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Neural circuit dysfunction in mouse models of neurodevelopmental disorders

Isabel del Pino[1,3], Beatriz Rico[1,2] and Oscar Marín[1,2]

Neuropsychiatric disorders arise from the alteration of normal brain developmental trajectories disrupting the function of specific neuronal circuits. Recent advances in human genetics have greatly accelerated the identification of genes whose variation increases the susceptibility for neurodevelopmental disorders, most notably for autism spectrum disorder (ASD) and schizophrenia. In parallel, experimental studies in animal models — most typically in mice — are beginning to shed light on the role of these genes in the development and function of specific brain circuits. In spite of their limitations, understanding the impact of pathological gene variation in animal models at the level of specific neuronal populations and circuits will likely contribute to orienting human clinical studies in the search for precise disease mechanisms and novel treatments.

Addresses
[1] Centre for Developmental Neurobiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE1 1UL, United Kingdom
[2] MRC Centre for Neurodevelopmental Disorders, King's College London, London SE1 1UL, United Kingdom

Corresponding authors: Rico, Beatriz (beatriz.rico@kcl.ac.uk), Marín, Oscar (oscar.marin@kcl.ac.uk)
[3] Present address: Neurocentre Magendie INSERM U1215, 33077 Bordeaux, France.

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Introduction

Our understanding of the etiology of psychiatric disorders has increased exponentially over the last decade due to massive advances in human genetics and epidemiology studies. These studies suggest that neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia are highly polygenic, with pleiotropic risk alleles and a complex background of gene-environment interactions underlying the pathophysiology. In this puzzling scenario, where genetic risk and pathogenic mechanisms overlap across multiple conditions [1], an emerging hypothesis is that unrelated genetic abnormalities may lead to similar psychiatric disturbances by altering the function of the same brain circuits. In addition, it has been proposed that neurodevelopmental disorders may primarily segregate by the timing when brain development deviates from a normal trajectory [2,3].

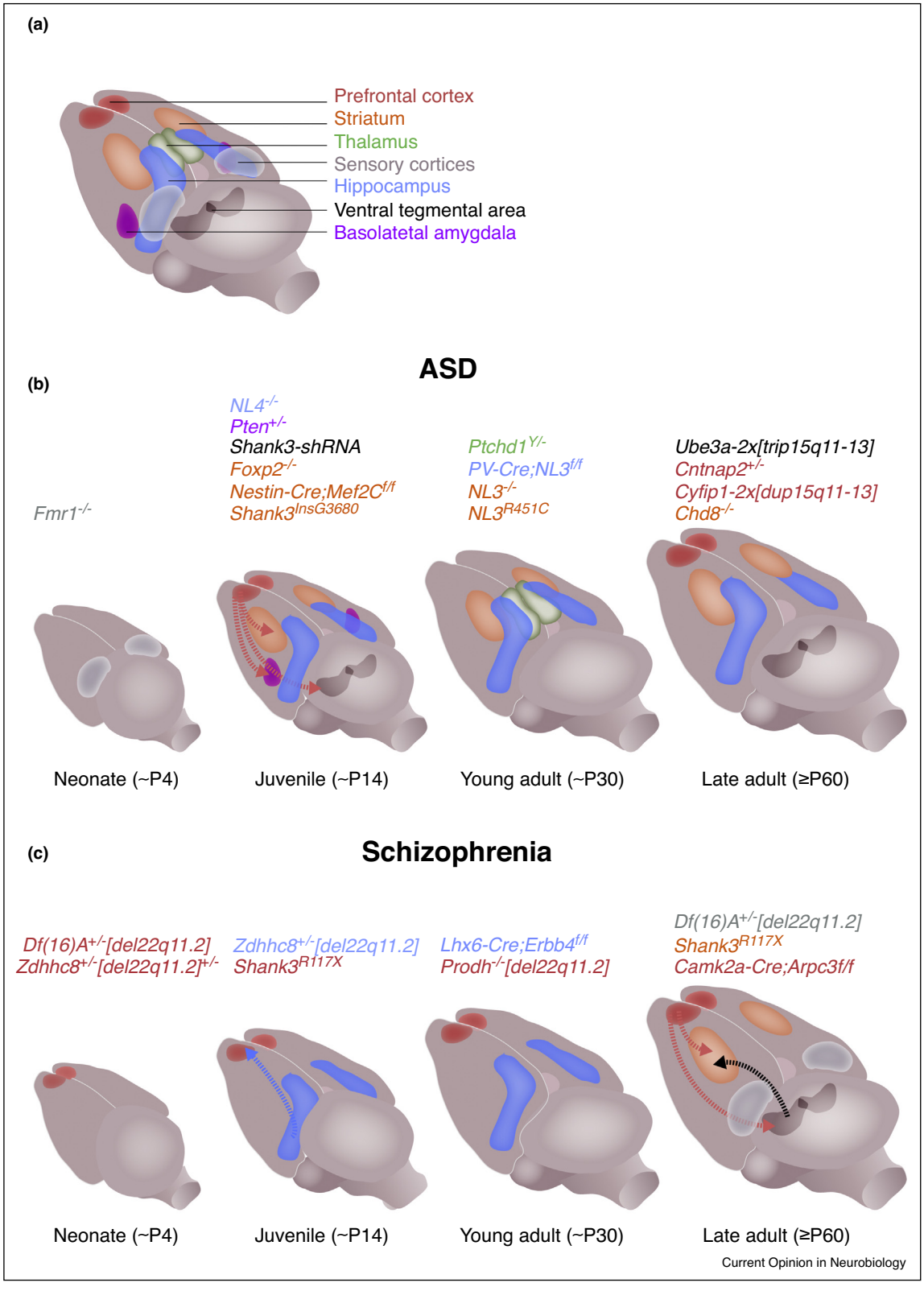
Research on animal models of neurodevelopmental disorders is also progressively shifting from an almost exclusive focus on behavior to the identification of neural circuit alterations linked to specific behavioral traits in an attempt to isolate etiological mechanisms that explain specific symptomatology [4]. Most of these studies concentrate on the analysis of genes whose variation has highly penetrant effects in humans, such as those linked to syndromic conditions, which illustrate the difficulties that exist in the field for the modeling of complex genetic variation. Here, we review recent work on animal models of neurodevelopmental disorders that point to converging defects in brain circuits across multiple conditions. This dissection of specific neural circuit dysfunctions largely concentrates on the analysis of genes linked to autism spectrum disorders (ASD) and schizophrenia. Whenever possible, emphasis is made on the impact of gene variation on developmental trajectories, as opposed to concentrating on the analysis of adult phenotypes.

Cortical circuits

Functional deficits in long-range cortico-cortical circuits are thought to be implicated in the pathophysiology of several neurodevelopmental disorders (Figure 1). For example, cognitive dysfunction is common in schizophrenia and has been associated with deficits in functional connectivity between the hippocampus and the prefrontal cortex (PFC) [5,6]. Consistently, mice modeling a human microdeletion (22q11.2), a well known genetic risk factor for schizophrenia, have profound deficits in the synchronization of PFC and hippocampal networks during working memory demands [7]. Recent work has shown that these defects are likely due to the deficient growth of pyramidal cell axons in the PFC at perinatal stages [8•]. Notably, these functional alterations can be rescued by interfering with the signaling cascades controlling axonal growth during early development [8•,9••].

Functional magnetic resonance imaging (MRI) has been used to consistently identify disturbances in cortico-cortical circuits in ASD patients. In particular, it is suggested that long-range connectivity is reduced in the neocortex, while local connectivity is enhanced [10]. Recent studies in

Figure 1



Summary of neural circuit dysfunctions in mouse models of ASD and schizophrenia during postnatal development. **(a)** Schematic showing brain regions disrupted in mouse models of autism and schizophrenia. **(b, c)** Schematics displaying brain regions and connections disrupted in mouse models of ASD (b) and schizophrenia (c). Brain regions and connections are color-matched to specific mouse strains in which defects have been

animal models carrying loss of function alleles for genes linked to syndromic forms of autism have demonstrated comparable defects. Mutations in *CNTNAP2*, a gene encoding the neurexin-related cell-adhesion protein Caspr2, are strongly linked to multiple neurodevelopmental conditions, including autism and epilepsy [11]. Functional MRI studies have shown that mice carrying homozygous *Cntnap2* mutations exhibit prominent deficits in functional connectivity between posteromedial cortical areas and the PFC, which are probably caused by a deficit in pyramidal cells projecting to the PFC [12]. Long-range cortico-cortical connectivity also seems impaired in $Fmr1^{-/y}$ mice, a model of Fragile X syndrome. Diffusion tensor MRI and viral tracing experiments revealed reduced connectivity between the primary visual cortex and other cortical areas in $Fmr1^{-/y}$ mice compared to controls [13]. These defects likely arise during neonatal stages and are readily evident in juvenile mice [14]. Finally, mice heterozygous for a loss of function mutation in PTEN, which encodes a protein phosphatase that regulates mTOR signaling and is linked to macrocephaly and autism, also exhibit prominent defects in long-range cortical projections. In particular, $Pten^{+/-}$ mice have exuberant projections from the PFC to the amygdala, a phenotype that underlies the social behavior defects observed in these mice [15]. Although this study focused on the connectivity between the prefrontal cortex and the amygdala, altered cortical connectivity is unlikely to be restricted to this circuit in $Pten^{+/-}$ mice. Consistent with this idea, the analysis of mice carrying duplications in the ASD-linked gene *Cyfip1* (Cytoplasmic FMR1 interacting protein 1) also revealed defective mTOR signaling and abnormal development of PFC neurons [16].

Dysfunction in long-range cortical circuits often occurs concomitantly with local-circuit alterations. Impaired homeostatic responses to perturbations of excitatory-inhibitory balance in the cerebral cortex are widespread among mouse models of neurodevelopmental disorders [17]. Mouse models of Rett syndrome, caused by loss of function mutations in the gene encoding methyl-CpG-binding protein 2 (*MECP2*), exhibit prominent defects in the organization and maturation of inhibitory circuits [18,19] and display increased susceptibility to hyperexcitability. Interestingly, *Mecp2* duplications, which are also pathogenic in humans, cause similar neural circuit abnormalities than loss of function *Mecp2* mutations [19]. Conditional deletion of *Pten*, another ASD-associated gene, also causes widespread defects in dendrites and axon tracts in the telencephalon [20], along with abnormal variation in the ratios of different classes of interneurons [21].

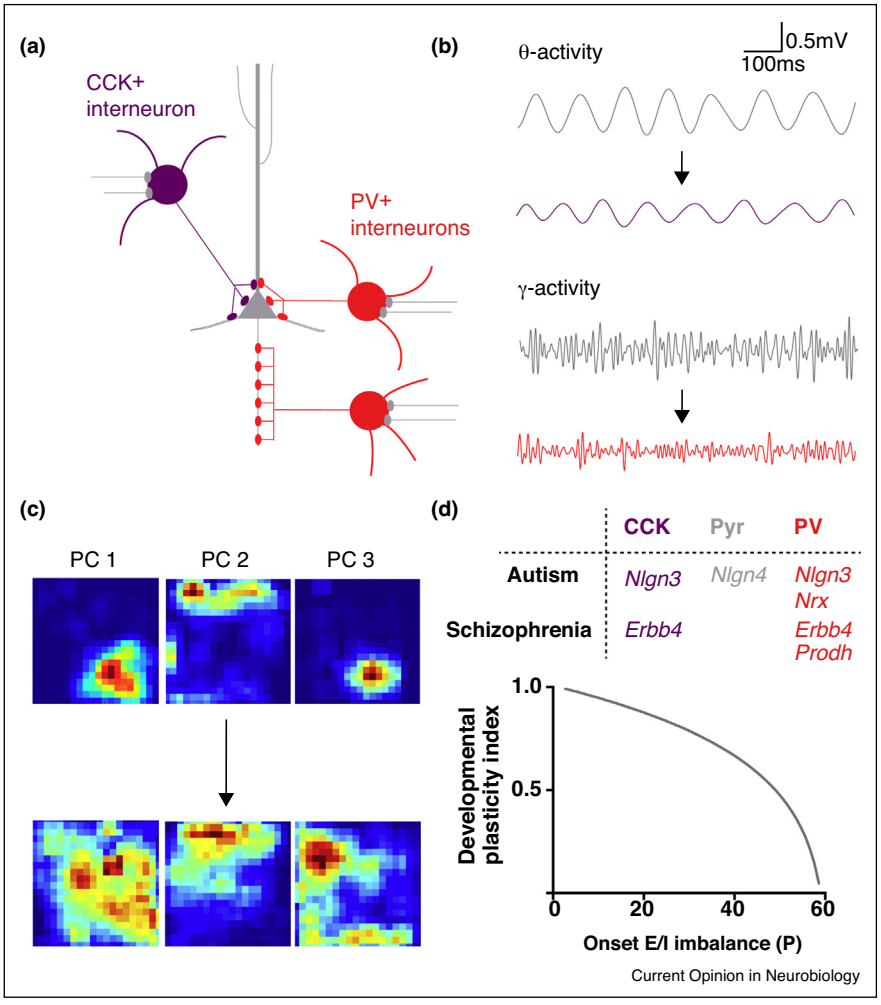
Cognitive deficits in schizophrenia have been linked to deficits in GABAergic interneurons at multiple levels. Human postmortem studies have identified synaptic deficits in fast spiking interneurons [22,23], a population of GABAergic cells that are involved in the modulation of gamma rhythms and working memory [24]. Consistent with these observations, human studies have linked alterations in gamma rhythms to profound deficits in working memory performance [25–29]. Recent work has shown that similar alterations (decreased levels of GABA and specific deficits in gamma-band oscillations) are recapitulated in mice carrying mutations in the gene encoding Proline dehydrogenase (*Prodh*), which resides within the schizophrenia-linked 22q11.2 deletion [30].

Synchronization of local and long-range pyramidal cell activity can result from defects in the wiring and function of specific classes of cortical interneurons. The recruitment of fast-spiking Parvalbumin-expressing (PV+) interneurons is compromised in mice carrying mutations in genes linked to autism and schizophrenia. Conditional deletion of Neuroligin-3 (NL3) from PV+ interneurons impairs the properties of excitatory input, which in turn reduces gamma oscillations and perturbs behavior [31]. Similarly, conditional removal of the tyrosine kinase receptor ErbB4 from PV+ interneurons impairs the development of synaptic excitatory input and alters the balance between neuronal excitation and inhibition in cortical circuits [32]. A similar synaptic phenotype is observed when ErbB4 is deleted from CCK+ interneurons, although the functional consequences are very different. While perturbing the recruitment of PV+ interneurons by pyramidal cells impairs gamma oscillations and a wide range of cognitive tasks [32], deficient recruitment of CCK+ interneurons decreases theta oscillatory activity and alters spatial coding by place cells (Figure 2a–c) [33••]. Interestingly, recent studies have also shown reduced spatial map stability in mice modeling the human 22q11.2 microdeletion [34], which reinforces the view that disruption of local assemblies in the hippocampus is a common feature of schizophrenia.

Defects in the formation of inhibitory synapses onto pyramidal cells have also been described in several mouse models of neurodevelopmental disorders. Cell adhesion molecules linked to neurological disease such as Neurexins and Neuregulins regulate the synaptic output of GABAergic interneurons in a cell type-specific manner. For example, complete deletion of all neurexin forms decreases dramatically the number of PV+ inhibitory synapses onto pyramidal cells [35•]. Loss of *Nlgn4*, one of the most common genes whose variation has been linked to ASD, also disrupts perisomatic inhibitory synaptic neurotransmission onto pyramidal cells [36]. Conversely, deletion of ErbB4 — the receptor mediating

(Figure 1 Legend Continued) reported for those areas. Chromosomal copy number variants in humans that encompass genetic mutations modeled in mice are indicated between square brackets. Arrows indicate the brain connections that have been characterized. Del, deletion; dup, duplication; trip, triplication.

Figure 2



Local microcircuits regulating excitatory/inhibitory (E/I) balance are affected in animal models of neurodevelopmental disorders. **(a)** Schematic of local microcircuits composed of cortical glutamatergic pyramidal cells (gray), GABAergic basket cells expressing cholecystokinin (CCK+, purple) and GABAergic basket as well as chandelier cells expressing parvalbumin (PV+, red). **(b)** Abnormal synchronization of hippocampal activity results from developmental disruption in E/I balance. Schematic examples of altered oscillatory activity in the low frequency (filtered LFP signal in the θ-band, upper panel) and/or high frequency (filtered LFP signal in the γ-band, lower panel) range displayed by animal models of neurodevelopmental disorders. **(c)** Stability of firing fields of place cells (PC) responsible for encoding spatial information is altered in mouse models of schizophrenia. **(d)** Genes associated with neurodevelopmental disorders that regulate the structure and function of local microcircuits illustrated in (a). Disruption of E/I balance during development can induce neural assembly destabilization and circuit reorganization through developmental plasticity. The degree of rearrangement in neural circuits, i.e. developmental plasticity index, varies as a function of the temporal onset in E/I imbalance during postnatal development (P: postnatal day in mouse development).

neuregulin function in interneurons [37] — specifically impairs the formation of chandelier cell synapses [32] and CCK+ basket cells [33••]. These findings suggest that each interneuron class requires specific synaptic machineries to integrate into local networks, and that defects in specific inhibitory synapses are common in neurodevelopmental disorders.

Acute manipulation of the balance between neuronal excitation and inhibition in the cerebral cortex may have therapeutical potential. For instance, decreasing the excitatory-inhibitory balance in the medial PFC in mouse models of ASD or schizophrenia (by either optogenetically increasing the excitability of inhibitory PV+ interneurons or decreasing the excitability of pyramidal cells) acutely rescues prominent deficits affecting social and cognitive domains [38•,39]. Although optogenetic manipulations might be difficult to implement in humans, these experiments suggest that equivalent pharmacological interventions — provided that they achieve the desired specificity — might be beneficial in autism and perhaps other disorders. Importantly, perturbation of E/I balance early in development might destabilize neural assemblies persistently [40] through developmental plasticity

mechanisms that might not be reverted by acutely restoring E/I balance. The potential of neural circuits to undergo adaptive structural rearrangements in response to environmental stimuli decreases progressively during postnatal development (Figure 2d). Therefore, therapeutic interventions directed to restore circuit dysfunction by manipulating E/I balance are required to be timely fitted to counteract pathological developmental trajectories [2].

Striatal circuits

Restricted, repetitive patterns of behavior are among the most characteristic clinical features of ASD. As these behaviors are hallmarks of other basal ganglia-related disorders such as Tourette syndrome and obsessive-compulsive disorder (OSD), recent work on animal models of ASD has largely focused on the analysis of corticostriatal circuits. Electrophysiological studies in mice have shown that the development of corticostriatal connections occurs during a narrow postnatal period that is characterized by extensive glutamatergic synaptogenesis in striatal projection neurons and a parallel increase in corticostriatal circuit activity [41••]. The functional coupling between these two areas is so efficient during this critical period that early alterations in the activity of cortical neurons may have a massive impact in the long-term configuration of corticostriatal circuits. Consistently, a mouse model of ASD carrying mutations in *Shank3* alleles exhibits cortical hyperactivity at early postnatal stages and progressively develops hyperconnectivity between cortical pyramidal cells and striatal projection neurons [41••]. Interestingly, repeated hyperactivation of corticostriatal synapses induces repetitive behaviors in mice [42], which suggest that abnormal activation of corticostriatal circuits during early postnatal development may underlie the motor stereotypies that characterize multiple neurodevelopmental disorders. In agreement with this idea, ASD-linked mutations in *Shank3* seem to have an earlier impact on neural circuits than schizophrenia-linked mutations in the same gene [43••] (Figure 1).

Other studies suggest that decrease activation of corticostriatal circuits during development may also cause prominent phenotypes. For instance, *FOXP2* mutations in humans are linked to spoken language disabilities and defects in corticostriatal circuits. Mice carrying loss of function *Foxp2* alleles develop reduced numbers of corticostriatal synapses at the juvenile stage which impacts on ultrasonic vocalizations [44]. Thus, abnormal development of corticostriatal projections may have different functional implications, depending on the timing and nature of the alterations. Altogether, these studies strongly suggest that early developmental disruption of corticostriatal circuits leads to increase repetitive behavior and motor abnormalities in mice. Importantly, some of these alterations may also compromise social communication by affecting motor routines such as those required for the generation of ultrasonic vocalization.

Enhanced motor learning has been associated with the consolidation of repetitive motor routines, a prominent feature of ASD patients. Consistently, acquired motor learning is commonly increased among ASD mouse models [20,45–48]. In rotarod performance tests, for example, mice carrying ASD mutations typically outperform control mice, achieving higher levels of motor performance than controls over the same period of time [46,48]. Previous work has linked the basal ganglia with the acquisition of repetitive and stereotyped behaviors [49], but the specific neuronal circuits underlying the enhanced motor learning ability of ASD mouse models have remained unknown until recently. Several studies have now shown that neural circuit defects in the nucleus accumbens enhance the acquisition of repetitive motor behaviors in mice [46,48]. For instance, NL3 mutations associated to ASD cause defects in the inhibitory control of striatal projection neurons, through a shift in the E/I balance in D1 (dopamine receptor 1)-expressing medium spiny neurons, likely enhancing the output of this pathway [46]. Specific deletion of NL3 in the ventral striatum recapitulates the motor behavioral abnormalities observed in null NL3 mutants [46], suggesting that this region is prominently affected by the loss of NL3 function.

Heterozygous mice for a loss of function *Cdh8* allele, which encodes an ATP-dependent chromatin remodeler linked to ASD [50], also exhibit repetitive behavior [51] and enhanced motor learning in rotarod tests [48]. Although the effects of the loss of Cdh8 function in brain development are likely diverse [51,52], electrophysiological experiments have shown that medium spiny neurons in the striatum of $Cdh8^{+/-}$ mice received enhanced excitation and decreased inhibition, which probably contribute to increase the output of these neurons [48]. Remarkably, deletion of *Cdh8* from neurons in the core of the nucleus accumbens is also sufficient to recapitulate the motor behavioral phenotype [48]. Together, these studies link the abnormally enhanced acquisition of motor tasks that characterize mouse models of ASD with defects in ventral striatal circuits.

Neuromodulation of long-range and local circuitries

Dopamine plays a critical role in regulating social behavior and repetitive actions by modulating the activity of neurons at different levels of cortico-striatal-thalamic-cortical circuits. As such, defects in the function of dopaminergic neurotransmission have been described in multiple neurodevelopmental disorders. For instance, human studies suggest that cortical hypodopaminergia and striatal hyperdopaminergia are common in schizophrenia patients [53], and recent work have consistently reported that PV+ interneurons in mice modeling the schizophrenia-linked 22q11.2 deletion are less susceptible to modulation via D2 receptors, which disrupts

the ability of these cells to influence E/I balance [54]. Interestingly, disruption of E/I balance in the cortex may in turn impact the activity of dopaminergic cells in the midbrain. In agreement with this, mice with defects in PFC neuron excitability exhibit abnormally increased striatal dopamine release [55••] (Figure 1; *Camk2a-Cre; Arpc3$^{fl/f}$*). This study provides a potential explanation for apparently unrelated observations in schizophrenia, such as loss of dendritic spines in pyramidal cells, enhanced excitation, and altered striatal dopamine.

Several lines of evidence also point to impaired dopaminergic function in reward circuits in ASD [56], which is likely caused by a decrease in the activity of midbrain dopaminergic neurons. In mice, specific loss of *Shank3* function in the ventral tegmental area leads to reduction in the activity of dopaminergic neurons that impairs social reward mechanisms [57]. These results are consistent with the analysis of mice engineered to expressed abnormally increased levels of Ube3a in the VTA, which model a common and highly penetrant form of ASD found in humans carrying 15q11-13 triplications. Overexpression of Ube3a in this region disrupts excitatory neurotransmission in glutamatergic neurons in the VTA and impairs normal social behavior [58].

Sensory circuits

Autism spectrum disorder involves deficits in sensory processing, including aberrant reactivity to sensory stimuli [59,60]. Previous work has primarily focussed on sensory responses in primary cortical areas, but recent studies in animal models of ASD have revealed that defects in sensory processing might originate from perturbations in other stations of sensory pathways. For instance, mice harboring mutations in ASD-associated genes in humans such as *Mecp2*, *Gabrb3*, *Shank3* and *Fmr1* exhibit tactile hypersensitivity that is primarily caused by a reduction of presynaptic inhibition in primary sensory neurons [61••]. This suggests that at least some of the sensory alterations that characterize ASD patients are caused by circuit deficits in the spinal cord. In addition, these studies indicate that anxiety and aberrant social behaviors in ASD patients might be secondary to disruption of sensory responses.

Sensory processing defects in ASD might also be linked to defects in thalamocortical connectivity. Recent studies revealed that the function of the reticular thalamic nucleus, a structure involved in gating thalamocortical circuits, is altered in *Ptchd1*-deficient mice, a gene mutated in some patients with ASD, intellectual disability and attention deficit hyperactivity disorder [62]. *Ptchd1* is strongly expressed in the reticular nucleus at neonatal stages, and its deletion from this structure is sufficient to replicate some of the behavioral deficits observed in humans carrying PTCHD1 mutations.

Concluding remarks

Advances in human genetics over the last decade have led to the identification of dozens of genes whose variation is associated with neuropsychiatric abnormalities, most typically in syndromic forms of ASD and other neurodevelopmental disorders. Understanding the impact of pathological gene variation in the context of neural circuit dysfunction during postnatal development is perhaps the most promising approach to increase our understanding of the etiology of these conditions. In other words, animal models have the potential to help us move from 'which' (gene) to 'where' (in the brain) and 'when' (during development). Linking these variables should lead to the identification of critical developmental windows during which specific neural circuits are particularly sensitive to pathological insults [2]. A better understanding of pathophysiological trajectories at the level of specific neural circuits should also guide the development of new therapeutical approaches.

The analysis of neural circuit abnormalities and their associated behavioral traits reveal important differences among neurodevelopmental disorders. For example striatal hyperdopaminergia and psychosis are perhaps uniquely characteristic of schizophrenia arising relatively late in postnatal development, whereas the abnormal function of corticostriatal circuits and its impact of repetitive behaviors are more frequently associated with ASD and occur relatively early in development. Cognitive deficits, on the other hand, seem to be prevalent across a wide range of neurodevelopmental disorders. Consistent with this idea, copy number variants conferring risk of ASD or schizophrenia also modulate cognition in healthy controls [63]. In this context, perturbation of the balance between excitatory and inhibitory neurons in the cerebral cortex, and of the mechanisms that control the homeostatic regulation of this balance, have been shown to disrupt cognition (working memory, cognitive flexibility, spatial coding, sensory perception) and appear early during development across a wide range of animal models. Thus, disruption of cortical assemblies might be a common early signature of neurodevelopmental disorders.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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