Developmental timing and critical windows for the treatment of psychiatric disorders

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There is a growing understanding that pathological genetic variation and environmental insults during sensitive periods in brain development have long-term consequences in brain function, which range from learning disabilities to complex psychiatric disorders such as schizophrenia. Furthermore, recent experiments in animal models suggest that therapeutic interventions during sensitive periods, typically before the onset of clear neurological and behavioral symptoms, may prevent or ameliorate the development of specific pathologies. These studies suggest that understanding the dynamic nature of the pathophysiological mechanisms underlying psychiatric disorders is critical for the development of effective therapies. In this Perspective, I explore the emerging concept of developmental windows in psychiatric disorders, their relevance for understanding disease progression, and their potential for the design of new therapies. The limitations and caveats of early interventions in psychiatric disorders are also discussed in this context.

Psychiatric disorders are a major socio-economic burden, mostly because of the indirect costs derived from social support and unemployment[1,2]. Current treatments are based on symptoms, are not disease modifying, and have low response rates. For example, current treatments for schizophrenia only ameliorate psychotic symptoms in some patients and generally fail to improve cognition and other behavioral abnormalities[3], and there are no effective pharmacological therapies for autism spectrum disorders (ASD) and related intellectual disabilities. Many factors contribute to the absence of effective treatments for psychiatric disorders, not least the lack of a clear understanding of their neurobiological substrates. In some cases, however, our knowledge of the underlying pathophysiology seems sufficient for the development of novel therapies, yet results are disappointing when new drugs are tested in adult patients[4].

Emerging data indicate that most neuropsychiatric disorders arise from the alteration of normal developmental trajectories, even if the age at which they are clinically diagnosed varies significantly, from toddlers in ASD to young adults in schizophrenia (Figure 1a). Transcriptomic analyses suggest that genes associated with psychiatric disorders are highly expressed during development[5,6], and indeed many of the genes whose pathological variation confers susceptibility to psychiatric disorders play fundamental roles in brain development[7-9]. In addition, environmental risk factors such as hypoxia and maternal infection are early-life events[10]. Moreover, since neuronal circuits continue to exhibit robust plasticity –that is to say, remain able to reorganize in response to experience– well into adulthood[11,12], the pathological organization of brain circuits in adult patients is probably the result of multiple homeostatic (compensatory) mechanisms operating over a protracted period.

Given the importance of developmental trajectories in mental illness, an emerging idea is that therapeutical intervention may impact brain function differently depending on the stage of the disorder, and that treatment in the adult brain might be less effective than at earlier stages[13,14]. Although development is a continuous process, the brain seems to be particularly vulnerable to insults (genetic and environmental) around specific sensitive periods in which changes in brain structure have long-lasting impact over the lifespan[11]. The existence of these critical windows in brain development suggests that early interventions might be necessary to overcome subsequent deficits, which are secondary to earlier perturbations.

This Perspective explores the dynamic nature of the pathophysiological mechanisms underlying psychiatric disorders, with an emphasis on the developmental milestones that may critically influence disease progression and so the design of new therapies. While the article focuses on schizophrenia as an example of a psychiatric disorder that may benefit from early interventions, attention is also paid to syndromic neurodevelopmental disorders for which experimental therapeutics are being developed based on our current mechanistic understanding of these disorders. Finally, the limitations and caveats of therapeutics interventions in the context of development are also outlined.

Developmental milestones in the assembly of neural circuits

Brain development spans over two decades in humans, from embryonic patterning to synaptic pruning in adolescence[15] (Figure 1b). Several developmental milestones that are essential for the assembly and fine-tuning of neural circuits characterize this protracted period. Developmental milestones are sensitive time windows of particular transcendence for brain development because they have a long-lasting influence in the organization of brain circuits. For example, abnormal visual experience during a relatively narrow time

window in early development dramatically changes cortical circuits processing vision and has a major impact on visual ability[16], whereas transient blindness in adulthood has much less severe functional consequences. It is therefore conceivable that even the most subtle variation in the organization of brain circuits during these sensitive time windows contributes to functional alterations that persist throughout life, as shown in animal studies[17]. These critical developmental windows exist for different brain regions, including those linked to high-order functions such as language and executive planning[18,19] (Figure 2). Consequently, anatomical and functional changes during these periods –due to gene variation or environmental pressure– are a major source of inter-individual variability in brain organization, which in extreme cases is pathogenic.

Increasing evidence suggests that variation in the assembly and dynamic maintenance of specific neural circuits, primarily in the cerebral cortex and subcortical structures such as the basal ganglia and the amygdala, are at the core of psychiatric disease[20-23] . The most sensitive time windows for vulnerability in the assembly of these neural circuits stretch from perinatal stages to adolescence. During this period, normal developmental progression is linked to the maturation of specific populations of cells. For example, oligodendrocytes are responsible for myelination in the CNS, and so defects in the maturation of these cells eventually impact long-range connectivity in the brain. In addition, although other populations of cells may have important functions at specific developmental windows, growing evidence suggest that neurons that use ɣ-aminobutyric acid (GABA) as their main neurotransmitter (also known as GABAergic neurons) play critical roles in the assembly of neuronal circuits at several consecutive stages (Figure 3), which may explain their prominent involvement in psychiatric disease[24].

GABA may be an inhibitory or excitatory neurotransmitter depending on the intracellular concentration of chloride ions present in the receiving cell. Studies in rodents and non-human primates have shown during embryonic and early postnatal development GABA depolarizes –excites– because the intracellular concentration of chloride in the postsynaptic targets is higher than in the extracellular space[25]. During this period, GABA-induced currents are the main source of depolarization and are critical for the generation of synchronized patterns of activity that characterize developing networks[26]. Early synchronous events are thought to play a fundamental role in the maturation of neuronal circuits[27,28].

Shortly before delivery a reduction in the intracellular chloride concentration of neurons induced by oxytocin leads to a transitory excitatory-to-inhibitory switch of GABA actions[29]. This is thought to increase the resistance of neurons to hypoxia and ischemic damage during delivery. Delivery is associated with high risks to the fetal brain and preterm babies have a much higher incidence of neurological and cognitive impairments[30]. The perinatal period therefore represents one of the first developmental milestones in the assembly of cortical circuits[31].

At the end of the first postnatal week in the mouse there is a definitive switch of GABAergic signals from excitatory to inhibitory due to a progressive decrease in the expression of the ion co-transporter NKCC1 (Sodium/Potassium-Chloride Co-transporter 1), which imports chloride, and a parallel increase in the expression of KCC2 (Potassium-Chloride Co-transporter 2), which exports chloride[25]. The shift of GABA from excitatory to inhibitory corresponds with a sharp decrease in the correlated firing of cortical neurons[32]. This is an emerging property of mature cortices, in which information is

massively distributed across neurons and only small sets of neurons respond to any given stimulus. Thus, this is another crucial milestone in brain development.

The desynchronization of spontaneous network activity coincides temporally with the increasing influence of sensory experience, through which external signals begin to shape synaptic connectivity by outcompeting internally generated activity[33]. During a period of time that varies according to the lifespan of species and the sensory modality, neuronal circuits are particularly receptive to different types of perceptual experience, from vision to fear[34]. These sensitive windows are known as critical periods[35], and constitute another major milestone in the development of brain circuits. Because different brain areas process distinct types of information, critical periods are very diverse: some are linked to primary functions, such as vision, others to more complex tasks that involve cognitive experience, such as language acquisition or specific social behaviors. In any case, activity-dependent changes in brain circuits induced during a critical period have long lasting effects in brain function. In the mouse visual system, for example, critical period plasticity drives binocular matching, the process through which binocular neurons in the visual cortex (those that respond to information from both retinas) match their orientation preference[36]. It is conceivable that many unique features of neural computations are similarly established during critical periods across different brain areas and are important for disease.

The onset and length of critical periods are strongly influenced by the maturation of GABAergic interneurons. In mice, genetic loss of GABAergic function and sensory deprivation delays plasticity, whereas $GABA_A$ receptor agonists such as benzodiazepines can trigger precocious onset of the critical period[37]. Fast-spiking interneurons expressing the calcium binding protein parvalbumin (PV+) are the main modulators of critical period

plasticity (Figure 4). These cells provide very strong inhibition to pyramidal cells[38], and so their maturation rapidly restricts the influence of sensory experience in pyramidal cells and leads to the closure of critical period plasticity. In addition, the maturation of PV+ interneurons is crucial for the development of oscillatory activity across the neocortex and hippocampus. Fast-spiking PV+ interneurons synchronize local assemblies of pyramidal cells in the gamma frequency, which contributes to the emergence of functional interactions between the hippocampus and the prefrontal cortex[39].

In sum, the development of neural circuits in the cerebral cortex and associated subcortical structures is characterized by a number of developmental milestones that have long-lasting effect in the brain function. In the following sections, this conceptual framework will be used to illustrate how understanding of critical developmental time windows and homeostatic mechanisms that operate in different psychiatric conditions may inform about the appropriate timing of therapeutic interventions.

Neurodevelopment and disease-modifying strategies in schizophrenia

Schizophrenia is a chronic disorder characterized by a constellation of very diverse symptoms that affects approximately 1% of the population worldwide. Current treatments with antipsychotics are relatively effective in the management of psychotic symptoms (delusions, hallucinations, bizarre thoughts, paranoia), but they have modest impact upon negative symptoms (decreased expression, avolition)[40], and fail to improve cognitive deficits, which are directly linked to poor real-world function[41].

Although schizophrenia is usually diagnosed in young adults at the time of the first episode of psychosis, our current understanding of its genetic and environmental causes links this disorder with abnormal neurodevelopment[42,43]. According to this view, psychosis is not the onset of the disorder, but rather a prominent consequence of a developmental

path toward schizophrenia that can be perhaps prevented through early intervention[44]. The notion that schizophrenia pathology worsen over time is supported by studies that suggest that long-term morbidity increases in the absence of any treatment[45,46]. This observation strongly reinforces the need for early interventions before pathological defects cascade into an irreversible state.

The pathophysiology of schizophrenia remains poorly understood, but two of the most robust and replicated clinical findings are the elevated presynaptic dopamine function in the striatum[47] and the existence of neuroanatomical and electrophysiological alterations in the medial temporal lobe, including the hippocampus, and in different areas of the prefrontal cortex[48]. In addition, several lines of evidence suggest that disruption of PV+ fast spiking interneurons is a core feature of schizophrenia[49]. For instance, the levels of one of the enzymes that contributes to the synthesis of GABA, GAD67, are consistently lower in the cortex of subjects with schizophrenia, and these defects are more prominent in PV+ interneurons [49]. Moreover, the expression of several GABA receptors and markers of inhibitory synapses are also altered in schizophrenia[50]. Interestingly, some of these deficits are already present –albeit in a less pronounced manner– in individuals at ultra-high risk for psychosis. These patients have attenuated psychotic symptoms, and about 30% of them will develop a psychotic disorder within three years of their first clinical assesment[51]. Longitudinal imaging studies in humans have shown that levels of striatal dopamine increases progressively as subjects make the transition from high-risk to psychosis[52]. Similarly, small anatomical differences have been found in the medial temporal and frontal lobes of individuals prior to psychosis[53], and cognitive impairment is already evident during adolescence in individuals that will subsequently develop schizophrenia[54]. Based on

these observations, disease-modifying strategies currently focus on identifying appropriate targets for treatment prior to the onset of psychosis.

Several studies have exploited animal models to determine whether experimental treatments in juvenile mice can prevent schizophrenia-like phenotypes in adults (Table 1). One important limiting factor for this approach is that schizophrenia lacks clear monogenic syndromes that can be modeled in animals. For this reason, alternative experimental models have been generated that reproduce some of the symptoms observed in schizophrenia[13]. These are primarily based on pharmacological lesions of the developing hippocampus, such as the prenatal exposure to methylazoxymethanol acetate (MAM) and the neonatal ventral hippocampal lesion (NVHL) models[55,56]. Both models reproduce some of the defects observed in schizophrenia, including functional deficits in PV+ fast spiking interneurons. In addition, mice carrying mutations in a handful of genes reproduce neuroanatomical, functional and behavioral deficits observed in schizophrenia[57], and stem cell-based models are beginning to be used for characterizing cellular defects linked to pathological gene variation[58-60]. The prominent differences that exist between rodents and humans in social cognition and communication have also led to the exploration of non-human primate models for research in psychiatric disorders[61].

Since antipsychotics act on central dopamine receptors[3], one possible strategy for prevention or course alteration in individuals at risk of schizophrenia is the use of antipsychotics on individuals at ultra-high risk for psychosis. This idea is supported by studies in the NVHL model for schizophrenia, in which administration of antipsychotics during adolescence diminishes schizophrenia-like phenotypes in adults[62]. However, clinical trials have failed so far to provide clear evidence that antipsychotics can prevent conversion to schizophrenia in at-risk individuals[63]. One possible explanation for this

failure could be that by the time presynaptic dopamine function is abnormally increased, several other changes have occurred that limit prevention. Indeed, since dopamine is already elevated in some patients when they first seek help[52], it is conceivable that striatal dopamine changes are secondary to other defects and preventive treatments should aim for an earlier developmental window for course alteration. Consistent with this idea, abnormally elevated excitation in cortical pyramidal neurons may lead to striatal hyperdopaminergia in mice[64], and studies in the MAM model have shown that the changes in dopaminergic neurons might be secondary to the disruption of cortical circuits[56].

In humans, psychosis has also been associated with increased hippocampal glutamate levels[65,66], although it is worth noting that changes in cortical glutamate levels may vary with the age and treatment history of the patients[67]. Mechanistically, increased activity of pyramidal cells might be a consequence of abnormal interneuron function, as previously shown in a genetic mouse model for schizophrenia[68], and multiple lines of evidence suggest that interneuron function is disrupted in schizophrenia[49]. While additional studies are required to demonstrate that dysfunction in PV+ fast spiking interneurons precedes other defects in schizophrenia, deficits in gamma oscillations (a type of fast oscillatory activity that requires the function of PV+ fast spiking interneurons) has been reported in first episode schizophrenia patients[69,70]. It would be important to establish how early in the disease process GABAergic interneurons become compromised, as this will inform –based on their prominent role in cortical circuit assembly– about other possible alterations that might occur downstream of their altered function. At any rate, these studies suggest that restoring the balance between cortical pyramidal cells and interneurons in early phases of the disorder may prevent the onset of psychosis.

In addition to a possible link with striatal hyperdopaminergia, studies in animal models have shown that developmental disruption of PV+ fast spiking interneurons causes other phenotypes that are characteristic of schizophrenia, including abnormal gamma oscillations and long-range synchrony defects between the hippocampus and the prefrontal cortex[68]. In humans, normal gamma rhythms and hippocampal-prefrontal synchrony are critical for multiple cognitive tasks that are disrupted in schizophrenia[28,39], and so several strategies have been devised to stimulate the function of fast spiking interneuron in schizophrenia. These include the use of $GABA_A$-α2 agonists and inhibitors for the Na-K-Cl cotransporter NKCC1, as in ASD (see below). While the results of these studies in adult patients are not encouraging[13], it remains to be established whether normalization of GABAergic function well in advance to the onset of psychosis might lead to better outcomes. This approach is supported by the idea that GABAergic interneurons play fundamental roles in the establishment of neural circuits, as explained above. Consistent with this view, reducing stress sensitivity in juvenile MAM-treated rats with benzodiazepines prevents the abnormal increase in the activity of dopaminergic neurons and reduces hyperlocomotion in adult rats[71]. Since benzodiazepines enhance the effect of GABA on $GABA_A$ receptors[72], these experiments reinforce the view that early modulation of cortical inhibitory circuits might contribute to prevent the onset of psychosis in schizophrenia.

Considering the clinical heterogeneity of schizophrenia, it seems likely that different pathophysiological mechanisms may operate in different groups of patients, even if the final behavioral and functional deficits are relatively conserved. Despite limitations in the understanding of schizophrenia genetics, several animal models have been generated that are beginning to shed light into the heterogeneous mechanisms that lead to schizophrenia.

Some of the most relevant genetic models to date are based on relatively rare syndromic versions of schizophrenia, but it is expected that new mouse models will soon follow the recent discoveries derived from genome-wide association studies[73]. For example, *Df(16)A*$^{+/-}$ mice are a model of DiGeorge syndrome, caused by a microdeletion (22q11.2) that accounts for a small percentage of schizophrenia cases[74]. Human 22q carriers have cognitive deficits[75], and approximately one third of them develop schizophrenia[76]. *Df(16)A*$^{+/-}$ mice have prominent working memory deficits that are likely caused by impaired functional connectivity between the hippocampus and the prefrontal cortex[77]. The observation that haploinsufficiency of *Zdhhc8*, one of the genes in the 22q11.2 microdeletion, might be responsible for the developmental disconnection between the hippocampus and the prefrontal cortex found in *Df(16)A*$^{+/-}$ mice has led to the identification of a new possible target for the treatment of DiGeorge syndrome. In *Zdhhc8*$^{+/-}$ mice, abnormally high levels of Gsk3β during development seem to contribute to axonal branching deficits in these mice[78]. Consistent with this hypothesis, inhibition of Gsk3β signaling in juvenile *Df(16)A*$^{+/-}$ mice rescues the functional connectivity between the hippocampus and prefrontal cortex and improves working memory in these mice[79]. This work reinforces the notion that developmental interventions might be potentially transformative in the treatment of schizophrenia.

Another indication of the potential of early intervention therapies for schizophrenia is the link between oxidative stress and schizophrenia. Decreased brain levels of glutathione (GSH), the most abundant endogenous antioxidant, have been observed in schizophrenia[80], and mouse mutants with GSH deficits or mitochondrial dysfunction show morphological, electrophysiological and behavioral anomalies that are common to schizophrenia[81]. Treatment of adolescent NVHL rats with the GSH precursor *N*-acetylcysteine prevents the

electrophysiological and behavioral deficits that are characteristic of this animal model[82]. Interestingly, redox dysregulation severely impacts the development of PV+ fast spiking interneurons[81,83] and, consequently, also disrupts critical period plasticity in the developing cortex of mice[84]. Consistent with this, results from a small-scale trial suggest that *N*-acetylcysteine (in addition to antipsychotics) may improve negative symptoms and social functioning in schizophrenia patients[85]. Although larger clinical trials would be required to confirm its efficacy, these studies seem to support the idea that redox dysregulation contributes to aberrant developmental trajectories in schizophrenia and that early correction of this imbalance may have therapeutic potential[86].

Several lines of evidence suggest that non-pharmacological interventions may increase their therapeutical value when applied early. For example, environmental enrichment (enhancing the development of sensorimotor and cognitive functions through improved housing conditions stimulations) in juvenile mice reduces the impact of pharmacological manipulations that cause cognitive deficits in adult mice[87]. Similarly, cognitive training during adolescence improves cognitive function mediated by the prefrontal cortex and the hippocampus in adult NVHL rats[88]. Although the neural mechanisms underlying these effects remain unclear, these studies reinforced the notion that early interventions may have a profound impact in the reorganization of brain circuits affected in schizophrenia.

Lessons from syndromic disorders with childhood diagnosis

Syndromic neurodevelopmental disorders that are diagnosed early in life represent a small fraction of psychiatric disease diagnoses, but insights from their study may allow the identification of therapeutic targets and critical windows that might also be relevant for idiopathic disorders. While frequently grouped under the large umbrella of ASD and related intellectual disabilities, many of these disorders follow divergent trajectories that

suggest that treatments should be tailored accordingly. The differences in disease progression, which correlate with distinct temporal dynamics in the experience-dependent maturation of neural circuits, are very prominent in two of the best-characterized syndromic neurodevelopmental disorders, Fragile X syndrome and Rett syndrome.

Fragile X syndrome

Fragile X syndrome (FXS) is an X-linked neurodevelopmental disorder associated with autism, learning disabilities, abnormal attention, hyperactive and impulsive behaviors, and epilepsy, affecting approximately 1 in 4,000 males[89]. Females are typically less affected and their clinical presentation is more variable, as they still carry one active copy of the affected gene. The disorder is primarily caused by expansion of a CGG triplet repeat in the 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene that cause a reduction of the FMR1 protein, although several other mutations in *FMR1* have been described[90]. FMR1 is an RNA-binding protein that regulates neuronal protein synthesis[91]. Studies in animal models have shown that FMR1 regulates synaptic plasticity by inhibiting protein synthesis downstream of group 1 metabotropic glutamate receptors (mGluR), which is responsible for the stable internalization of AMPA receptors required for long-term depression (LTD) [92]. In the absence of FMR1, uncontrolled mGluR signaling leads to exacerbated LTD and deceleration of synapse maturation, thereby contributing to the cognitive impairment associated with FXS[92].

One of the aspects that the mGluR theory of FXS fails to capture comprehensively is the transient nature of many of the defects found in *Fmr1* mutant mice. Delays in the developmental trajectories of motor, speech, and social skills are behavioral hallmarks of FXS[93]. *Fmr1* mutant mice have a significant delay in the stabilization of dendritic spines and in the maturation of thalamocortical and corticocortical synapses[94-98], defects

associated with a temporal shift in the critical period for sensory-induced plasticity across different cortical areas[94,97,99-101]. This suggests that Fmr1 is particularly important for the refinement of neuronal circuits during this developmental time window.

In addition to developmental delay, FXS patients are characterized by a high incidence of hyperexcitable EEG patterns and cortically derived seizures[102]. Consistently, *Fmr1* mutant mice are highly susceptible to seizures[103] and exhibit abnormally high cortical network synchrony during juvenile stages[104]. Hypersynchrony is due to a higher than normal proportion of active pyramidal cells, which are intrinsically more excitable and have increased firing rates[104,105]. While persistent mGluR5 activation has been shown to increase the excitability of pyramidal cells[106], defects in GABAergic signaling may also contribute to the hyperexcitability observed in *Fmr1* mutant mice[107]. In particular, there is a prominent delay in the normal excitatory to inhibitory switch of GABA during postnatal development due to abnormally high levels of NKCC1 beyond P10 in *Fmr1* mutant mice[108,109]. In addition, widespread defects in GABAergic signaling across cortical and subcortical regions may also contribute to the abnormal hyperexcitability of juvenile *Fmr1* mutants[107].

Preclinical studies have primarily focused on mGluR5 signaling as potential targets for treatment in adult mice[99,110-113]. However, several drug development programs based on the inhibition of mGluR signaling for the treatment of FXS (Novartis and Seaside Therapeutics) were recently closed because efficacy studies in adolescents and adults showed no measurable benefits[114,115]. Similarly, treatment with $GABA_A$ and $GABA_B$ receptor modulators seems to control hyperexcitability in *Fmr1* mutant mice, but similar approaches in human patients have failed to yield positive outcomes[107,116]. While the results of these studies may indicate that preclinical studies in mice are not directly translatable to

humans, an alternative interpretation is that the developmental window of intervention used in these trials might be desynchronized with the developmental timing of alterations in FXS patients. In that context, a recent clinical trial with bumetanide, a drug that inhibits NKCC1, has shown improved accuracy in facial emotional labeling and enhanced communication in a group of ASD children between the ages of 3 and 11 years[117,118]. Bumetanide has also been shown to prevent pathology in a genetic epilepsy mouse model when administered transiently during early postnatal development[119]. These results reinforce the view that treatment benefits may only be seen if started in early childhood.

Rett syndrome

Recent work on another neurodevelopmental disorder illustrates the increasing recognition of developmental milestones for designing effective treatments. Rett Syndrome (RTT) is an X-linked neurodevelopmental disorder that is primarily caused by mutations in the gene coding for methyl CpG-binding protein 2 (MECP2). Most affected individuals are female heterozygotes who are somatic mosaics for normal and mutant *MECP2*[120]. The disease is characterized by seemingly normal postnatal development followed by a sudden deceleration in growth associated with progressive loss of acquired motor and language skills, stereotypic hand movements, muscle hypotonia, autonomic dysfunctions and severe cognitive impairment[121]. MECP2 is global transcriptional modulator and multifunctional mediator of protein interactions that is strongly expressed in the CNS at a time that correlates with neuronal maturation and synaptogenesis[122].

The consequences of MeCP2 dysfunction on neuronal networks have been extensively explored in mice lacking MeCP2 and those with a conditional hemizygous deletion, but the results vary considerably possibly due to differences in the age of the mice in the analysis (juvenile, young adults and adults) and the specific characteristics of each cortical

area[123,124]. Recent studies suggest that the abnormal activity of cortical circuits might be caused by the precocious development of GABAergic interneurons, a hypothesis that has been primarily tested in the visual cortex. In a pattern that resembles the relapse of RTT patients, vision acuity initially develops normally in *Mecp2* mutants but regresses in young adult mice[125]. Loss of vision is preceded by the accelerated development of Parvalbumin-expressing (PV+) fast-spiking basket cells that provide perisomatic inhibition to pyramidal cells[125-127]. Consistent with the observation that maturation of PV+ interneurons triggers the onset of the critical period[128] (Figure 2), *Mecp2* mutants have a precocious onset and closure of critical period plasticity[125,126]. Inhibitory function seems to normalize in young adult mice[129], perhaps due to homeostatic compensations following long-term reduction of activity levels[126], but the early alterations in neural networks cause long-term functional deficits[125].

The precocious window of critical period plasticity observed in *Mecp2* mutant mice (which reduces the influence of visual experience on the developing cortex) can be rescued by reducing sensory inputs (dark-rearing), decreasing the activation of PV+ interneurons by pyramidal cells (NMDA receptor disruption) or reducing GABAergic neurotransmission (Gad67 reduction)[125-127]. These results indicate that MeCP2 function is required for experience-dependent synaptic remodeling during postnatal development and suggest possible pathways – and most importantly, timing – for therapeutical interventions.

Preclinical studies have shown that disinhibition of pyramidal cells through low (sub-anesthetic) doses of ketamine, an NMDAR antagonist that acts preferentially on PV+ interneurons reducing the excitatory drive onto these cells[130], normalizes inhibitory connectivity, prevents the silencing of cortical circuits, and extends the lifespan of *Mecp2* mutants[131]. Ketamine treatment normalizes cortical activity in both young adults and adult

mice[131,132], but it remains to be tested whether early and late treatments achieve similar results in restoring function.

In summary, animal studies of neurodevelopmental disorders such as FXS and RTT reinforce the view that sensitive periods during early postnatal development are likely critical for the emergence of many of the deficits observed in these disorders. It should be noted that these conclusions seem at odd with work suggesting that behavioral deficits in mouse models FXS and RTT can be reverted in adulthood[133]. The most likely explanation for this apparent discrepancy is that the proteins involved in these disorders also play important functions in the mature brain[133,134]. Consequently, behavioral phenotypes are likely caused by both developmental and adult pathophysiology, and early interventions stand a better chance to restore the original deficits.

Practical considerations and caveats of early intervention

Early intervention in psychiatric disorders have practical considerations and limitations that are common to therapeutic approaches in adulthood, such as the difficulty in assessing the impact of treatments in non-syndromic conditions In particular, with regard to treating children and adolescents, attention should be given to the identification of target groups, the adverse effects of early treatments, the translational potential of rodent brain development studies, and ethical concerns.

Since most risk factors to which at risk individuals are potentially exposed in early development only contribute minimally to non-syndromic neurodevelopmental disorders, assessing the benefits of early treatment is very difficult. For this reason, I recommend that the development of early interventions should initially focus on those with the highest relative risk for developing a psychiatric condition. This would include individuals carrying mutations associated with syndromic neurodevelopmental disorders such as

22q11 deletion syndrome, or individuals with a first-degree relative with a psychiatric condition[135,136] or greatly vulnerable, such as extreme premature babies or adolescents at ultra-high risk for psychosis[137,138]. Even within these relatively constricted populations, additional biomarkers would be required to improve our ability to assess treatment success though much research is required before such biomarkers will be available. A universal genetic biomarker of the risk of transition to schizophrenia is not currently available, although studies are beginning to link specific gene variation with increased risk for transition to psychosis[139]. In addition, biochemical[140,141], imaging[52,142,143], and electrophysiological measurements[144] may help segregating patients into higher- and lower-risk groups. However, since not every individual develops at exactly the same pace[145], the developmental trajectory of specific measurements is probably more important for defining early risk than deficits at specific time points during development. For example, attention to eyes is progressively loss during a period of several months in children later diagnosed with ASD[146], and it is likely that many biomarkers of schizophrenia and other psychiatric disorders that are diagnosed in young adults may have a similar longitudinal dimension. While this approach may increase our ability to stratify patient groups, the cost of the longitudinal assessment of 'at risk' populations should not be underestimated.

There are several important considerations in relation to the safety of early interventions. First, while early intervention may prevent subsequent symptoms caused by the dynamic reorganization of developing circuits, the adverse effect of treatments may also cascade over time when targeted to children or adolescents[13,14]. For instance, weight gain caused by atypical antipsychotic drugs may have a more profound impact on child behavior than in adults[147]. Secondly, treatment in children and adolescents may trigger

unexpected side effects that are unique to these patient populations. As described above, many therapeutical interventions in ASD and schizophrenia aim to target inhibitory interneurons, and these treatments have minor secondary effects in healthy adults. In young rodents and primates, however, acute exposure to NMDA blockers and $GABA_A$ receptor agonists triggers widespread apoptotic death of neurons in the developing brain[148-150]. If these drugs were to affect human brain development in a similar manner, the developmental window for this vulnerability may well extent for several years after birth. Thirdly, the clinical output of 'at risk' populations is not homogeneous. Individuals carrying 22q11 deletions may develop ASD, schizophrenia, depression or anxiety disorders, among other conditions[151], and most individuals at ultra-high risk for psychosis transition to a psychiatric disorder other than schizophrenia, including major depressive disorder or bipolar disorder[138]. In the absence of additional markers for patient stratification, early treatments would need to take into consideration the diversity of behavioral outcomes that may arise from divergent developmental trajectories.

As discussed above, studies in animal models for syndromic neurodevelopmental disorders such as FXS and RTT have substantially advanced our understanding of the pathophysiological mechanisms operating in these conditions. Yet, discoveries are not easily translatable to humans[4]. Although it is unlikely that the affected proteins play very different roles in rodents and humans, several studies have shown species-specific patterns of expression for some genes that play important roles in neurodevelopment, in particular in the organization of the cerebral cortex[15]. In addition, since the behavior of humans and rodents is highly divergent, animal model studies should shift their emphasis from behavioral analyses to the identification of more translatable circuit-based electrophysiological deficits[61]. Most notably, the vital cycle of rodents is very different

from humans. From the perspective of developmental trajectories, a four-week treatment in newborn mice would be equivalent to over a decade of life in children. However, receptor sensitization might have similar dynamics in both species, and so a four-week treatment may indeed have similar effects in rodents and humans from a pharmacological point of view. Addressing these questions would be critical for the design of clinical trials based on early interventions.

Finally, developing new treatments for children and adolescents have important ethical and regulatory implications. Assessing efficacy and safety of newly developed compounds to treat neuropsychiatric diseases in adults seems counterproductive, as benefits might only be appreciated if individuals are treated as children or young adolescents. On the other hand, testing new pharmacological treatments in children may have unwanted consequences. Moreover, since we are currently unable to reliably predict pathological trajectories in 'at risk' populations and not everyone from these groups will go on to develop a psychiatric condition, treatment will impact the developmental trajectories of potentially healthy individuals. Finally, with the possibility of reliable biomarkers in the future, we may be able to improve 'pre-symptomatic' diagnosis. Another key ethical question is whether telling children about their 'at risk' status may harm them, and even increase their risk by exacerbating other risk factors, such as anxiety.

Conclusions and outlook

Recognizing the developmental context of neuropsychiatric disorders is giving new impetus to research in this field. Neural network dynamics are extremely complex and change dramatically with disease progression, as shown in animal model studies exploring the function of specific neural circuits at different stages. This is contributing to shift the emphasis of therapeutic approaches to neuropsychiatric disorders from symptomatic

treatment (typically in the adult) to course-alteration (ideally before the onset of main symptoms.

Studies in animal models are also shifting from the analysis of behavioral deficits to the interrogation of neural circuit abnormalities[61], which is proving more powerful for the identification of pathophysiological mechanisms. This approach has revealed that the developmental trajectories of relatively close clinical conditions may diverge substantially, even when they share common behavioral deficits. In the case of psychiatric disorders that are diagnose relatively late in life such as schizophrenia, a better understanding of the longitudinal time course of initial symptoms will be necessary for the successful implementation of early therapies. Finally, and perhaps most importantly, clinical trial design for neurodevelopmental disorders must begin considering appropriately how developmental timing and critical windows will impact prospective results. Lumping together children and adolescents in the same clinical trials with no consideration for the dynamic changes that operate during brain development may reduce the possibilities of identifying potentially successful treatments. Looking forward, our ability to develop disease-modifying interventions that are time-matched to the specific state of neural networks at any given stage of development may prove indispensable for the treatment of many psychiatric disorders.

ACKNOWLEDGEMENTS

I apologize for not citing all relevant references due to space limitations. I thank B. Rico and members of the Marín lab for valuable discussions and critical reading of this manuscript. The Simons Foundation Autism Research Initiative (SFARI 239766OM) and De Spoelberch Foundation support work on this topic in my laboratory. Oscar Marín is a Wellcome Trust Investigator.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

REFERENCES

1. Gore, F.M., *et al.* Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet* **377**, 2093-2102 (2011).
2. Lee, F.S., *et al.* Mental health. Adolescent mental health--opportunity and obligation. *Science* **346**, 547-549 (2014).
3. van Os, J. & Kapur, S. Schizophrenia. *Lancet* **374**, 635-645 (2009).
4. Jeste, S.S. & Geschwind, D.H. Clinical trials for neurodevelopmental disorders: At a therapeutic frontier. *Science Transl. Med.* **8**, 321fs321 (2016).
5. Johnson, M.B., *et al.* Functional and evolutionary insights into human brain development through global transcriptome analysis. *Neuron* **62**, 494-509 (2009).
6. Jaffe, A.E., *et al.* Developmental regulation of human cortex transcription and its clinical relevance at single base resolution. *Nat. Neurosci.* **18**, 154-161 (2015).
7. Hall, J., Trent, S., Thomas, K.L., O'Donovan, M.C. & Owen, M.J. Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity. *Biol. Psychiatry* **77**, 52-58 (2015).
8. Willsey, A.J. & State, M.W. Autism spectrum disorders: from genes to neurobiology. *Curr. Opin. Neurobiol.* **30**, 92-99 (2015).
9. Sekar, A., *et al.* Schizophrenia risk from complex variation of complement component 4. *Nature* **530**, 177-183 (2016).
10. Schmitt, A., Malchow, B., Hasan, A. & Falkai, P. The impact of environmental factors in severe psychiatric disorders. *Front Neurosci* **8**, 19 (2014).
11. Hubener, M. & Bonhoeffer, T. Neuronal plasticity: beyond the critical period. *Cell* **159**, 727-737 (2014).

12. Kalia, A.*, et al.* Development of pattern vision following early and extended blindness. *Proc. Natl. Acad. Sci. USA* **111**, 2035-2039 (2014).

13. Millan, M.J.*, et al.* Altering the course of schizophrenia: progress and perspectives. *Nat. Rev. Drug Discov.* **15**, 485-515 (2016).

14. Veenstra-VanderWeele, J. & Warren, Z. Intervention in the context of development: pathways toward new treatments. *Neuropsychopharmacology* **40**, 225-237 (2015).

15. Silbereis, J.C., Pochareddy, S., Zhu, Y., Li, M. & Sestan, N. The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. *Neuron* **89**, 248-268 (2016).

16. Wiesel, T.N. & Hubel, D.H. Extent of recovery from the effects of visual deprivation in kittens. *J. Neurophysiol.* **28**, 1060-1072 (1965).

17. Greenhill, S.D.*, et al.* Adult cortical plasticity depends on an early postnatal critical period. *Science* **349**, 424-427 (2015).

18. Anderson, P.J. & Reidy, N. Assessing executive function in preschoolers. *Neuropsychol. Rev.* **22**, 345-360 (2012).

19. Friedmann, N. & Rusou, D. Critical period for first language: the crucial role of language input during the first year of life. *Curr Opin Neurobiol* **35**, 27-34 (2015).

20. Rakic, P., Bourgeois, J.P. & Goldman-Rakic, P.S. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. *Prog. Brain Res.* **102**, 227-243 (1994).

21. Ebert, D.H. & Greenberg, M.E. Activity-dependent neuronal signalling and autism spectrum disorder. *Nature* **493**, 327-337 (2013).

22. Penzes, P., Cahill, M.E., Jones, K.A., VanLeeuwen, J.E. & Woolfrey, K.M. Dendritic spine pathology in neuropsychiatric disorders. *Nat. Neurosci.* **14**, 285-293 (2011).

23. Sudhof, T.C. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* **455**, 903-911 (2008).

24. Marín, O. Interneuron dysfunction in psychiatric disorders. *Nat. Rev. Neurosci.* **13**, 107-120 (2012).

25. Ben-Ari, Y. Excitatory actions of gaba during development: the nature of the nurture. *Nat. Rev. Neurosci.* **3**, 728-739. (2002).

26. Ben-Ari, Y., Gaiarsa, J.L., Tyzio, R. & Khazipov, R. GABA: a pioneer transmitter that excites immature neurons and generates primitive oscillations. *Physiol. Rev.* **87**, 1215-1284 (2007).

27. Kirkby, L.A., Sack, G.S., Firl, A. & Feller, M.B. A role for correlated spontaneous activity in the assembly of neural circuits. *Neuron* **80**, 1129-1144 (2013).

28. Uhlhaas, P.J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A. & Singer, W. Neural synchrony and the development of cortical networks. *Trends Cogn. Sci.* **14**, 72-80 (2010).

29. Tyzio, R.*, et al.* Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. *Science* **314**, 1788-1792 (2006).

30. Mwaniki, M.K., Atieno, M., Lawn, J.E. & Newton, C.R. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet* **379**, 445-452 (2012).

31. Ben-Ari, Y. Is birth a critical period in the pathogenesis of autism spectrum disorders? *Nat. Rev. Neurosci.* **16**, 498-505 (2015).

32. Rochefort, N.L.*, et al.* Sparsification of neuronal activity in the visual cortex at eye-opening. *Proc. Natl. Acad. Sci. USA* **106**, 15049-15054 (2009).

33. Toyoizumi, T.*, et al.* A theory of the transition to critical period plasticity: inhibition selectively suppresses spontaneous activity. *Neuron* **80**, 51-63 (2013).

34. Nabel, E.M. & Morishita, H. Regulating critical period plasticity: insight from the visual system to fear circuitry for therapeutic interventions. *Front. Psychiatry* **4**, 146 (2013).

35. Hubel, D.H. & Wiesel, T.N. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *Journal of Physiology* **206**, 419-436 (1970).

36. Wang, B.S., Sarnaik, R. & Cang, J. Critical period plasticity matches binocular orientation preference in the visual cortex. *Neuron* **65**, 246-256 (2010).

37. Hensch, T.K. Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* **6**, 877-888 (2005).

38. Hu, H., Gan, J. & Jonas, P. Fast-spiking, parvalbumin(+) GABAergic interneurons: from cellular design to microcircuit function. *Science* **345**, 1255263 (2014).

39. Sigurdsson, T. & Duvarci, S. Hippocampal-Prefrontal Interactions in Cognition, Behavior and Psychiatric Disease. *Front. Syst. Neurosci.* **9**, 190 (2015).

40. Leucht, S.*, et al.* Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* **373**, 31-41 (2009).

41. Green, M.F. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am. J. Psychiatry* **153**, 321-330 (1996).

42. Weinberger, D.R. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch. Gen. Psychiatry* **44**, 660-669 (1987).

43. Rapoport, J.L., Giedd, J.N. & Gogtay, N. Neurodevelopmental model of schizophrenia: update 2012. *Mol. Psychiatry* **doi: 10.1038/mp.2011.163. [Epub ahead of print]**(2012).

44. Insel, T.R. Rethinking schizophrenia. *Nature* **468**, 187-193 (2010).

45. Wyatt, R.J. Neuroleptics and the natural course of schizophrenia. *Schizophr. Bull.* **17**, 325-351 (1991).

46. Robinson, D.*, et al.* Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch. Gen. Psychiatry* **56**, 241-247 (1999).

47. Howes, O.D.*, et al.* The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch. Gen. Psychiatry* **69**, 776-786 (2012).

48. Honea, R., Crow, T.J., Passingham, D. & Mackay, C.E. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am. J. Psychiatry* **162**, 2233-2245 (2005).

49. Lewis, D.A., Curley, A.A., Glausier, J.R. & Volk, D.W. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* **35**, 57-67 (2012).

50. Lewis, D.A., Hashimoto, T. & Volk, D.W. Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* **6**, 312-324 (2005).

51. Fusar-Poli, P.*, et al.* Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch. Gen. Psychiatry* **69**, 220-229 (2012).

52. Howes, O.*, et al.* Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol. Psychiatry* **16**, 885-886 (2011).

53. Fusar-Poli, P.*, et al.* Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci. Biobehav. Rev.* **37**, 1680-1691 (2013).

54. Davidson, M.*, et al.* Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am. J. Psychiatry* **156**, 1328-1335 (1999).

55. Lipska, B.K., Jaskiw, G.E. & Weinberger, D.R. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology* **9**, 67-75 (1993).

56. Modinos, G., Allen, P., Grace, A.A. & McGuire, P. Translating the MAM model of psychosis to humans. *Trends Neurosci.* **38**, 129-138 (2015).

57. Jones, C.A., Watson, D.J. & Fone, K.C. Animal models of schizophrenia. *Br. J. Pharmacol.* **164**, 1162-1194 (2011).

58. Yoon, K.J.*, et al.* Modeling a genetic risk for schizophrenia in iPSCs and mice reveals neural stem cell deficits associated with adherens junctions and polarity. *Cell Stem Cell* **15**, 79-91 (2014).

59. Shcheglovitov, A.*, et al.* SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients. *Nature* **503**, 267-271 (2013).

60. Brennand, K.J.*, et al.* Modelling schizophrenia using human induced pluripotent stem cells. *Nature* **473**, 221-225 (2011).

61. Kaiser, T. & Feng, G. Modeling psychiatric disorders for developing effective treatments. *Nat. Med.* **21**, 979-988 (2015).

62. Richtand, N.M., *et al.* Risperidone pretreatment prevents elevated locomotor activity following neonatal hippocampal lesions. *Neuropsychopharmacology* **31**, 77-89 (2006).

63. McGlashan, T.H., *et al.* Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am. J. Psychiatry* **163**, 790-799 (2006).

64. Kim, I.H., *et al.* Spine pruning drives antipsychotic-sensitive locomotion via circuit control of striatal dopamine. *Nat. Neurosci.* **18**, 883-891 (2015).

65. Kraguljac, N.V., White, D.M., Reid, M.A. & Lahti, A.C. Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. *JAMA Psychiatry* **70**, 1294-1302 (2013).

66. Schobel, S.A., *et al.* Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron* **78**, 81-93 (2013).

67. Brugger, S., Davis, J.M., Leucht, S. & Stone, J.M. Proton magnetic resonance spectroscopy and illness stage in schizophrenia--a systematic review and meta-analysis. *Biol. Psychiatry* **69**, 495-503 (2011).

68. del Pino, I., *et al.* Erbb4 deletion from fast-spiking interneurons causes schizophrenia-like phenotypes. *Neuron* **79**, 1152-1168 (2013).

69. Andreou, C., *et al.* Increased Resting-State Gamma-Band Connectivity in First-Episode Schizophrenia. *Schizophr. Bull.* **41**, 930-939 (2015).

70. Sun, L., *et al.* Evidence for dysregulated high-frequency oscillations during sensory processing in medication-naive, first episode schizophrenia. *Schizophr. Res.* **150**, 519-525 (2013).

71. Du, Y. & Grace, A.A. Peripubertal diazepam administration prevents the emergence of dopamine system hyperresponsivity in the MAM developmental disruption model of schizophrenia. *Neuropsychopharmacology* **38**, 1881-1888 (2013).

72. Rudolph, U. & Knoflach, F. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. *Nat. Rev. Drug Discov.* **10**, 685-697 (2011).

73. Schizophrenia Working Group of the Psychiatric Genomics, C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421-427 (2014).

74. Karayiorgou, M.*, et al.* Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc. Natl. Acad. Sci. USA* **92**, 7612-7616 (1995).

75. Karayiorgou, M., Simon, T.J. & Gogos, J.A. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat. Rev. Neurosci.* **11**, 402-416 (2010).

76. Green, T.*, et al.* Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *J. Am. Acad. Child. Adolesc. Psychiatry* **48**, 1060-1068 (2009).

77. Sigurdsson, T., Stark, K.L., Karayiorgou, M., Gogos, J.A. & Gordon, J.A. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature* **464**, 763-767 (2010).

78. Mukai, J.*, et al.* Molecular substrates of altered axonal growth and brain connectivity in a mouse model of schizophrenia. *Neuron* **86**, 680-695 (2015).

79. Tamura, M., Mukai, J., Gordon, J.A. & Gogos, J.A. Developmental Inhibition of Gsk3 Rescues Behavioral and Neurophysiological Deficits in a Mouse Model of Schizophrenia Predisposition. *Neuron* **89**, 1100-1109 (2016).

80. Do, K.Q.*, et al.* Schizophrenia: glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. *Eur. J. Neurosci.* **12**, 3721-3728 (2000).

81. Steullet, P.*, et al.* Redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations, and related behaviors. *J. Neurosci.* **30**, 2547-2558 (2010).

82. Cabungcal, J.H.*, et al.* Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. *Neuron* **83**, 1073-1084 (2014).

83. Behrens, M.M.*, et al.* Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. *Science* **318**, 1645-1647 (2007).

84. Morishita, H., Cabungcal, J.H., Chen, Y., Do, K.Q. & Hensch, T.K. Prolonged Period of Cortical Plasticity upon Redox Dysregulation in Fast-Spiking Interneurons. *Biol. Psychiatry* **78**, 396-402 (2015).

85. Farokhnia, M.*, et al.* N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. *Clin. Neuropharmacol.* **36**, 185-192 (2013).

86. Do, K.Q., Cabungcal, J.H., Frank, A., Steullet, P. & Cuenod, M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr. Opin. Neurobiol.* **19**, 220-230 (2009).

87. Koseki, T.*, et al.* Exposure to enriched environments during adolescence prevents abnormal behaviours associated with histone deacetylation in phencyclidine-treated mice. *Int. J. Neuropsychopharmacol.* **15**, 1489-1501 (2012).

88. Lee, H.*, et al.* Early cognitive experience prevents adult deficits in a neurodevelopmental schizophrenia model. *Neuron* **75**, 714-724 (2012).

89. Hagerman, R.J.*, et al.* Advances in the treatment of fragile X syndrome. *Pediatrics* **123**, 378-390 (2009).

90. Penagarikano, O., Mulle, J.G. & Warren, S.T. The pathophysiology of fragile x syndrome. *Annu. Rev. Genom. Hum. Genet.* **8**, 109-129 (2007).

91. Santoro, M.R., Bray, S.M. & Warren, S.T. Molecular mechanisms of fragile X syndrome: a twenty-year perspective. *Annu. Rev. Pathol.* **7**, 219-245 (2012).

92. Bear, M.F., Huber, K.M. & Warren, S.T. The mGluR theory of fragile X mental retardation. *Trends Neurosci.* **27**, 370-377 (2004).

93. Garber, K.B., Visootsak, J. & Warren, S.T. Fragile X syndrome. *Europ. J. Hum. Genet.* **16**, 666-672 (2008).

94. Bureau, I., Shepherd, G.M. & Svoboda, K. Circuit and plasticity defects in the developing somatosensory cortex of FMR1 knock-out mice. *J. Neurosci.* **28**, 5178-5188 (2008).

95. Cruz-Martin, A., Crespo, M. & Portera-Cailliau, C. Delayed stabilization of dendritic spines in fragile X mice. *J. Neurosci.* **30**, 7793-7803 (2010).

96. Galvez, R. & Greenough, W.T. Sequence of abnormal dendritic spine development in primary somatosensory cortex of a mouse model of the fragile X mental retardation syndrome. *Am. J. Med. Genet. A* **135**, 155-160 (2005).

97. Harlow, E.G.*, et al.* Critical period plasticity is disrupted in the barrel cortex of FMR1 knockout mice. *Neuron* **65**, 385-398 (2010).

98. Nimchinsky, E.A., Oberlander, A.M. & Svoboda, K. Abnormal development of dendritic spines in FMR1 knock-out mice. *J. Neurosci.* **21**, 5139-5146 (2001).

99. Dolen, G.*, et al.* Correction of fragile X syndrome in mice. *Neuron* **56**, 955-962 (2007).

100. Kim, H., Gibboni, R., Kirkhart, C. & Bao, S. Impaired critical period plasticity in primary auditory cortex of fragile X model mice. *J. Neurosci.* **33**, 15686-15692 (2013).

101. Till, S.M.*, et al.* Altered maturation of the primary somatosensory cortex in a mouse model of fragile X syndrome. *Hum. Mol. Genet.* **21**, 2143-2156 (2012).

102. Berry-Kravis, E.*, et al.* Seizures in fragile X syndrome: characteristics and comorbid diagnoses. *Am. J. Intellect. Dev. Disabil.* **115**, 461-472 (2010).

103. Musumeci, S.A.*, et al.* Audiogenic seizures susceptibility in transgenic mice with fragile X syndrome. *Epilepsia* **41**, 19-23 (2000).

104. Goncalves, J.T., Anstey, J.E., Golshani, P. & Portera-Cailliau, C. Circuit level defects in the developing neocortex of Fragile X mice. *Nat. Neurosci.* **16**, 903-909 (2013).

105. Gibson, J.R., Bartley, A.F., Hays, S.A. & Huber, K.M. Imbalance of neocortical excitation and inhibition and altered UP states reflect network hyperexcitability in the mouse model of fragile X syndrome. *J. Neurophysiol.* **100**, 2615-2626 (2008).

106. Sourdet, V., Russier, M., Daoudal, G., Ankri, N. & Debanne, D. Long-term enhancement of neuronal excitability and temporal fidelity mediated by metabotropic glutamate receptor subtype 5. *J. Neurosci.* **23**, 10238-10248 (2003).

107. Braat, S. & Kooy, R.F. The GABAA Receptor as a Therapeutic Target for Neurodevelopmental Disorders. *Neuron* **86**, 1119-1130 (2015).

108. He, Q., Nomura, T., Xu, J. & Contractor, A. The developmental switch in GABA polarity is delayed in fragile X mice. *J. Neurosci.* **34**, 446-450 (2014).

109. Tyzio, R.*, et al.* Oxytocin-mediated GABA inhibition during delivery attenuates autism pathogenesis in rodent offspring. *Science* **343**, 675-679 (2014).

110. de Vrij, F.M.*, et al.* Rescue of behavioral phenotype and neuronal protrusion morphology in Fmr1 KO mice. *Neurobiol. Dis.* **31**, 127-132 (2008).

111. Michalon, A.*, et al.* Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. *Neuron* **74**, 49-56 (2012).

112. Su, T.*, et al.* Early continuous inhibition of group 1 mGlu signaling partially rescues dendritic spine abnormalities in the Fmr1 knockout mouse model for fragile X syndrome. *Psychopharmacology (Berl)* **215**, 291-300 (2011).

113. Yan, Q.J., Rammal, M., Tranfaglia, M. & Bauchwitz, R.P. Suppression of two major Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. *Neuropharmacology* **49**, 1053-1066 (2005).

114. Berry-Kravis, E.*, et al.* Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. *Sci. Transl. Med.* **8**, 321ra325 (2016).

115. Scharf, S.H., Jaeschke, G., Wettstein, J.G. & Lindemann, L. Metabotropic glutamate receptor 5 as drug target for Fragile X syndrome. *Curr. Opin. Pharm.* **20**, 124-134 (2015).

116. Berry-Kravis, E.M.*, et al.* Effects of STX209 (arbaclofen) on neurobehavioral function in children and adults with fragile X syndrome: a randomized, controlled, phase 2 trial. *Science Transl. Med.* **4**, 152ra127 (2012).

117. Lemonnier, E.*, et al.* A randomised controlled trial of bumetanide in the treatment of autism in children. *Transl. Psychiatry* **2**, e202 (2012).

118. Hadjikhani, N.*, et al.* Improving emotional face perception in autism with diuretic bumetanide: a proof-of-concept behavioral and functional brain imaging pilot study. *Autism* **19**, 149-157 (2015).

119. Marguet, S.L.*, et al.* Treatment during a vulnerable developmental period rescues a genetic epilepsy. *Nat. Med.* **21**, 1436-1444 (2015).

120. Chahrour, M. & Zoghbi, H.Y. The story of Rett syndrome: from clinic to neurobiology. *Neuron* **56**, 422-437 (2007).

121. Hagberg, B. Clinical manifestations and stages of Rett syndrome. *Ment. Retard. Dev. Disabil. Res. Rev.* **8**, 61-65 (2002).

122. Ausio, J., Martinez de Paz, A. & Esteller, M. MeCP2: the long trip from a chromatin protein to neurological disorders. *Trends Mol. Med.* **20**, 487-498 (2014).

123. Katz, D.M.*, et al.* Rett Syndrome: Crossing the Threshold to Clinical Translation. *Trends Neurosci.* **39**, 100-113 (2016).

124. Lombardi, L.M., Baker, S.A. & Zoghbi, H.Y. MECP2 disorders: from the clinic to mice and back. *J. Clin. Invest.* **125**, 2914-2923 (2015).

125. Durand, S.*, et al.* NMDA receptor regulation prevents regression of visual cortical function in the absence of Mecp2. *Neuron* **76**, 1078-1090 (2012).

126. Krishnan, K.*, et al.* MeCP2 regulates the timing of critical period plasticity that shapes functional connectivity in primary visual cortex. *Proc. Natl. Acad. Sci. USA* **112**, E4782-4791 (2015).

127. Mierau, S.B., Patrizi, A., Hensch, T.K. & Fagiolini, M. Cell-Specific Regulation of N-Methyl-D-Aspartate Receptor Maturation by Mecp2 in Cortical Circuits. *Biol. Psychiatry* **79**, 746-754 (2016).

128. Huang, Z.J.*, et al.* BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* **98**, 739-755 (1999).

129. Dani, V.S.*, et al.* Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome. *Proc. Natl. Acad. Sci. USA* **102**, 12560-12565 (2005).

130. Moghaddam, B. & Krystal, J.H. Capturing the Angel in "Angel Dust": Twenty Years of Translational Neuroscience Studies of NMDA Receptor Antagonists in Animals and Humans. *Schizophr. Bull.* **38**, 942-949 (2012).

131. Patrizi, A.*, et al.* Chronic Administration of the N-Methyl-D-Aspartate Receptor Antagonist Ketamine Improves Rett Syndrome Phenotype. *Biol. Psychiatry* **79**, 755-764 (2016).

132. Kron, M.*, et al.* Brain activity mapping in Mecp2 mutant mice reveals functional deficits in forebrain circuits, including key nodes in the default mode network, that are reversed with ketamine treatment. *J. Neurosci.* **32**, 13860-13872 (2012).

133. Ehninger, D., Li, W., Fox, K., Stryker, M.P. & Silva, A.J. Reversing neurodevelopmental disorders in adults. *Neuron* **60**, 950-960 (2008).

134. McGraw, C.M., Samaco, R.C. & Zoghbi, H.Y. Adult neural function requires MeCP2. *Science* **333**, 186 (2011).

135. Green, J.*, et al.* Intervention for infants at risk of developing autism: a case series. *J. Autism Dev. Disord.* **43**, 2502-2514 (2013).

136. Miklowitz, D.J.*, et al.* Family-focused treatment for adolescents and young adults at high risk for psychosis: results of a randomized trial. *J. Am. Acad. Child Adolesc.* **53**, 848-858 (2014).

137. Larroque, B.*, et al.* Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* **371**, 813-820 (2008).

138. Lin, A.*, et al.* Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *Am. J. Psychiatry* **172**, 249-258 (2015).

139. Bousman, C.A.*, et al.* Effects of NRG1 and DAOA genetic variation on transition to psychosis in individuals at ultra-high risk for psychosis. *Transl. Psychiatry* **3**, e251 (2013).

140. Corcoran, C.M.*, et al.* HPA axis function and symptoms in adolescents at clinical high risk for schizophrenia. *Schizophr. Res.* **135**, 170-174 (2012).

141. Perkins, D.O.*, et al.* Towards a psychosis risk blood diagnostic for persons experiencing high-risk symptoms: preliminary results from the NAPLS project. *Schizophr. Bull.* **41**, 419-428 (2015).

142. Egerton, A., Fusar-Poli, P. & Stone, J.M. Glutamate and psychosis risk. *Curr. Pharm. Des.* **18**, 466-478 (2012).

143. Tognin, S.*, et al.* Using structural neuroimaging to make quantitative predictions of symptom progression in individuals at ultra-high risk for psychosis. *Front. Psychiatry* **4**, 187 (2013).

144. Bodatsch, M., Brockhaus-Dumke, A., Klosterkotter, J. & Ruhrmann, S. Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. *Biol. Psychiatry* **77**, 951-958 (2015).

145. Wolff, J.J.*, et al.* Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am. J. Psychiatry* **169**, 589-600 (2012).

146. Jones, W. & Klin, A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature* **504**, 427-431 (2013).

147. Maayan, L. & Correll, C.U. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J. Child Adolesc. Psychopharmacol.* **21**, 517-535 (2011).

148. Ikonomidou, C.*, et al.* Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* **283**, 70-74 (1999).

149. Bittigau, P.*, et al.* Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc. Natl. Acad. Sci. USA* **99**, 15089-15094 (2002).

150. Brambrink, A.M.*, et al.* Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *Anesthesiology* **112**, 834-841 (2010).

151. Schneider, M.*, et al.* Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am. J. Psychiatry* **171**, 627-639 (2014).

152. Kessler, R.C.*, et al.* Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry* **20**, 359-364 (2007).

153. Kessler, R.C.*, et al.* Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* **6**, 168-176 (2007).

154. Le Magueresse, C. & Monyer, H. GABAergic interneurons shape the functional maturation of the cortex. *Neuron* **77**, 388-405 (2013).

Figure legends

Figure 1. Age of diagnosis for several neuropsychiatric disorders in relation to key processes in human neurodevelopment. (**a**) Most neuropsychiatric disorders have an age of onset in childhood or adolescence. Neurodevelopmental conditions in the autism spectrum disorders (ASD) can be diagnosed shortly after birth, typically before two years of age. Most impulse-control disorders (such as Attention deficit hyperactivity disorder, ADHD) and anxiety disorders (such as phobias) also begin in childhood, whereas schizophrenia and bipolar are typically diagnosed in late adolescence or early adulthood. Mood disorders have a protracted period of onset. Numbers inside the horizontal bars represent median age of diagnosis. Diagnostic age for autism varies greatly across countries. Adapted from Refs [152,153]. (**b**) The figure provides a timeline of human development during prenatal (in post conception weeks, pcw) and postnatal (in years) periods, in which the horizontal bars represent the approximate timing of key neurobiological processes and developmental milestones. The illustrations show gross anatomical features and relative size of the brain at different stages. See Ref. [15] and references therein for details about specific developmental events.

Figure 2. Brain regions affected in schizophrenia. Prefrontal cortex, hippocampus, basal ganglia, amygdala.

Figure 3. Milestones in the development of neural networks in the rodent neocortex. The figure provides a timeline of mouse development during prenatal (in post conception days, pcd) and postnatal (in postnatal days, pnd) periods, in which the horizontal bars represent

the approximate timing of key stages in the maturation of neural networks in the rodent neocortex. The scheme represents processes in the primary visual cortex. Some of the main processes involved with the assembly of neural networks are directly linked to the maturation of GABAergic interneurons, including the switch from excitatory to inhibitory GABA, the generation of transient (early network oscillation, ENO; giant depolarizing potentials, GDP) and mature (theta, gamma) oscillatory rhythms, and the critical period for ocular dominance (OD) plasticity. Adapted from Refs. [31,37,154].

Figure 4. Regulation of critical periods of plasticity by PV+ interneurons under the influence of sensory stimuli.