and JPIX are essential for GABA receptor synaptic stability and inhibitory neurotransmission. Cell Rep. 2014; 9(1): 298–310.

230. Arias-Vásquez A, Alink TE, Rommelse NN, et al.: CDH13 is associated with working memory performance in attention deficit/hyperactivity disorder. Genes Brain Behav. 2011; 10(6): 844–51.

231. Zhou K, Dempfe A, Aros-Burgos M, et al.: Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B(8): 1392–8.

232. Rivero O, Sich S, Popp S, et al.: Impact of the ADHD-susceptibility gene CDH13 on development and function of brain networks. Eur Neuropsychopharmacol. 2013; 23(6): 492–507.

233. Kitlen AC, Barber M, Paulin NJW, et al.: Protective role of Cadherin 13 in interneuron development. Brain Struct Funct. 2017; 222(8): 3567–3585.

234. Benaroch EE: GABA receptors: structure, functions, and clinical implications. Neurology. 2012; 78(9): 757–84.

235. Lössner C, Jan LY, Stoffel M, et al.: G-protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. Neuron. 1997; 19(3): 687–95.

236. Ikeda SR: Voltage-dependent modulation of N-type calcium channels by G-protein beta gamma subunits. Nature. 1996; 380(6571): 255–8.

237. Mintz IM, Bean BP: GABAA receptor inhibition of P-type Ca2+ channels in central neurons. Neuro. 1993; 10(5): 889–98.

238. Muzikian M, Sasaki M, Ishikawa M, et al.: Immunohistochemical localization of gamma-aminobutyric acid receptor in the hippocampus of subjects with schizophrenia. Neurosci Lett. 2000; 283(1): 101–4.

239. Muzikian M, Ishikawa M, Hidak S, et al.: Immunohistochemical localization of GABAA receptor in the entorhinal cortex and inferior temporal cortex of schizophrenia brain. Prog Neuropsychopharmacol Biol Psychiatry. 2002; 26(3): 393–6.

240. Ishikawa M, Muzikian K, Iwasaki M, et al.: Immunohistochemical and immunoblot analysis of gamma-aminobutyric acid B receptor in the prefrontal cortex of subjects with schizophrenia and bipolar disorder. Neurosci Lett. 2005; 383(3): 272–7.

241. Fatemi SH, Folsom TD, Thuras PD: Deficits in GABAA receptor system in schizophrenia and mood disorders: a postmortem study. Schizophr Res. 2011; 128(1–3): 37–43.

242. Seiten MM, Meyer F, Ba W, et al.: Increased GABA receptor signaling in a rat model for schizophrenia. Sci Rep. 2016; 6: 34240.

243. Wierolska JM, Kusak M, Tokarska K, et al.: The GABA receptor agonist CGP44532 and the positive modulator GS39783 reverse some behavioural changes related to positive syndromes of psychosis in mice. Br J Pharmacol. 2011; 163(3): 1034–47.

244. Wierolska JM, Klczek N, Woźniak M, et al.: mGlu5/GABAA interplay in animal models of positive, negative and cognitive symptoms of schizophrenia. Neurechem Int. 2015; 88: 95–103.

245. Lurjian GG: The dialectic of Hebb and homeostasis. Philos Trans R Soc Lond B Biol Sci. 2017; 372(1715): pii: 20160258.

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