Interneuron dysfunction in psychiatric disorders

Oscar Marín

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.

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. The balance between excitation and inhibition is crucial for cortical function and, consequently, important developmental and physiological mechanisms have evolved to maintain this dynamic equilibrium (BOX 1).

GABAergic interneurons are considered to be the main cellular elements that control hyperexcitability in the brain. Indeed, severe GABAergic deficits can cause pathological hyperexcitability and many of the genes that have been linked to epilepsy regulate interneuron development and function. 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, and they do so as part of an extremely dynamic process, which is often dependent on the brain state.

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 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 fulfill in the healthy brain should provide insight into the possible contribution of abnormal interneuron function to neuropsychiatric illness. Development of such
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. The various cortical interneuron subtypes have distinct or only partially overlapping morphological, electrophysiological and neurochemical characteristics, which makes their unequivocal identification a complex endeavour.

Extensive interneuron diversity also exists in the amygdala and striatum, two other telencephalic regions that are of particular relevance in psychiatric diseases.

Interneurons are ‘tailor-made’ to influence the excitability of pyramidal cells or other interneurons in unique ways. 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, 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). 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. 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 decarboxylase (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.

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.

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.

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. An increasing body of evidence suggests that abnormal inhibitory function in the prefrontal cortex of individuals with schizophrenia might cause the observed cognitive disturbances.

Indeed, deficits in cortical inhibition have been reported both in vivo and in analyses of post-mortem brain tissue from patients with schizophrenia, and cognitive functions such as working memory seem to depend on normal interneuron performance. 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 — and this might certainly be the case in some patients — more-recent
Table 1 | Mouse models of schizophrenia showing disruption of the cortical excitatory–inhibitory balance

<table>
<thead>
<tr>
<th>Schizophrenia-associated human gene (chromosome)</th>
<th>Mouse model of schizophrenia</th>
<th>Pathophysiology in mice</th>
<th>Pathological mechanism in mice</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG1 (8p12)</td>
<td>Nrg1+/−</td>
<td>Defective synaptic plasticity and long-term potentiation; hyperactivity; impaired PPI and working memory</td>
<td>Decreased number of functional NMDA-type glutamate receptors</td>
<td>60, 171</td>
</tr>
<tr>
<td></td>
<td>Nrg1+/− (deletion of type III isoform only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERBB4 (2q33)</td>
<td>Erbb4+/−</td>
<td>Hyperactivity; defective gamma synchrony; hyperexcitability; impaired PPI and working memory</td>
<td>Reduced number of PV− interneurons</td>
<td>55, 60, 162</td>
</tr>
<tr>
<td></td>
<td>Erbb4+/−; HER4lox/lox (deletion of Erbb4; rescued expression of ERBB4 in heart)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nestin−Cre; Erbb4lox/lox (deletion of Erbb4 in neurons and glia)</td>
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<tr>
<td>Dlx5/6−/−; Cre; Erbb4lox/lox (deletion of Erbb4 in forebrain GABAergic neurons)</td>
<td>Cortical hyperexcitability; motor hyperactivity; impaired PPI and working memory</td>
<td>Reduced number of inhibitory synapses to axon initial segment of pyramidal cells; impaired inhibitory neurotransmission; reduced number of excitatory synapses to PV− interneurons</td>
<td>52, 56, 57</td>
<td></td>
</tr>
<tr>
<td>PV−/−</td>
<td>PV−/− (deletion of Erbb4 in PV− neurons)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRIN1 (9q34)</td>
<td>Ppp1r2−/−; Nr1lox/lox (deletion of Grin1 in forebrain GABAergic neurons)</td>
<td>Cortical hyperexcitability; defective gamma synchrony; impaired PPI and working memory; abnormal social behaviour</td>
<td>Reduced excitation of PV− interneurons; reduced levels of PV, GAD67 and GABA; impaired inhibitory function</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>PV−/− (deletion of Grin1 in PV− neurons)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISC1* (1q42.1)</td>
<td>DN−DISC1; Disc1 knockout</td>
<td>Hyperactivity; altered sensorimotor gating; anhedonia-like behaviour</td>
<td>Reduced PV expression or loss of PV− interneurons</td>
<td>64,65</td>
</tr>
<tr>
<td>DNTBP1 (6p22.3)</td>
<td>Dmbp1−/−</td>
<td>Hyperactivity</td>
<td>Reduced excitability of PV− interneurons</td>
<td>70</td>
</tr>
</tbody>
</table>

DISC1, disrupted in schizophrenia 1; Dlx5/6, distal-less homeobox 5 and 6 intergenic region; DN−DISC1, dominant-negative DISC1; DNTBP1, dysbindin; ERBB4, receptor tyrosine-protein kinase ERBB4 (also known as HER4); GRIN1, glutamate receptor, ionotopic, 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 disorder37, 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 range40,41. Consistent with this notion, gamma-frequency oscillations are abnormal in the prefrontal cortex of patients with schizophrenia who are performing working-memory tasks39,42,43. Thus, PV− GABAergic interneurons that do not fulfill 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 terminals44. 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 receptors45, and these compounds produce a syndrome in humans that resembles schizophrenia46. 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 antagonists47–49. Finally, a reduced excitatory drive to PV− interneurons consistently causes a decrease in GAD67 mRNA levels46,47, 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

<table>
<thead>
<tr>
<th>Clinical features*</th>
<th>Gene and/or chromosome associated with human disease</th>
<th>Mouse model of disease</th>
<th>Pathophysiology in mice</th>
<th>Pathological mechanism in mice</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angelman’s syndrome</strong></td>
<td></td>
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</tr>
<tr>
<td>Intellectual disability; impaired language; motor problems; frequent laughter; smiling and looking happy; epilepsy</td>
<td>15q11–15q13 deletion in the maternal copy of the chromosome (including UBE3A and GABRB3)*</td>
<td>Ube3a–Gabrb3 deletion in the maternal copy of the chromosome</td>
<td>Increased ultrasound vocalization; epilepsy; motor dysfunction; learning and memory impairment; anxiety</td>
<td>Not known</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ube3a+/- (null allele inherited from mother)</td>
<td>Abnormal dendritic spines; impaired motor function and spatial learning; epilepsy</td>
<td>Not known</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabrb3–/-</td>
<td>Epilepsy; impairment of motor coordination; hyperactivity</td>
<td>Reduced GABA&lt;sub&gt;\text{A}&lt;/sub&gt; receptor density; impaired inhibition</td>
<td>109</td>
</tr>
<tr>
<td><strong>Autism</strong></td>
<td>NLGN3 (Xq13)</td>
<td>Nlgn3–/-</td>
<td>Reduced ultrasound vocalization; lack of social novelty preference; olfactory deficiency</td>
<td>Not known</td>
<td>167</td>
</tr>
<tr>
<td>Deficits in social interaction and communication; repetitive behaviours or interests; substantial comorbidity with epilepsy and fragile X syndrome</td>
<td>NLGN4 (Xp22)</td>
<td>Nlgn4–/-</td>
<td>Reduced social interactions and ultrasonic vocalization</td>
<td>Not known</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>NRXN1 (2p16)</td>
<td>Nrxn1–/-</td>
<td>Decreased PPI; increased grooming; defects in nesting; no impairment in social behaviours or spatial learning</td>
<td>Decreased cortical excitatory function with no obvious defects in inhibition</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>SHANK3 (22q13)</td>
<td>Shank3–/-</td>
<td>Reduced social interactions and ultrasonic vocalization</td>
<td>Decreased cortical excitatory neurotransmission</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>CNTNAP2 (7q35)</td>
<td>Cntnap2–/-</td>
<td>Impaired communication; stereotyped movements; impaired sociability; epilepsy</td>
<td>Reduced number of interneurons; migration deficits; abnormal cortical synchrony</td>
<td>105</td>
</tr>
<tr>
<td><strong>Down’s syndrome</strong></td>
<td>~300 genes on chromosome 21</td>
<td>Ts65Dn#</td>
<td>Impaired spatial memory and context discrimination</td>
<td>Excessive inhibition in hippocampal circuits</td>
<td>122</td>
</tr>
<tr>
<td>Intellectual disability; learning and memory deficits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fragile X syndrome</strong></td>
<td>FMR1 (Xq27)</td>
<td>Fmr1–/-</td>
<td>Impaired social interaction; learning deficits; decreased anxiety</td>
<td>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)</td>
<td>111–116</td>
</tr>
<tr>
<td>Intellectual disability; learning impairments; comorbidity with autism and epilepsy</td>
<td>NF1 (17q11)</td>
<td>Nf1–/-</td>
<td>Spatial learning deficits</td>
<td>Increased cortical inhibition</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syn1–Cre; Nf1&lt;sup&gt;lox/lox&lt;/sup&gt; (deletion of NF1 in neurons)</td>
<td>Spatial learning deficits</td>
<td>Not determined</td>
<td>125</td>
</tr>
<tr>
<td>Neurofibromatosis type I</td>
<td>Dbx5/6–Cre; Nf1&lt;sup&gt;lox/lox&lt;/sup&gt; (deletion of NF1 in forebrain GABAergic neurons)</td>
<td>Spatial learning deficits</td>
<td>Increased cortical inhibition owing to augmented GABA release from interneurons</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>
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 exist43, 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 schizophrenia44. 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+ interneurons32–34. 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 cells45. 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 cells43, a phenotype that is highly reminiscent of the findings from post-mortem analyses of brain tissue from patients with schizophrenia46. In addition, PV+ interneurons lacking ERBB4 receive less input from pyramidal cells than do PV+ interneurons that express this protein32,34. As a result, pyramidal cells tend to be overexcitable, and mice lacking Erbb4 null mutant mice exhibit schizophrenia-relevant phenotypes (including impaired working memory) that are similar to those observed in Nrg1- or Erbb4-null mutant mice34. Considering that NRG1 and ERBB4 are encoded by genes that have been repeatedly linked to schizophrenia34–41, 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 family42. DISC1 is a scaffolding protein that is widely expressed in the brain and that has multiple functions during brain development and in the adult brain43. 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 GABAergic cells. For example, transgenic mice that overexpress a truncated form of human DISC1 in pyramidal cells have reduced PV immunoreactivity in the prefrontal cortex44, and similar findings have been reported following Disc1 knockdown in pyramidal cells45. 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.

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

<table>
<thead>
<tr>
<th>Clinical features*</th>
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<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rett’s syndrome</td>
<td>Mecp2** (Xq28)</td>
<td>Nestin–Cre; Mecp2lox/lox (deletion of Mecp2 in CNS neurons and glia)</td>
<td>Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability; breathing problems</td>
<td>Not known</td>
<td>74,75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viatt–Cre; Mecp2lox/lox (deletion of Mecp2 in GABAergic neurons)</td>
<td>Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability; breathing problems</td>
<td>Impaired inhibitory function owing to decreased levels of GAD65, GAD67 and GABA</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dlx5/6–Cre; Mecp2lox/lox (deletion of Mecp2 in forebrain GABAergic neurons)</td>
<td>Motor dysfunction; stereotyped movements; learning and memory deficits; hyperexcitability</td>
<td>Not determined</td>
<td>76</td>
</tr>
</tbody>
</table>

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, neuroligin 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.
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; NKK2-1, homeobox protein NKK2-1; SOX6, transcription factor SOX6.
Interestingly, the excitability of basal ganglia, the amygdala well as the telencephalon. The anterior region of the brain and Forebrain

The association between abnormal interneuron function and neuropsychiatric disease has now been linked to multiple neuropsychiatric conditions, but they were first associated with schizophrenia. 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. The subsequent finding that such patients had increased GABA_A receptor binding activity in pyramidal cells was thought to be consistent with this idea, but several other studies failed to find similar reductions in the number of interneurons in individuals with schizophrenia. 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.

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. 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. The association between abnormal interneuron function and neuropsychiatric diseases has received increased attention in the past few years (TABLE 2).

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. 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. The subsequent finding that such patients had increased GABA_A receptor binding activity in pyramidal cells was thought to be consistent with this idea, but several other studies failed to find similar reductions in the number of interneurons in individuals with schizophrenia. 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.

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(REF. 66), another important schizophrenia susceptibility gene. Dysbindin is involved in intracellular trafficking (including the trafficking of dopamine receptors), and the expression of this protein is reduced in the prefrontal cortex and hippocampus of patients with schizophrenia. Interestingly, the excitability of cortical and striatal PV^+ interneurons is decreased in Dtnb1-knockout mice, and this leads to reduced inhibition of pyramidal cells. 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 (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. 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. 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). MECP2 is a nuclear protein that binds methylated DNA and functions as a transcriptional repressor. 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, whereas neuronal- or region-specific deletions of MeCP2 cause neurological phenotypes that resemble some of the features of Rett's syndrome. 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.

Not of, 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. 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, 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. 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), which has a crucial role in the development and maturation of inhibitory connections in the brain. In addition, MECP2 controls the expression of Gad65 and Gad67 in GABAergic neurons in a cell-autonomous manner.

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. Neuroligins and neurexins are neural adhesion molecules that cooperate in the formation of brain synapses...
through specific heterophilic interactions. Neuroligin–neurexin complexes promote both glutamatergic and GABAergic synapse formation, 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. 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. 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.

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. Together with the observations made in conditional Mecp2-mutant animals, 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. Since then, several genetic studies have provided additional evidence for the involvement of CNTNAP2 in autism. CNTNAP2 is a member of the neurexin family.

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. 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 receptors have been observed in pyramidal cells. The numbers of dendritic spines are also reduced in pyramidal cells taken from patients with schizophrenia. 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.
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, 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. Interestingly, the cortex of Cntnap2-knockout mice seems to have a reduced number of interneurons. 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.

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.
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.

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. 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. 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. 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. 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, several environmental factors seem to influence GABAergic interneurons. For example, there is a high prevalence of cannabis abuse in first-episode schizophrenia, and recent studies indicate that the cortical inhibitory deficits that are observed in patients with schizophrenia are enhanced by cannabis. 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). Activation of CB1 suppresses GABA release from synaptic terminals of CCK-expressing (CCK⁺) interneuron cells, 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. 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. 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. 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. The association of some oxytocin...
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) to alleles containing intrinsic single-nucleotide polymorphisms that modify the expression of different ERBB4 isoforms. 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. 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. 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, whereas conditional removal of Erbb4 disrupts behaviour but does not seem to cause epilepsy. These observations indicate that there might be a close interaction between genetic variation and developmental windows that shapes specific disorders.

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. 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. 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, 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. 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.
Schizophrenia is the core of the disorder. The evidence is supported by a number of studies indicating that cognitive deficits in relatives of schizophrenia is the core of the disorder. Postnatal development of prefrontal inhibitory circuits is critical for working memory as revealed by deficits in small interneurons in the prefrontal cortex of subjects with schizophrenia. Nature. 2013, 557–568 (2008).

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Psychiatry protein 2 in the forebrain is sufficient to mediate heightened anxiety in a mouse model of Rett behavior, aggression, and the response to stress. This elegant genetic dissection of the role of MECP2 in the brain. This study reveals that Rett's syndrome is primarily glutamatergic terminals of the hippocampal formation.


This study delineates a molecular pathway that might help us to understand the induction of schizophrenia-like behaviours by NM0A agonists, such as ketamine.


REVIEWS

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Acknowledgements
I would like to thank M. Maravall and B. Rico for their thoughtful comments on earlier versions of this manuscript, M. Selton for editorial assistance and the many colleagues who have shared their thoughts on this topic, including all the members of my laboratory. Our work is supported by grants from the Spanish Ministry of Science and Innovation (SAF2008-00049-E and CONSOLIDER CSD2007-0023), the Brain and Behaviour Research Foundation (NARSAD) and the Fundación La Marató.

Competing interests statement
The authors declare no competing financial interests.

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