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Interneuron dysfunction in psychiatric disorders

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Abstract | Schizophrenia, autism and intellectual disabilities are best understood as spectrums of diseases that have broad sets of causes. However, it is becoming evident that these conditions also have overlapping phenotypes and genetics, which is suggestive of common deficits. In this context, the idea that the disruption of inhibitory circuits might be responsible for some of the clinical features of these disorders is gaining support. Recent studies in animal models demonstrate that the molecular basis of such disruption is linked to specific defects in the development and function of interneurons — the cells that are responsible for establishing inhibitory circuits in the brain. These insights are leading to a better understanding of the causes of schizophrenia, autism and intellectual disabilities, and may contribute to the development of more-effective therapeutic interventions.

Pyramidal cells
Pyramidal cells are the principal neurons of the cerebral cortex — constituting ~80% of the total number of neurons in this brain region — and use glutamate as a neurotransmitter.

GABAergic interneurons
GABAergic interneurons have diverse morphologies but are typically aspiny and localized to the cerebral cortex. They constitute ~20% of the total number of neurons in this region.

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Complex brain circuitries comprise hierarchical networks of excitatory and inhibitory neurons. For example, the main elements of the microcircuits in the cerebral cortex are excitatory glutamatergic pyramidal cells and inhibitory GABAergic interneurons. Pyramidal cells specialize in transmitting information between different cortical areas and from cortical areas to other regions of the brain, whereas interneurons primarily contribute to local neural assemblies, where they provide inhibitory inputs and shape synchronized oscillations[1]. The balance between excitation and inhibition is crucial for cortical function[2–4] and, consequently, important developmental and physiological mechanisms have evolved to maintain this dynamic equilibrium[5] (BOX 1).

GABAergic interneurons are considered to be the main cellular elements that control hyperexcitability in the brain[6]. Indeed, severe GABAergic deficits can cause pathological hyperexcitability[7,8], and many of the genes that have been linked to epilepsy regulate interneuron development and function[9,10]. Epilepsy, however, might not be the only consequence of disrupting interneuron function. Recent studies in humans and in animal models indicate that more-subtle perturbations in the excitatory–inhibitory balance exist in multiple psychiatric conditions (TABLES 1,2).

Interneurons not only contribute to the global balance of activity in cortical networks but also mediate the precise gating of information through specific signalling pathways. They achieve these goals by controlling — both spatially and temporally — the amounts of excitatory and inhibitory inputs that individual neurons receive[11], and they do so as part of an extremely dynamic process, which is often dependent on the brain state[12]. Considering the diverse functions that interneurons have in the brain, how do we move from the increasingly commonplace idea that the alteration of the excitatory–inhibitory balance is associated with various neuropsychiatric disorders to a mechanistic understanding of the contribution of interneurons to each unique pathophysiology? Unfortunately, this question does not have a straightforward answer. If interneurons are somehow involved in the aetiology of neuropsychiatric disorders such as schizophrenia, autism and Rett's syndrome, we should aim to understand how specific interneuron deficits might contribute to the pathophysiology of each of these conditions. In other words, we must understand which specific cellular elements are affected in each disease and how specific brain circuits might be altered. Only then can we begin to understand how subtle interneuron deficits can contribute to aberrant information processing in neuropsychiatric illnesses, whereas gross disruption of inhibitory circuits causes epilepsy. The purpose of this Review is to critically summarize current evidence that supports a link between interneuron dysfunction and cognitive impairment in neuropsychiatric diseases.

Interneuron diversity

Knowledge of the functional roles that interneurons fulfil in the healthy brain should provide insight into the possible contribution of abnormal interneuron function to neuropsychiatric illness. Development of such

Axon initial segment
(AIS). The axon initial segment is the proximal end of the axon, close to the neuron soma, and is where action potentials are generated.

Oscillatory activity
Oscillatory activity comprises rhythmic or repetitive neural activity that enables coordinated activity during normal brain functioning.

Gamma-frequency
The gamma frequency constitutes a type of neural oscillation and occurs at a prototypical frequency of approximately 40 Hz, although it may range from 30 to 80 Hz.

knowledge, however, has been hampered by the astonishing diversity of interneuron populations that exists in the adult brain. In the cerebral cortex, for example, over 20 different classes of interneuron have been identified[1,13,14]. The various cortical interneuron subtypes have distinct or only partially overlapping morphological, electrophysiological and neurochemical characteristics, which makes their unequivocal identification a complex endeavour[15]. Extensive interneuron diversity also exists in the amygdala and striatum, two other telencephalic regions that are of particular relevance in psychiatric diseases[16,17].

Interneurons are 'tailor-made' to influence the excitability of pyramidal cells or other interneurons in unique ways[1,13] (FIG. 1). This specialization arises not only from the intrinsic features of each class of interneuron but also from their ability to innervate specific subcellular regions of their target cells. For example, Martinotti cells form synapses onto the dendrites of pyramidal cells, whereas basket cells and chandelier cells primarily contact the soma and axon initial segment (AIS), respectively, of pyramidal cells. As the spatial location of synapses is one of the features that determine the effect of interneurons on a postsynaptic target[18], each class of interneuron modulates pyramidal cell function in a unique manner. Specific classes of interneuron also contribute to the generation and pacing of different forms of rhythmic activity, which help ensembles of pyramidal cells to fire simultaneously. For example, parvalbumin-expressing (PV^+) interneurons give rise to oscillatory activity in the gamma-frequency range (30–80 Hz), whereas non-adapting, non-fast-spiking interneurons that express somatostatin generate beta-frequency oscillations (15–30 Hz)[19]. Thus, the functional consequences of a deficit in GABAergic inhibition might depend on which type of interneuron is affected.

Multiple lines of evidence suggest that cortical interneuron diversity arises during development through the interaction of specific genetic and environmental factors[20–22]. As in other regions of the brain, the specification of each class of cortical interneuron is initially defined in progenitor cells by a group of transcription factors that coordinate the expression of effector proteins (FIG. 1). In turn, these proteins determine the intrinsic features — for example, ion channel composition — of each particular class of interneuron, as well as the migration and integration of these cells into specific neural assemblies in the cerebral cortex. Some of these effector proteins — such as the two GABA-synthesizing enzymes 65 kDa glutamate decarboxylase (GAD65; also known as GAD2) and 67 kDa glutamate decarboxyase (GAD67; also known as GAD1) — are common to all interneuron classes, whereas others (for example, PV) are specific to only certain subtypes of interneuron. The fact that cortical interneurons are genetically specified early during development might be particularly relevant to neuropsychiatric disorders, because many of these conditions emerge early in life and are thought to be caused by defects in brain development[23,24]. Indeed, it is conceivable that some genetic alterations might affect the development of specific classes of interneuron, whereas other genetic alterations might disrupt the function of many classes. Furthermore, the timing of genetic disruption might influence interneurons in a wide range of ways, especially as the development of cortical interneurons is protracted and can extend well into postnatal life[25]. For example, mutations that affect the early development of interneurons might modify the number or location of these cells, whereas genetic changes that cause late alterations might primarily affect interneuron patterns of connectivity. In conclusion, the existence of partially divergent genetic programmes that control the development of specific classes of interneuron might explain the differential contributions of such classes to disease.

Schizophrenia

Schizophrenia is a severe neuropsychiatric illness that is characterized by the following three symptom clusters: positive symptoms, such as delusions and hallucinations; negative symptoms, including apathy and social withdrawal; and cognitive symptoms, such as deficits in attention and working memory. Although positive symptoms are the most noticeable manifestations of this disease, cognitive deficits are perhaps the most distinctive[26].

Patients with schizophrenia can have severe deficits in memory, attention and executive function, and milder cognitive deficits are often present in unaffected relatives of these individuals[27,28]. An increasing body of evidence suggests that abnormal inhibitory function in the prefrontal cortex of individuals with schizophrenia might cause the observed cognitive disturbances[29–31]. Indeed, deficits in cortical inhibition have been reported both *in vivo* and in analyses of post-mortem brain tissue from patients with schizophrenia[30–33], and cognitive functions such as working memory seem to depend on normal interneuron performance[29,34,35]. Although it was originally suggested that the GABAergic deficits that are observed in schizophrenia might be caused by a deficit in the number of interneurons[36] — and this might certainly be the case in some patients — more-recent

Box 1 | Excitatory–inhibitory balance in cortical circuits

It is generally accepted that excitation and inhibition are balanced globally in cortical networks[144,145]. In this scenario, individual neurons receive similar amounts of excitatory and inhibitory inputs, which tend to annul each other. However, information processing requires that pertinent signals propagate through specific pathways, and this propagation involves the precise modulation of the excitatory–inhibitory balance in individual cells. It has been suggested that signal propagation is a default state in information processing and that inhibitory mechanisms are used to deactivate such signalling[146,147]. As an alternative, it has been proposed that the default state comprises balanced networks and that inhibitory mechanisms are used for the gating of relevant signals[11]. Small temporal differences between the timing of excitation and inhibition seem to be crucial for the proper control of signal gating[148].

Homeostatic mechanisms exist that maintain the balance between excitation and inhibition in individual neurons and in neuronal networks[5,148], so that gating is relatively robust in the face of small perturbations. However, disrupted homeostatic mechanisms or severe deficits in inhibitory function might lead to a permanent imbalance between excitation and inhibition, and this imbalance in turn might cause instability in neural networks and, as a consequence, epilepsy. Furthermore, disruption of the balance between excitation and inhibition has been suggested to lead to gating defects that are related to cognitive impairment, as is observed in schizophrenia and autism[11,149].

Table 1 | **Mouse models of schizophrenia showing disruption of the cortical excitatory–inhibitory balance**

Schizophrenia-associated human gene (chromosome)	Mouse model of schizophrenia	Pathophysiology in mice	Pathological mechanism in mice	Refs
NRG1 (8p12)	*Nrg1*$^{+/-}$	Defective synaptic plasticity and long-term potentiation; hyperactivity; impaired PPI and working memory	Decreased number of functional NMDA-type glutamate receptors	60, 171
	Nrg1$^{+/-}$ (deletion of type III isoform only)			
ERBB4 (2q33)	*Erbb4*$^{+/-}$	Hyperactivity; defective gamma synchrony; hyperexcitability; impaired PPI and working memory	Reduced number of PV^{+} interneurons	55, 60, 162
	Erbb4$^{-/-}$; *HER4*^{heart} (deletion of *Erbb4*; rescued expression of ERBB4 in heart)			
	Nestin–Cre; *Erbb4*$^{lox/lox}$ (deletion of *Erbb4* in neurons and glia)			
	Dlx5/6–Cre; *Erbb4*$^{lox/lox}$ (deletion of *Erbb4* in forebrain GABAergic neurons)	Cortical hyperexcitability; motor hyperactivity; impaired PPI and working memory	Reduced number of inhibitory synapses to axon initial segment of pyramidal cells; impaired inhibitory neurotransmission; reduced number of excitatory synapses to PV^{+} interneurons	52, 56, 57
	PV–Cre; *Erbb4*$^{lox/lox}$ (deletion of *Erbb4* in PV^{+} neurons)			
GRIN1 (9q34)	*Ppp1r2*–Cre; *Nr1*$^{lox/lox}$ (deletion of *Grin1* in forebrain GABAergic neurons)	Cortical hyperexcitability; defective gamma synchrony; impaired PPI and working memory; abnormal social behaviour	Reduced excitation of PV^{+} interneurons; reduced levels of PV, GAD67 and GABA; impaired inhibitory function	49
	PV–Cre; *Nr1*$^{lox/lox}$ (deletion of *Grin1* in PV^{+} neurons)	Cortical hyperexcitability; defective synchrony; impaired working memory	Reduced excitation of PV^{+} interneurons; impaired inhibitory function	47,48
*DISC1** (1q42.1)	DN-DISC1	Hyperactivity; altered sensorimotor gating; anhedonia-like behaviour	Reduced PV expression or loss of PV^{+} interneurons	64,65
	Disc1 knockdown			
DTNBP1 (6p22.3)	*Dtnbp1*$^{-/-}$	Hyperactivity	Reduced excitability of PV^{+} interneurons	70

DISC1, disrupted in schizophrenia 1; Dlx5/6, distal-less homeobox 5 and 6 intergenic region; DN-DISC1, dominant-negative DISC1; *DTNBP1*, dysbindin; *ERBB4*, receptor tyrosine-protein kinase *ERBB4* (also known as *HER4*); *GRIN1*, glutamate receptor, ionotropic, NMDA 1; *NRG1*, neuregulin 1; PPI, prepulse inhibition; *Ppp1r2*, protein phosphatase inhibitor 2; PV, parvalbumin. **DISC1* also segregates with bipolar disorder and depression.

studies indicate that GABAergic dysfunction in this disorder might be a consequence of more-subtle alterations in inhibitory circuits (BOX 2). Interestingly, some of the deficits observed in individuals with schizophrenia are similar to those observed in patients with bipolar disorder[37], which may reflect common underlying causes across these disorders.

Only certain classes of cortical interneuron seem to be affected in schizophrenia. In particular, PV^{+} interneurons in the dorsolateral prefrontal cortex of adults with schizophrenia show a decrease in the expression of *GAD67* (REFS 38,39), possibly rendering these cells less capable of inhibiting pyramidal cells (FIG. 2). As the PV^{+} interneuron class comprises basket and chandelier cells, this defect might reflect a perturbation of both perisomatic and axo-axonic inhibition of pyramidal neurons, as well as impairment of synchronization in the gamma range[40,41]. Consistent with this notion, gamma-frequency oscillations are abnormal in the prefrontal cortex of patients with schizophrenia who are performing working-memory tasks[29,42,43]. Thus, PV^{+} GABAergic interneurons that do not fulfil their inhibitory role might contribute to the cognitive deficits and, perhaps, other symptoms that are associated with schizophrenia.

At least two possible mechanisms exist that could explain the reduced activity of PV^{+} interneurons in schizophrenia (FIG. 2). First, this reduction might reflect defective inhibitory transmission from interneurons to pyramidal cells, a phenotype caused, for example, by a reduced number of inhibitory synapses. Consistent with this idea, patients with schizophrenia seem to have a decrease in the number of cortical chandelier axon terminals[44]. Second, as PV^{+} interneurons are recruited through a potent excitatory drive from pyramidal cells, defects in this process might also lead to impaired inhibitory function of PV^{+} interneurons. Several lines of evidence suggest that deficient excitation of interneurons exists in mouse models of schizophrenia and in humans with the disease. Of note, PV^{+} interneurons are highly sensitive to antagonists of NMDA glutamatergic receptors[45], and these compounds produce a syndrome in humans that resembles schizophrenia[46]. Moreover, conditional deletion of the gene encoding the NR1 subunit of NMDA receptors from PV^{+} interneurons in mice leads to disinhibition of excitatory pyramidal cells, a reduction in neuronal synchrony and, ultimately, the emergence of schizophrenia-like symptoms that are similar to those described after systemic treatment with NMDA receptor antagonists[47–49]. Finally, a reduced excitatory drive to PV^{+} interneurons consistently causes a decrease in *GAD67* mRNA levels[46,49], which might in turn contribute to the reduced activity of this population of interneurons. Thus, to summarize, several possible mechanisms exist that might contribute to the disruption of inhibitory

Table 2 | **Other neurodevelopmental disorders that are associated with disruption of the excitatory–inhibitory balance**

Clinical features*	Gene and/or chromosome associated with human disease	Mouse model of disease	Pathophysiology in mice	Pathological mechanism in mice	Refs
Angelman's syndrome					
Intellectual disability; impaired language; motor problems; frequent laughter, smiling and looking happy; epilepsy	15q11–15q13 deletion in the maternal copy of the chromosome (including *UBE*3A and *GABRB3*)‡	*Ube3a–Gabrb3* deletion in the maternal copy of the chromosome	Increased ultrasound vocalization; epilepsy; motor dysfunction; learning and memory impairment; anxiety	Not known	108
		Ube3a$^{+/-}$ (null allele inherited from mother)	Abnormal dendritic spines; impaired motor function and spatial learning; epilepsy	Not known	106
		Gabrb3$^{-/-}$	Epilepsy; impairment of motor coordination; hyperactivity	Reduced $GABA_A$ receptor density; impaired inhibition	109
Autism					
Deficits in social interaction and communication; repetitive behaviours or interests; substantial comorbidity with epilepsy and fragile X syndrome	*NLGN3* (Xq13)	*Nlgn3*$^{-/-}$	Reduced ultrasound vocalization; lack of social novelty preference; olfactory deficiency	Not known	167
		Nlgn3^{R451C}	Mild impairment of social interactions; enhanced spatial learning abilities (results contested by other studies)	Increased cortical inhibitory function (phenotype not present in *Nlgn3*$^{-/-}$ mice)	94,168
	NLGN4 (Xp22)	*Nlgn4*$^{-/-}$	Reduced social interactions and ultrasonic vocalization	Not known	169
	NRXN1§ (2p16)	*Nrxn1*$^{-/-}$	Decreased PPI; increased grooming; defects in nesting; no impairment in social behaviours or spatial learning	Decreased cortical excitatory function with no obvious defects in inhibition	170
	SHANK3‖ (22q13)	*Shank3*$^{-/-}$	Reduced social interactions and ultrasonic vocalization	Decreased cortical excitatory neurotransmission	97
	CNTNAP2¶ (7q35)	*Cntnap2*$^{-/-}$	Impaired communication; stereotyped movements; impaired sociability; epilepsy	Reduced number of interneurons; migration deficits; abnormal cortical synchrony	105
Down's syndrome					
Intellectual disability; learning and memory deficits	~300 genes on chromosome 21	Ts65Dn#	Impaired spatial memory and context discrimination	Excessive inhibition in hippocampal circuits	122
Fragile X syndrome					
Intellectual disability; learning impairments; comorbidity with autism and epilepsy	*FMR1* (Xq27)	*Fmr1*$^{-/-}$	Impaired social interaction; learning deficits; decreased anxiety	Impaired GABAergic neurotransmission (various causes reported, including a reduction in the number of interneurons and GABA receptors, and a decrease in the expression of GAD65 and GAD67)	111–116
Neurofibromatosis type I					
Neurofibromas; learning disabilities and other cognitive impairments	*NF1* (17q11)	*Nf1*$^{+/-}$	Spatial learning deficits	Increased cortical inhibition	124
		Syn1–Cre; *Nf1*$^{lox/+}$ (deletion of *Nf1* in neurons)	Spatial learning deficits	Not determined	125
		Dlx5/6–Cre; *Nf1*$^{lox/+}$ (deletion of *Nf1* in forebrain GABAergic neurons)	Spatial learning deficits	Increased cortical inhibition owing to augmented GABA release from interneurons	125

Table 2 (cont.) | **Other neurodevelopmental disorders that are associated with disruption of the excitatory–inhibitory balance**

Clinical features*	Gene and/or chromosome associated with human disease	Mouse model of disease	Pathophysiology in mice	Pathological mechanism in mice	Refs
Rett's syndrome					
Progressive developmental disability; motor abnormalities; seizures; features of autism	*MECP2*** (Xq28)	Nestin–Cre; *Mecp2*$^{lox/y}$ (deletion of *Mecp2* in CNS neurons and glia)	Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability; breathing problems	Not known	74,75
		Viatt–Cre; *Mecp2*$^{lox/y}$ (deletion of *Mecp2* in GABAergic neurons)	Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability; breathing problems	Impaired inhibitory function owing to decreased levels of GAD65, GAD67 and GABA	76
		Dlx5/6–Cre; *Mecp2*$^{lox/y}$ (deletion of *Mecp2* in forebrain GABAergic neurons)	Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability	Not determined	76

CNTNAP2, contactin-associated protein-like 2; *FMR1*, fragile X mental retardation 1; *GABRB3*, GABA receptor subunit β3; GAD, glutamate decarboxylase; *MECP2*, methyl-CpG-binding protein 2; *NF1*, neurofibromin 1; *NLGN*, neuroligin; *NRXN1*, neurexin 1; PPI, prepulse inhibition; *SHANK3*, SH3 and multiple ankyrin repeat domains gene 3; *Syn1*, synapsin 1; *UBE3A*, ubiquitin protein ligase E3A; *Viatt*, vesicular inhibitory amino acid transporter. *Neurological and neuropsychological phenotypes exclusively. ‡These genes are expressed in the brain predominantly from the maternal allele, which may explain the genetics of this disorder. *UBE3A* and *GABRB3* have also been linked to autism and Rett's syndrome. §*NRXN1* copy number variants have been linked to schizophrenia. ‖*De novo* mutations in *SHANK3* have also been identified in individuals with schizophrenia. ¶Disease-causing mutations in *CNTNAP2* were first identified in cortical dysplasia focal epilepsy syndrome. #These mice are trisomic for a fragment of mouse chromosome 16, which carries genes that are orthologous to those found in the region of human chromosome 21 that is thought to be responsible for many Down's syndrome phenotypes. **A missense mutation in *MECP2* has been found to be associated with childhood-onset schizophrenia, and some patients diagnosed with Angelman's syndrome carry mutations in this gene.

function that is observed in schizophrenia, all of which converge and identify PV$^+$ interneurons as central elements in this disorder. As several distinct classes of cortical PV$^+$ interneuron exist[50], a more-detailed evaluation of their status in schizophrenia is required.

On the basis of the information summarized above, it seems reasonable to postulate that variation in genes that control the development of PV$^+$ interneurons might confer susceptibility to schizophrenia[51]. One of these genes encodes the receptor tyrosine-protein kinase ERBB4, which is a transmembrane receptor that is preferentially expressed by embryonic and postnatal PV$^+$ interneurons[52–54]. ERBB4 seems to perform sequential functions during the development of PV$^+$ interneurons. First, it directs the migration of these interneurons towards the cerebral cortex in response to neuregulin 1 (NRG1), which acts as a chemoattractive molecule for these cells[55]. Second, it controls the integration of different populations of PV$^+$ interneurons into specific cortical circuits, a function that seems to be also mediated by NRG1. Indeed, conditional deletion of *Erbb4* in PV$^+$ chandelier cells in the mouse cortex causes these cells to make fewer synapses onto pyramidal cells[52], a phenotype that is highly reminiscent of the findings from post-mortem analyses of brain tissue from patients with schizophrenia[44]. In addition, PV$^+$ interneurons lacking ERBB4 receive less input from pyramidal cells than do PV$^+$ interneurons that express this protein[52,56]. As a result, pyramidal cells tend to be overexcitable, and mice lacking ERBB4 exclusively in PV$^+$ neurons exhibit schizophrenia-relevant phenotypes (including impaired working memory) that are similar to those observed in *Nrg1*- or *Erbb4*-null mutant mice[57]. Considering that NRG1 and ERBB4 are encoded by genes that have been repeatedly linked to schizophrenia[58–61], the findings described above provide a plausible biological link between this signalling system and the aetiology of this disorder.

Another schizophrenia susceptibility gene that has been implicated in the development of cortical PV$^+$ interneurons is disrupted in schizophrenia 1 (*DISC1*). This gene was initially linked to neuropsychiatric disease through the discovery that a large chromosomal translocation in the middle of its open reading frame segregated with schizophrenia, bipolar disorder and depression in a large Scottish family[62]. DISC1 is a scaffolding protein that is widely expressed in the brain and that has multiple functions during brain development and in the adult brain[63]. Among these functions, several lines of evidence suggest that DISC1 is required, probably in a non-cell-autonomous manner, for the normal functioning of cortical PV$^+$ interneurons. For example, transgenic mice that overexpress a truncated form of human DISC1 in pyramidal cells have reduced PV immunoreactivity in the prefrontal cortex[64], and similar findings have been reported following *Disc1* knockdown in pyramidal cells[65]. Although it is presently unclear whether the reduction in PV immunoreactivity reflects a loss of PV$^+$ interneurons or abnormal expression of this protein, these results strongly suggest that DISC1 function is required for the normal functioning of specific classes of cortical GABAergic cells.

As stated, the abnormal function of DISC1 has been linked to various diseases. Given the scaffolding function of this protein, and hence its multiple binding partners, it is conceivable that the specific disease to which a DISC1 variant confers susceptibility may be affected by concurrent deficits in DISC1 binding partners. One of the possible binding partners of DISC1 is dysbindin, which is encoded by *DTNBP1*

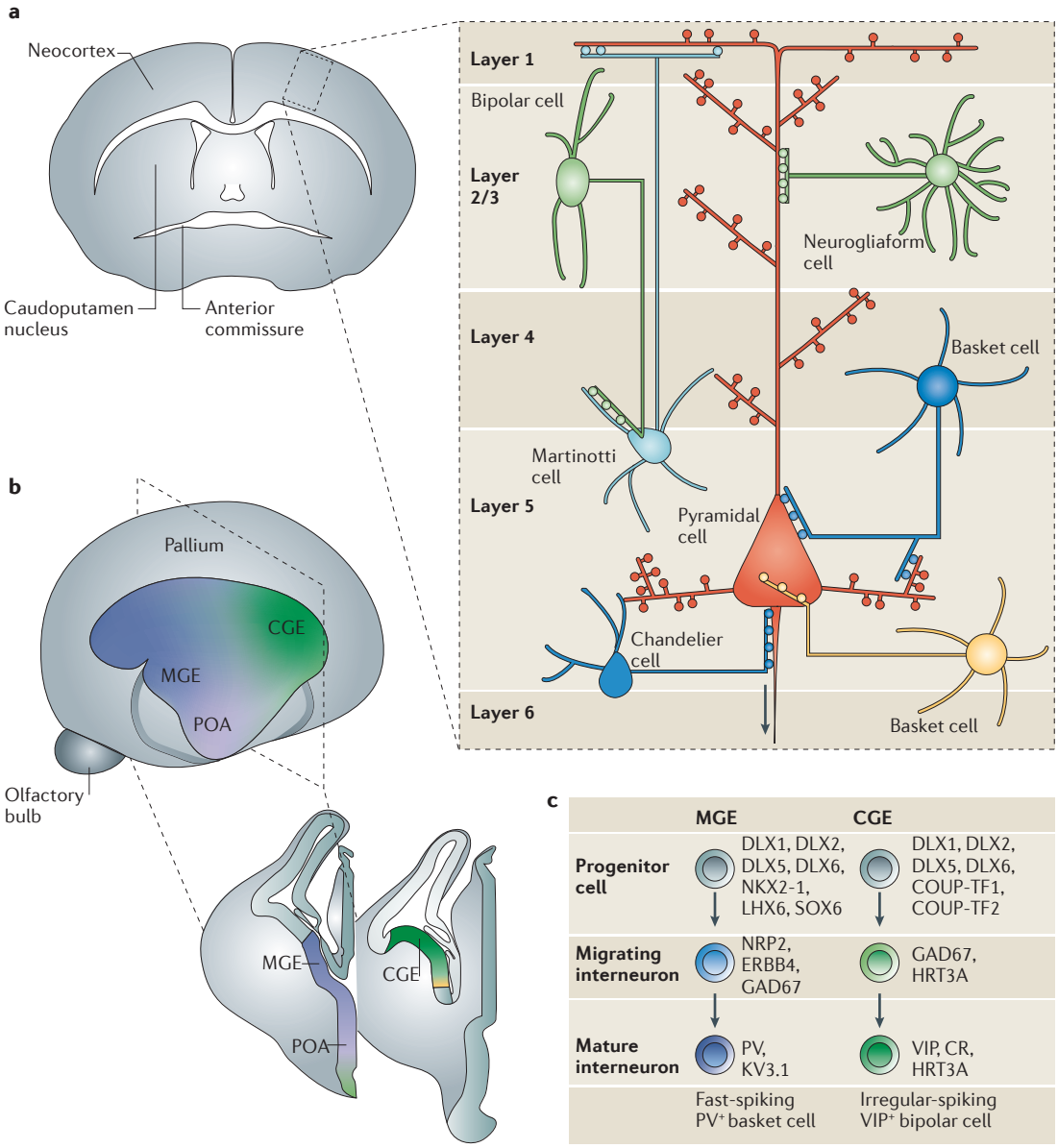


Figure 1 | **Cortical interneuron diversity and its developmental origin.** Different classes of cortical interneuron are distinguished on the basis of their morphology, neurochemical content, intrinsic electrophysiological properties and pattern of connectivity. **a** | In the mouse neocortex, for example, basket cells constitute a relatively heterogeneous population of interneurons that primarily target the soma and basal dendrites of pyramidal cells, whereas chandelier cells synapse on the axon initial segment. Other classes of interneuron, such as Martinotti and neurogliaform cells, primarily contact the dendrites of pyramidal cells, whereas some types of interneuron, including bipolar cells, are specialized in targeting other interneurons. **b** | The main sources of cortical interneurons are the caudal ganglionic eminence (CGE), the medial ganglionic eminence (MGE) and the preoptic area (POA). These regions contain progenitor cells that can be distinguished by their expression of transcription factors and other proteins. Each progenitor region produces a particular group of interneurons, although some interneuron classes may emerge from different progenitor domains. For example, the MGE gives rise to fast-spiking interneurons that express the calcium-binding protein parvalbumin (PV) — such as many basket and chandelier cells — and non-fast-spiking interneurons that contain the neuropeptide somatostatin. By contrast, the CGE produces bipolar interneurons that express vasoactive intestinal peptide (VIP) (sometimes in combination with the calcium-binding protein calretinin (CR)) as well as multipolar interneurons that contain neuropeptide Y or the glycoprotein reelin. The POA seems to produce a small fraction of different classes of cortical interneurons. **c** | Interneurons are largely specified at the progenitor cell state or shortly after becoming postmitotic. This process is controlled by a combination of transcription factors that regulate the expression of effector proteins that characterize each class of interneuron. The schematic depicts some of the transcription factors and effector proteins that define the identity of two main classes of interneurons at different stages of differentiation. COUP-TF, COUP transcription factor; DLX, homeobox protein DLX; ERBB4, receptor tyrosine-protein kinase ERBB4; GAD67, 67 kDa glutamate decarboxylase; HTR3A, 5-hydroxytryptamine receptor 3A; KV3.1, potassium voltage-gated channel subfamily C member 1; LHX6, LIM/homeobox protein LHX6; NKX2-1, homeobox protein NKX2-1; SOX6, transcription factor SOX6.

Box 2 | **The GABAergic hypothesis in neuropsychiatric disease**

Defects in GABAergic neurotransmission have now been linked to multiple neuropsychiatric conditions, but they were first associated with schizophrenia[150]. The observation that some patients with schizophrenia had reduced numbers of interneurons in the prefrontal and cingulate cortices led Benes and colleagues to propose that reduced GABAergic inputs to pyramidal cells may contribute to the pathophysiology of the disorder[36]. The subsequent finding that such patients had increased $GABA_A$ receptor binding activity in pyramidal cells was thought to be consistent with this idea[151,152], but several other studies failed to find similar reductions in the number of interneurons in individuals with schizophrenia[38,153,154]. Although interneuron loss might exist in some patients with this disorder, it is now more widely accepted that GABAergic deficits preferentially occur at the level of specific synapses, as was originally proposed by Lewis and colleagues[44].

The idea that GABAergic deficits may also underlie the pathophysiology of autism dates to the early 2000s, when Hussman, Rubenstein and Merzenich proposed that at least some forms of autism may result from the disruption of the normal excitatory–inhibitory balance that exists in cortical circuits[155,156]. Although the evidence obtained from post-mortem brain tissue analyses is still relatively sparse, several studies have shown that patients with autism have specific defects in the GABAergic system[157,158]. The association between abnormal interneuron function and neuropsychiatric conditions has received increasing attention in the past few years (TABLE 2).

(REF. 66), another important schizophrenia susceptibility gene[67]. Dysbindin is involved in intracellular trafficking (including the trafficking of dopamine receptors[68]), and the expression of this protein is reduced in the prefrontal cortex and hippocampus of patients with schizophrenia[69,70]. Interestingly, the excitability of cortical and striatal PV^+ interneurons is decreased in *Dtnbp1*-knockout mice, and this leads to reduced inhibition of pyramidal cells[68]. Although the mechanisms underlying this alteration remain unclear, it is worth noting that the net effect on cortical circuitry is remarkably similar to that found in conditional *Erbb4*-mutant mice[52,56,57] (FIG. 1).

In summary, post-mortem analyses and mouse model studies strongly suggest that GABAergic deficits exist in schizophrenia and that susceptibility genes may have an important role in the development of inhibitory neurons (TABLE 1). These studies also illustrate how defects in the development of a specific group of GABAergic cells — fast-spiking PV^+ interneurons — might predispose an individual to a particular psychiatric condition.

Autism spectrum disorders

The results summarized above suggest that the pathophysiology of schizophrenia might involve remarkable cellular specificity. By contrast, other neurodevelopmental disorders might have more-general disruptions to the balance between cortical excitation and inhibition. Such a scenario probably occurs in Rett's syndrome, an autism spectrum disorder (ASD) that is characterized by impaired language skills, cognitive deficits, stereotypic behaviours and respiratory problems[71]. In contrast to other neuropsychiatric conditions, which have complex genetics, Rett's syndrome is usually caused (in 90% or more of cases) by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2)[72]. MECP2 is a nuclear protein that binds methylated DNA and functions as a transcriptional repressor[71,73]. Unfortunately, MECP2 is ubiquitously expressed in the brain and, thus, it has been particularly difficult to identify its function in specific neural circuits.

As the general function of MECP2 is in the regulation of gene expression, one could argue that deleting *MECP2* from any particular neuronal circuit would reproduce some of the symptoms of Rett's syndrome. Consistent with this idea, deletion of *Mecp2* from the entire nervous system in mice reproduces most of the neurological phenotypes of this syndrome[74,75], whereas neuron- or region-specific deletions of *Mecp2* cause neurological phenotypes that resemble some of the features of Rett's syndrome[76–80]. However, MECP2 function seems to be more crucial in some neural circuits than in others, which strongly suggests that Rett's syndrome (and perhaps other ASDs) might emerge as a consequence of abnormal function in specific neuronal populations (FIG. 3). Of note, a recent study showed that specific deletion of *Mecp2* from forebrain GABAergic neurons in mice recapitulates most of the features of Rett's syndrome, including repetitive behaviours, increased sociability, cognitive deficits, impaired motor coordination and abnormal electroencephalographic hyperexcitability[76]. These results are consistent with previous work showing that the cortex of *Mecp2*-null mice has deficient inhibitory function and might be prone to hyperexcitability[81–83], and they support the idea that the simultaneous disruption of GABAergic circuits in the basal ganglia, amygdala and cerebral cortex might underlie the emergence of autism-like symptoms. The extent to which each of these structures contributes to the pathophysiology of Rett's syndrome remains to be elucidated, as does the precise contribution of excitatory neurotransmission to this process.

The mechanisms leading to the impairment of inhibitory function in *Mecp2*-null mice are not yet entirely clear, because MECP2 binds throughout the genome and probably has the potential to regulate the same set of genes in different classes of neurons[71]. However, it is conceivable that the function of MECP2-targeted genes might be particularly important in GABAergic neurons. For example, MECP2 has been shown to regulate the expression of brain-derived neurotrophic factor (BDNF)[84], which has a crucial role in the development and maturation of inhibitory connections in the brain[85]. In addition, MECP2 controls the expression of *Gad65* and *Gad67* in GABAergic neurons in a cell-autonomous manner[76]. In the absence of MECP2, inhibitory neurons contain lower than normal levels of GABA, and this deficiency alone might be sufficient to explain the abnormal synaptic properties of these cells. Collectively, these results indicate that cell-autonomous defects in GABAergic neurons that are distributed throughout several key neural systems in the telencephalon are sufficient to reproduce many of the clinical features of Rett's syndrome.

Further evidence exists to support the involvement of GABAergic deficits in autism and related disabilities; for example, several genetic studies have linked genes encoding proteins of the neuroligin–neurexin complex with susceptibility to autism or Asperger's syndrome[86–90]. Neuroligins and neurexins are neural adhesion molecules that cooperate in the formation of brain synapses

Forebrain
The forebrain is the most anterior region of the brain and includes the diencephalon as well as the telencephalon. The basal ganglia, the amygdala and the cerebral cortex are all parts of the telencephalon.

through specific heterophilic interactions[91]. Neuroligin–neurexin complexes promote both glutamatergic and GABAergic synapse formation[92], and analyses of their function in mice indicates that they are important for the maintenance of an adequate balance between neuronal excitation and inhibition in the cerebral cortex[93,94]. The cellular basis for this requirement, however, remains unknown. A possible clue to this puzzle comes from the recent analysis of mutant mice lacking SH3 and multiple ankyrin repeat domains gene 3 (*Shank3*). *Shank3* encodes a scaffolding protein that interacts with neuroligins and has been linked to ASDs[95,96]. Consistently, *Shank3*-null mutant mice display repetitive grooming behaviour and deficits in social interaction, which are reminiscent of some of the symptoms associated with ASDs[97]. Interestingly, SHANK3 seems to be crucial for the normal development and function of the glutamatergic synapses that are made by cortical pyramidal cells onto GABAergic striatal neurons, but it is dispensable for glutamatergic neurotransmission between different pyramidal cells in the hippocampus[97]. Together with the observations made in conditional *Mecp2*-mutant animals[80], these results reinforce the notion that striatal function is perturbed in ASDs. In addition, these data suggest that the excitatory–inhibitory imbalance that is observed in other mouse models of ASDs might be related to defects in excitatory synapses that form onto GABAergic interneurons.

The gene encoding contactin-associated protein-like 2 (CNTNAP2) has also attracted a lot of interest in the field of autism since it was originally linked to a relatively rare syndrome that is characterized by cortical dysplasia, focal epilepsy and a high frequency of autism[98]. Since then, several genetic studies have provided additional evidence for the involvement of CNTNAP2 in autism[99–102]. *CNTNAP2* is a member of the neurexin

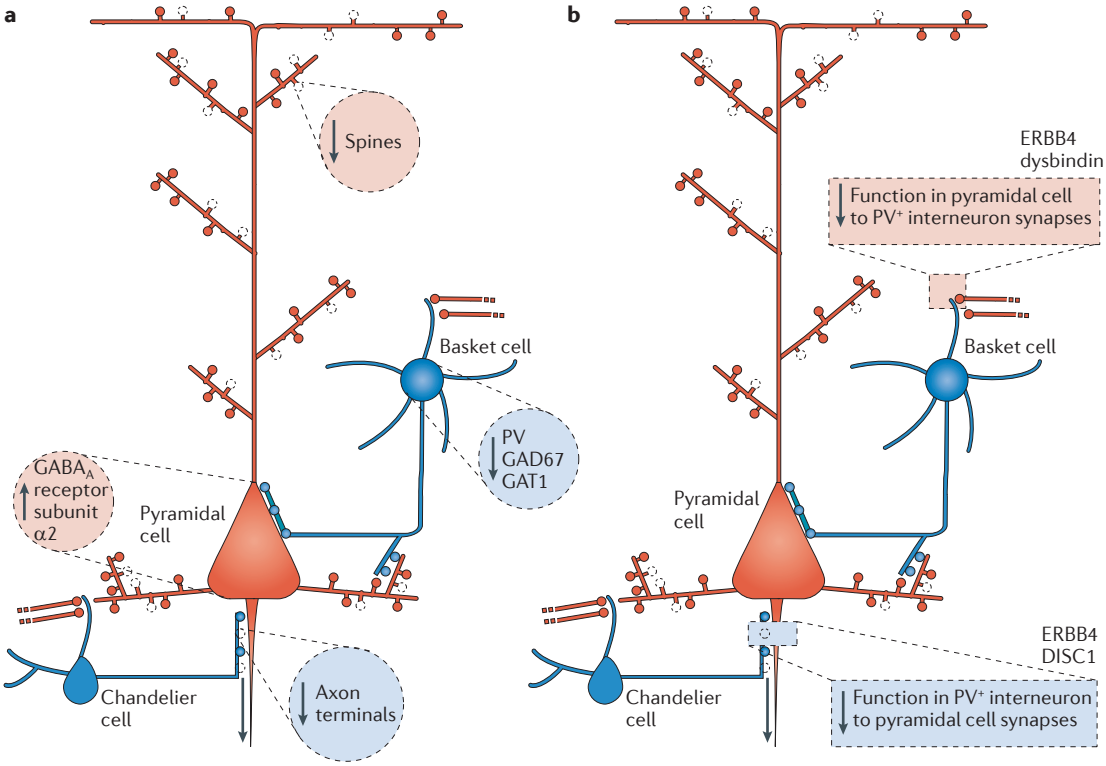


Figure 2 | **Alterations found in cortical circuits in patients with schizophrenia and in animal models of this disorder. a** | Reduced expression of 67 kDa glutamate decarboxylase (*GAD67*) mRNA in parvalbumin-expressing (PV$^+$) interneurons is a widely replicated finding in patients with schizophrenia and in animal models of this disorder. Other changes in the expression of GABA-related molecules have been interpreted as possible compensatory mechanisms to a primary reduction of inhibitory function[151,163,164]. For example, reduced expression of sodium- and chloride-dependent GABA transporter 1 (GAT1), a protein responsible for the re-uptake of GABA at synapses, and increased numbers of GABA$_A$ receptors have been observed in pyramidal cells. The numbers of dendritic spines are also reduced in pyramidal cells taken from patients with schizophrenia[165,166]. **b** | Genetic studies using mouse models suggest that two possible mechanisms underlie the interneuron defects that are found in schizophrenia: a presynaptic mechanism that is caused by a cell-autonomous impairment of specific classes of interneuron, such as chandelier cells (blue box), and/or a postsynaptic mechanism that is produced by a reduction of excitatory drive to PV$^+$ interneurons (tan box). A possible loss of inhibitory drive to pyramidal cells by PV$^+$ interneurons has been observed in mice with a conditional mutation in the gene encoding receptor tyrosine-protein kinase ERBB4 and in mice with impaired function of disrupted in schizophrenia 1 (DISC1) (blue box). In addition, mice lacking ERBB4 or dysbindin display reduced activation of PV$^+$ interneurons (tan box). As a consequence of the defects in interneuron function, it has been hypothesized that pyramidal cells might be hyperactive but asynchronous in the cortex of patients with schizophrenia.

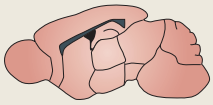
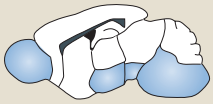
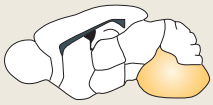
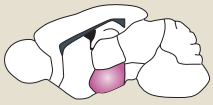
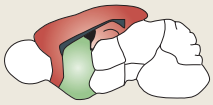
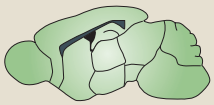
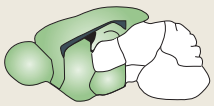
Brain region	Genetic deletion	Repetitive behaviour	Motor incoordination	Ataxia	Breathing irregularities	Anxiety	Social interaction	Aggressive behaviour
	Nestin–Cre; *Mecp2*$^{lox/y}$ CNS neurons		+	+	+	+		
	TH–Cre; *Mecp2*$^{lox/y}$ Catecholaminergic neurons	–	+		–	–	–	–
	*Pet1*–Cre; *Mecp2*$^{lox/y}$ Serotonergic neurons	–	–		–	–	–	+
	*Sim1*–Cre; *Mecp2*$^{lox/y}$ Hypothalamic neurons					+		+
	CaMKIIα–Cre; *Mecp2*$^{lox/y}$ Pyramidal cells in the cortex and GABAergic neurons in the striatum		+			+	+	
	*Viaat*–Cre; *Mecp2*$^{lox/y}$ GABAergic neurons	+	+	+	+	+	+	+
	Dlx5/6–Cre; *Mecp2*$^{lox/y}$ GABAergic neurons in the forebrain	+	+	+	–	–	+	–

Figure 3 | **Genetic dissection of methyl-CpG-binding protein 2 function in the mouse brain.** Methyl-CpG-binding protein 2 (MECP2) is widely expressed throughout the brain. Behavioural analyses of conditional mutant mice, in which MECP2 function has been deleted from specific neuronal populations, have shed light on the contribution of distinct neuronal circuits to the functional deficits observed in *Mecp2*-null mutant animals. These deficits resemble those found in patients with Rett's syndrome. Different neurological symptoms can be attributed at least in part to MECP2 deficiency in specific brain neurons. Plus and minus signs indicate the presence and absence, respectively, of a particular phenotype. No information exists for some of the mouse lines in the listed behavioural tests (indicated by empty cells). CaMKIIα, calcium/calmodulin-dependent protein kinase type II subunit α; Dlx5/6, distal-less homeobox 5 and 6 intergenic region; *Mecp2*, methyl-CpG-binding protein 2; *Pet1*, PC12 ETS domain-containing transcription factor 1; *Sim1*, single-minded homologue 1; TH, tyrosine hydroxylase; *Viatt*, vesicular inhibitory amino acid transporter.

superfamily that encodes a transmembrane protein that is widely expressed in the nervous system. Although CNTNAP2 is best known for its role at the nodes of Ranvier in the peripheral nervous system[103], recent work in humans has shown that some of the *CNTNAP2* variants that are linked to autism are also associated with perturbed brain functional connectivity in humans[104]. Interestingly, the cortex of *Cntnap2*-knockout mice seems to have a reduced number of interneurons[105]. In addition, these mice have epilepsy and deficits in all three core autism behavioural domains (that is, stereotypic behaviours, sociability and communication). Post-mortem studies should help to clarify whether similar GABAergic deficits are also found in patients carrying homozygous mutations in *CNTNAP2* (REF. 98).

In summary, several lines of evidence support the notion that GABAergic dysfunction has an important role in the aetiology of autism and related illnesses. As for other neurodevelopmental disorders, it is evident that defects in inhibitory circuits are perhaps only one of several alterations underlying the complex behavioural deficits observed in patients with autism.

Intellectual disabilities

A general disruption of inhibitory circuits might contribute to the cognitive deficits that are observed in various other neurodevelopmental disorders. Angelman's syndrome is a genetic condition that is associated with epilepsy and is caused by deletions of, or mutations in, the gene encoding ubiquitin protein ligase E3A

(UBE3A)[106,107]. This protein ubiquitylates other proteins and thus marks them for degradation, and so it is likely to influence many different biological events. Interestingly, individuals with *UBE3A* mutations usually have a milder condition than patients with Angelman's syndrome who have 15q11–15q13 deletions, and this phenomenon has led to the suggestion that deletion of other genes in this region might contribute to the latter disorder[108]. Among these genes, the $GABA_A$ receptor subunit β3 gene (*GABRB3*) is a good candidate because mice harbouring a mutant variant of this gene display epilepsy and behavioural deficits that are reminiscent of Angelman's syndrome[109]. In line with this idea, human imaging studies indicate that defective inhibitory function exists in the cortex of patients with Angelman's syndrome[110].

Mouse models of fragile X syndrome — a cognitive neurodevelopmental disorder with clinical manifestations that are reminiscent of autism — have notable defects in GABAergic cortical circuits[111–114]. Fragile X syndrome results from loss-of-function mutations in the gene encoding fragile X mental retardation 1 protein (FMR1), which is an mRNA-binding protein that is widely expressed in the brain[115]. As in the case of MECP2 in Rett's syndrome, the function of FMR1 in different neural circuits might explain the complexity of fragile X syndrome. For example, the extensive neocortical deficits might be at the root of the intellectual disabilities that characterize this syndrome, whereas the altered inhibitory function in the amygdala might account for some of the behavioural components of the syndrome[111].

The mechanisms responsible for the disruption of inhibitory transmission in fragile X syndrome remain unclear, as very different alterations in GABAergic signalling have been reported in different studies. The defects seem to range from a reduction in the number of GABAergic interneurons or their synapses[111,116] to defects in the expression of GABA-synthesizing enzymes or $GABA_A$ receptors[111,117]. Inhibitory deficits might be secondary to alterations in glutamatergic transmission, because reducing the levels of metabotropic glutamate receptor 5 (mGluR5) in *Fmr1*-null mice rescues many of the neurological phenotypes that are observed in the absence of FMR1 (REF 118). Nevertheless, additional studies are required to unequivocally establish the precise anatomical basis underlying the possible excessive activation of mGluRs in fragile X syndrome.

Defective inhibitory activity is only one possible means to disrupt the excitatory–inhibitory equilibrium in the brain. Insights from two other neurological conditions, namely Down's syndrome and neurofibromatosis type I, suggest that excessive inhibitory activity in key neural circuits might also initiate pathological processes. Down's syndrome is caused by trisomy of chromosome 21 and is characterized by intellectual disability and distinctive facial features. However, individuals with this condition also display specific deficits in cognitive processes that involve hippocampal function, such as spatial memory[119]. These deficits have been replicated in a mouse model of Down's syndrome[120], and the underlying mechanism seems to involve excessive inhibition in the dentate gyrus of the hippocampus[121,122].

Learning deficits are also common in patients with neurofibromatosis type I, an autosomal dominant disorder that is best known for the characteristic peripheral tumours that appear in the skin. Neurofibromatosis is caused by mutations in the gene encoding neurofibromin (NF1), which is a protein that is widely expressed in neurons and glia[123]. Like patients with this disease, mice with mutations in *Nf1* display spatial-learning deficits, and this impairment seems to be caused by enhanced inhibitory activity in the hippocampus[124]. Genetic deletion of *Nf1* exclusively from forebrain GABAergic neurons leads to a similar phenotype, and this seems to be caused by the abnormal enhancement of GABA release from these cells in the absence of NF1 (REF. 125). These studies illustrate how increased inhibitory activity in certain brain areas can contribute to disease.

Environmental influence

Neurodevelopmental disorders have a strong hereditary component; however, environmental factors probably also have a central role in their aetiology[126,127]. In the context of GABAergic dysregulation, it is necessary to define the environmental factors that trigger disease in genetically predisposed individuals. Beyond the involvement of epigenetic regulatory mechanisms in the pathogenesis of some of these conditions[128], several environmental factors seem to influence GABAergic interneurons. For example, there is a high prevalence of cannabis abuse in first-episode schizophrenia[129], and recent studies indicate that the cortical inhibitory deficits that are observed in patients with schizophrenia are enhanced by cannabis[130]. Cognitive impairment that is associated with cannabis consumption seems to be dependent on a specific subtype of interneuron that expresses the neuropeptide cholecystokinin (CCK) and that contains high levels of cannabinoid receptor 1 (CB1)[131]. Activation of CB1 suppresses GABA release from synaptic terminals of CCK-expressing (CCK^+) interneuron cells[132], hinting at a possible mechanism through which cannabis abuse can enhance cortical disinhibition and the asynchronous firing of pyramidal cells. In addition, CB1 molecules influence the target selection of CCK^+ interneurons during synaptogenesis[133]. Considering that inhibitory circuits continue to develop well into adolescence in humans, early drug abuse can influence the final wiring of cortical GABAergic circuits. These studies support the hypothesis that cannabis abuse increases the risk of schizophrenia by further enhancing GABAergic dysfunction in genetically at-risk individuals.

Many environmental events that have been associated with an increased risk of neuropsychiatric illness occur during the prenatal or perinatal periods of life, and these events include labour-delivery complications and infections[134]. Oxytocin release initiates parturition in mammals, and recent studies have revealed that this hormone also mediates the excitatory-to-inhibitory switch of GABA activity that occurs before birth[135]. It has been hypothesized that this switch reduces neuronal activity, thereby protecting fetal neurons from hypoxia, which is a perinatal risk factor for many neurodevelopmental disorders[135]. The association of some oxytocin

Cannabis
Cannabis is a genus of plants that contain high levels of Δ9-tetrahydrocannabinol, a psychoactive substance that acts as a partial agonist of cannabinoid receptors in the brain and that is responsible for the stimulating effect that is associated with cannabis-derived drugs.

Box 3 | **Temporal issues in developmental disorders**

The timing of genetic dysregulation might critically influence clinical outcomes in neurodevelopmental disorders. Many proteins are involved in development at multiple stages, so it is conceivable that variants of a particular gene may impair function at different stages of development. For example, various alleles of the gene encoding receptor tyrosine-protein kinase ERBB4 have been linked to schizophrenia. These alleles range from rare structural variants that produce a truncated form of the receptor (that lacks the entire intracellular kinase domain)[159] to alleles containing intronic single-nucleotide polymorphisms that modify the expression of different ERBB4 isoforms[160]. The various alleles might affect interneuron development in different ways, a hypothesis that is supported by recent findings in mice. Early deletion of *Erbb4* (equivalent to a 'strong' loss-of-function allele) causes a sizeable reduction in the number of parvalbumin-expressing (PV^+) interneurons in the postnatal cortex, owing to defects in their migration[55,161]. By contrast, late removal of this gene (equivalent perhaps to a 'mild' loss-of-function allele) bypasses the migratory defects and leads to a cortex with a normal number of interneurons but wiring abnormalities[52]. The functional consequences of the two types of mutation are also different. The loss of PV^+ interneurons in *Erbb4*-null animals disrupts gamma-frequency oscillations and renders these mice more susceptible to the generation of epileptiform activity in response to drugs[162], whereas conditional removal of *Erbb4* disrupts behaviour but does not seem to cause epilepsy[57]. These observations indicate that there might be a close interaction between genetic variation and developmental windows that shapes specific disorders.

receptor variants with autism further supports this gene–environment interaction[88].

Infections during pregnancy can also affect brain development by triggering the expression of pro-inflammatory cytokines. For instance, maternal interleukin-6 production during infection impairs the balance of cytokines at perinatal stages and causes behavioural defects in offspring[136]. Intriguingly, interleukin-6 signalling reproduces the effects of NMDA receptor antagonists on PV^+ interneurons[137]; these effects are thought to be mediated by a persistent increase in superoxide owing to the activation of NADPH oxidase[138]. These studies suggest that cytokines can alter the oxidative balance in this population of interneurons, and this in turn might contribute to the impaired function of these interneurons in schizophrenia.

Conclusions and perspectives

Elucidation of the biological mechanisms underlying the aetiology of psychiatric disorders will be crucial for the development of effective treatments for these conditions. In this context, the hypothesis that developmental disruption of GABAergic interneurons, resulting from various causes, underlies the aetiology of some of these conditions is gaining increasing support[49,52,76]. It is worth emphasizing that alterations to GABAergic circuits during development do not simply involve the loss of a given type of inhibitory mechanism. Rather, GABAergic interneurons are crucial for the maturation of neural circuits, most notably during the phases of activity-dependent remodelling[3,139]. Consequently, the phenotypes that eventually emerge following disrupted interneuron development probably reflect the dynamic adaptation of neural circuits to the activity-dependent processes that shape the brain during the first years of life. It is also worth noting that additional pathophysiological mechanisms involving other neurotransmitter systems are probably perturbed in each of these conditions, thereby contributing to the symptomatic complexity of such disorders.

Despite recent progress, we are a long way from fully understanding the role of GABAergic interneurons in neural circuits, let alone their potential pathophysiological roles in the diseased brain. Although the study of complex neuropsychiatric disorders in rodents has serious limitations[140], mouse genetics are becoming increasingly important for gaining a better understanding of the biological activity of candidate susceptibility genes during brain development. The genetic dissections of the functions of ERBB4, MECP2 and NF1 represent excellent examples of the power of this approach. However, additional genetic studies using mice with gene deletions in more-specific cell populations will be needed to clarify the precise anatomical basis for neuropsychiatric disorders. Furthermore, we will need to establish the function of each of these genes during specific developmental windows, as this is another possible source of aetiological variability in these complex disorders (BOX 3). In this context, although some of the genes that have been linked to neuropsychiatric diseases might contribute to the structural development of GABAergic interneurons (for example, *ERBB4*), others might only be required for the normal functioning of these cells (for example, *MECP2*). Such differences might be extremely important when designing rational therapies for these disorders. In the case of Rett's syndrome, for example, restoring MECP2 function after brain development or generally enhancing synaptic maturation might be sufficient to ameliorate neurological symptoms, as shown in animal models[141–143]. By contrast, early interventions might be required to correct the wiring abnormalities that seem to exist in other neurodevelopmental disorders.

A picture is emerging that links interneuron dysfunction to cognitive impairment in psychiatric disease. However, it is clear that a greater understanding of the involvement of different classes of GABAergic interneurons in the aetiology of psychiatric disorders is needed to define the precise pathophysiological mechanisms that occur in each condition. In the case of schizophrenia, converging evidence from post-mortem studies and animal models has contributed to the identification of specific cortical inhibitory circuits that might be affected in the disorder (FIG. 1). In a similar manner, future studies should bring us closer to being able to identify specific pathophysiological entities at the level of defined neuronal circuits for other neurodevelopmental disorders. Such a scenario is within reach, and this knowledge should be used to rationalize the design of effective treatments.

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Competing interests stateme

The authors declare no competing financial interests.

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