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Review

Cognitive functions associated with developing prefrontal cortex during adolescence and developmental neuropsychiatric disorders☆

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ABSTRACT

Cognitive functions including social cognition improve significantly during adolescence, the time period during which the brain typically handles a large volume of incoming information from the outside environment. Processing information and responding to environmental challenges allow the prefrontal cortex, a brain region important for cognition, to mature further and establish self-identity, social skills, and other cognitive abilities, thus helping individuals to function in society. People with vulnerable circuitries predisposed by either genetic or early environmental insults, may not be able to deal with social situations appropriately, and develop network dysfunction that may lead to the onset of schizophrenia, which often occurs during this period. Populations with higher risk for developing schizophrenia present "prodromal" phenotypes, including cognitive deficits, even before the onset of the disorder. Modulating circuit plasticity when the prefrontal cortex is particularly vulnerable allows us to support the development of cognitive functions in such populations and prevent them from transitioning into full-blown schizophrenia. For this approach to be successful, we need to conduct both human and animal studies side by side to better understand the neurobiology underlying the disorder, especially changes that occur over the disease trajectory that may be clinically relevant. By taking a multidisciplinary approach, there is a hope for precision medicine for schizophrenia in the future.

1. Introduction

"I cannot therefore consider the organism without its environment."
-Peter D. Mitchell, winner of the 1978 Nobel Prize for Chemistry for the Chemiosmotic theory

Cognitive function is the ability to actively guide one's behaviors based on the representations of the inner and outside world in the brain. It involves the coordination of a heterogeneous set of neural functions mediated by the prefrontal cortex (PFC), such as inhibitory control, performance monitoring, and working memory (Robbins, 2017), abilities essential for us to live and function in society, i.e., our environment. The human PFC is divided into anatomical subregions that are connected with other brain areas, forming distinct networks responsible for various functions (Fuster, 2015; Passingham and Wise, 2014). Even in the same subregion of PFC, individual neurons seem to make connections with different brain areas to form diverse networks, suggesting that neurons within subregions of PFC are also functionally heterogeneous (Parnaudeau et al., 2018). Maturation of these networks over the developmental trajectory correlates with the improvement of associated functions, and although each network follows its own trajectory, the majority of networks and their associated functions mature extensively during adolescence through continuous interactions with the environment (Casey et al., 2008; Huizinga et al., 2006).

Adolescence to early adulthood is also the time period in which many neuropsychiatric disorders emerge. In particular, psychosis, a typical manifestation of schizophrenia, appears during this period, representing a loss of mental connection with the real world (Keshavan et al., 2014). Schizophrenia patients show alterations in brain networks involving PFC (reviewed in Sakurai et al., 2015). Even before disease onset, most people who later develop schizophrenia show some cognitive impairment, depression, and negative symptoms (Jones et al., 2016; Mollon and Reichenberg, 2017). As a result, they may not be able to properly establish circuits/networks important for the maturation of cognitive function during adolescence, resulting in difficulty in keeping

Abbreviations: fMRI, functional magnetic resonance imaging; ADHD, attention-deficit/hyperactivity disorder; CSF, cerebrospinal fluid; HPA, hypothalamic-pituitary-adrenal; iPS, induced pluripotent stem

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up with the real world.

This review will first briefly discuss prodromal symptoms, a condition that people with increased risk for developing schizophrenia show during adolescence. Notably, these phenotypes are mostly related to cognitive function associated with PFC. Then, neurobiological changes that occur when prodromal symptoms transition into full-blown schizophrenia will be considered, focusing on those taking place during adolescence such as adaptation to social stress. Finally, translational research for schizophrenia will be discussed, in particular how the disease trajectory can be modeled in animals based on our neurobiological understanding and how we can devise therapeutic approaches by nurturing the vulnerable brain associated with prodromal symptoms.

2. Prodromal symptoms of schizophrenia

The developmental hypothesis of schizophrenia implies that genetic and environmental insults cause altered brain development, which in turn is responsible for precipitation of the disease (Birnbaum and Weinberger, 2017). Even before the onset of schizophrenia, altered brain development can result in the expression of some phenotypes and defines the prodromal state of schizophrenia (Cannon et al., 2003). Two studies for prodromal schizophrenia characterizing longitudinal cohorts are summarized below.

2.1. The North American Prodrome Longitudinal Study (NAPLS)

The North American Prodrome Longitudinal Study (NAPLS) is a multi-center collaborative study that followed cohorts with high risk for schizophrenia, and compared them with healthy controls using neuropsychological phenotypes, brain imaging, and blood samples. “High risk” was defined as having attenuated positive symptom syndrome, genetic risk and deterioration syndrome, or brief intermittent psychotic syndrome. Some of the high-risk individuals developed psychosis, and eventually full-blown schizophrenia (Addington et al., 2007). The study showed that the high-risk population, especially those who later developed psychosis, showed changes in baseline neurocognitive functions, including impaired attention, working memory, and declarative memory (Seidman et al., 2016). Furthermore, this population also showed impaired theory of mind and social perception (Barbato et al., 2015), supporting the idea that impaired social and neurocognitive functions might characterize people who later develop psychosis (Meyer et al., 2014). The degree of dysfunction was generally less severe than that observed in patients with first-episode schizophrenia, suggesting that further functional decline might occur after the baseline assessment of this population (Seidman et al., 2016). Brain imaging studies found that those who later developed full-blown schizophrenia exhibited accelerated thinning of the gray matter in broad cortical areas, including superior medial, lateral, and inferior PFC, superior temporal gyrus, and parietal cortex, as well as expansion of the ventricular system (Chung et al., 2017).

2.2. Longitudinal studies of 22q11.2 deletion syndrome

Individuals with the 22q11.2 chromosomal deletion are known to have higher risk for developing schizophrenia (Van et al., 2017). Children with the deletion have several physical conditions such as heart and facial defects, together called as the DiGeorge or velocardiofacial syndrome (McDonald-McGinn et al., 2015). They also show ADHD and intellectual disability during childhood, as well as psychosis during adolescence (about 30% of patients), eventually leading to full-blown schizophrenia (about 25% of patients) (Van et al., 2017). Longitudinal studies of these patients have shown that deficits in theory of mind during the earlier developmental period are a robust predictor of the onset of positive symptoms (Jalbrzikowski et al., 2012), supporting that proper development of social cognition skills may be important for them to not develop schizophrenia later in life. Longitudinal studies of the neuroanatomy in these patients suggest delayed maturation, as evident by slower decline in cortical thickness (Schaer et al., 2009) and greater gray matter volumes in the superior temporal gyrus and caudate nucleus compared to typically developing individuals (Gothelf et al., 2007). Interestingly, these alterations are the opposite of those observed in NAPLS, i.e., the accelerated thinning of the gray matter, as described above. Cross-sectional studies using fMRI also showed disruption in the default mode network involving a part of PFC in the population with the 22q11.2 deletion (Tang and Gur, 2018), which may be linked to their cognitive impairment (see below).

These two examples highlight three notable points regarding the prodromal phase preceding schizophrenia. First, there are already alterations in cognitive function and social cognition, which are functions related to PFC. Second, there may be continuous alterations in brain structure over the developmental trajectory, some of which may be associated with the onset of schizophrenia. Third, although these patients may be “vulnerable,” i.e., have some alterations in the brain, not all high-risk individuals develop schizophrenia later in life.

3. Adolescence and the “vulnerable” brain

As described above, about one third of the high-risk population eventually develops schizophrenia during adolescence and early adulthood (Millan et al., 2016). Several events associated with brain development take place during this period, which may be relevant to the progression of schizophrenia.

3.1. What is going on in the adolescent brain?

Throughout our lives, our brain functions are greatly influenced by both internal (biological) and external (environmental/sociological) challenges. One unique aspect of adolescence is the magnitude of changes in the environment and its challenges, such as physical changes including sexual maturation, and new societal roles such as becoming independent, finding partners, and eventually forming a family (Konrad et al., 2013).

As individuals become independent and explore the environment, PFC in particular receives and processes a large volume of external information. This change is further enhanced by the heightened sensitivity to stimuli in the adolescent brain, which may be related to increased reward seeking during this period (Galvan, 2010; Walker et al., 2017). By responding to these stimuli, PFC improves its information processing capacity, processing speed, integration ability, and control of cognition and emotion (Lourenco and Casey, 2013), all of which contribute to improved cognitive function (Konrad et al., 2013). In other words, we are constantly trained in society by being exposed to various stimuli, including moderately stressful environmental challenges that may help in the proper maturation of our adult brain functions.

It should be noted that both the concentration of sex hormones and expression of corresponding receptors drastically increase in the adolescent PFC (Piekarski et al., 2017). This means that 1) changes in sex hormones during adolescence can affect PFC maturation, and 2) there may be sex differences in their effects on maturation (Owens et al., 2018; Piekarski et al., 2017; Walder et al., 2013). Usually, females experience puberty earlier than males. Interestingly, during adolescence a higher rate of cortical thinning in females than males is observed in several brain regions including parts of PFC (Mutlu et al., 2013). It is also known that males tend to develop the disorder earlier than females, and that the male:female ratio of the incidence of schizophrenia is 1.4:1 (McGrath et al., 2008). There seems to be both puberty-dependent and puberty-independent processes in the development of the adolescent brain (Walker et al., 2017), and obviously, effects of puberty on schizophrenia onset are not so simple. Effects of sex hormones and puberty on adolescent brain development are discussed

Table 1
Brain areas involved in cognitive functions

Function	Brain area in primates	Brain area in rodents
Salience detection	Anterior insula, dorsal ACC	ACC
Attention	Dorsal attention network (infraparietal sulcus, frontal eye fields) Ventral attention network (right temporoparietal junction, VLPFC)	ACC, mPFC, thalamus
Working memory	Executive control network (DLPFC, VLPFC, premotor cortex, parietal cortex)	mPFC, ACC, thalamus
Cognitive inhibition	VLPFC, anterior insula, inferior frontal junction	mPFC, ACC
Cognitive flexibility/attention shifting	VLPFC, DLPFC, inferior and superior parietal cortex, posterior parietal cortex, ACC, right anterior insula, premotor cortex, inferior temporal cortex, occipital cortex, inferior frontal junction, caudate, thalamus	OFC, mPFC, ACC, striatum, thalamus
Impulsivity	Infralimbic cortex, insula, ventral hippocampus, cingulate cortex, NAc core, dorsal striatum (premature response) basolateral amygdala, hippocampus, OFC (delay discounting) medial OFC, amygdala (risk-based impulsivity)	mPFC, ACC, OFC, striatum, amygdala

Dajani and Uddin (2015), Dalley and Robbins (2017), Fuster (2015), Sakurai et al. (2015)
ACC, anterior cingulate cortex; VLPFC, ventrolateral PFC; DLPFC, dorsolateral PFC; NAc, nucleus accumbens; OFC, orbitofrontal cortex.

by others (Piekarski et al., 2017).

3.1.1. Cognitive function

Cognitive function is the result of coordination among many different brain areas including PFC (Table 1). For example, for salience detection, anterior cingulate cortex (ACC) is involved in both humans and rodents, whereas for working memory, dorsal lateral PFC, premotor, and parietal cortices are involved in humans, and ACC and medial PFC are involved in rodents (Sakurai et al., 2015). During adolescence, maturation takes place not only in PFC and networks connecting it to other brain regions, but also in the ability to efficiently switch between networks (Anticevic et al., 2012). Cognition also interacts with motivational, emotional, and social processes, such that its development is affected significantly by the development of these other components (Robbins, 2017). For example, adolescents show flexibility in PFC recruitment and cognitive control, which are particularly sensitive to social and affective contexts and the motivational salience of these contexts (Crone and Dahl, 2012, and see below).

Networks important for cognitive functions such as the default mode, frontoparietal, and cingulo-operucular salience networks, go through extensive refinement from adolescence to adulthood, strengthening connections particularly among the functional hubs including some areas of PFC (Grayson and Fair, 2017). In principle, PFC becomes more strongly linked to the sensory cortex and subcortical structures (Konrad et al., 2013; Liston et al., 2006). Recently, NIMH started an initiative called the "ABCD" (Adolescent Brain Cognitive Development) study (Volkow et al., 2017). This initiative is a longitudinal study to establish a large collection of adolescent brain imaging data, which would help in understanding the development of the adolescent brain, as well as individual variability in brain maturation and cognitive development, to tease apart many factors that influence the maturation processes (Volkow et al., 2017).

3.1.2. Social cognition

Social cognition is a key function that is extensively matured during adolescence. Basic social detection, i.e., knowledge and capacity to understand social situations, and a simple form of theory of mind, develop in early childhood, but more complex social cognitive skills such as mentalizing, i.e., the ability to make attributions about the mental states of others, and meta-cognition, i.e., the ability to understand others' perspectives, evolve mostly in adolescence (Blakemore and Mills, 2014; Crone and Dahl, 2012). The development of complex social skills is also driven by rapidly changing environmental demands and experiences during adolescence, namely adapting to peer groups, newly emerging romantic interests, and increased salience of the opinions and evaluations of peers, as greater need for adaptation grows during this period (Blakemore and Mills, 2014).

Furthermore, adolescence is characterized by heightened sensitivity to sociocultural signals in the environment, not only to positive ones like social reward, but also to negative social stimuli (Foulkes and Blakemore, 2016). This hypersensitivity is associated with hyperactivation of the frontal structures in the brain (Blakemore and Mills, 2014).

It is important to note that the developmental processes of social cognition and general cognitive function are tightly linked. As cognitive function matures during late adolescence to early adulthood, there is a steady increase in the ability to use cognitive control, to guide one's thoughts during social cognition (Kilford et al., 2016). On the other hand, the ability to navigate one's decision-making continues to develop beyond the acquisition of cognitive abilities like working memory and response inhibition, as one needs to integrate others' perspectives to help guide the decisions (Blakemore and Mills, 2014). Self-judgment of one's performance is another cognitive function that improves during adolescence by integrating peer evaluation, and follows a trajectory similar to that of the development of mentalizing abilities (Blakemore and Mills, 2014). These two examples illustrate how improvement in social skills affects the development of cognitive abilities (Blakemore and Mills, 2014). In addition to cognition, the development of motivational and emotional aspects of social skills also influences the maturation of social cognition (Crone and Dahl, 2012).

Fig. 1 illustrates the brain network involved in basic information

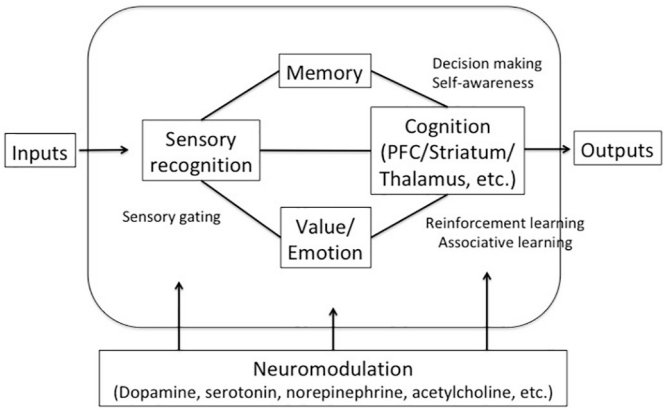

Fig. 1. Schematic working diagram of the brain circuitry involved in basic social behavior
Social stimuli are perceived by the sensory system (sensory cortex etc.). Social information is further integrated with memory (hippocampus etc.) and value (amygdala etc.), and is sent to PFC, where decision-making takes place for appropriate social behaviors in responding to the stimuli. The action plan is sent as outputs to the execution system. These processes can be modulated by the neuromodulatory systems (including sensory gating, motivation, etc.), reinforcement learning, and self-awareness. All these systems including cognitive function have to develop properly and work in coordination for the proper social cognition skills.

Table 2
Brain areas involved in social behaviors

Function	Brain area in primates	Brain area in rodents
Social motivation	VMPFC, ventral striatum, amygdala	mPFC, ventral striatum, amygdala
Social recognition/memory	mPFC, DMPFC	mPFC
Social hierarchy	mPFC, lateral PFC, ventral striatum, amygdala	ACC, mPFC, striatum, amygdala, thalamus
Social brain	posterior superior temporal sulcus, temporoparietal junction, anterior temporal cortex, inferior frontal gyrus, VMPFC, ACC, superior fusiform face area, amygdala	mPFC, ACC, striatum, amygdala

Bicks et al. (2015), Kilford et al. (2016), Sakurai et al. (2015)

processing for a simple form of social cognition. Social stimuli are perceived by the sensory system. Social information is further integrated with memory and value, and is sent to PFC, where decision-making takes place for appropriate social behaviors in responding to the stimuli. The action plan is sent as outputs to the execution system. These processes can be modulated by the neuromodulatory systems (including sensory gating, motivation, etc.), reinforcement learning, and self-awareness. In addition, brain networks among cortical areas involved in social cognition have been characterized (Table 2). In humans, many other cortical areas than PFC are involved in higher social cognition: these include posterior superior temporal sulcus, temporoparietal junction, anterior temporal cortex, and superior fusiform face area (Kilford et al., 2016). Brain areas involved in cognition and emotional processing are interconnected with those involved in social cognition. Extensive remodeling of these social cortical areas takes place during adolescence, which is correlated with further improvement of social cognition (Blakemore and Mills, 2014; Kilford et al., 2016). These will lead to formation of the network responsible for integration of many processes, such as cognition, emotion, memory, and experience etc.

3.1.3. Biological events in the brain

Adaptive changes in the structure and function of PFC as described above are the results of the brain's ability to change and remodel/refine synaptic structures. For example, synapses are always modulated: more active synapses become larger and stronger, while less active ones become smaller and weaker. In the human brain, synaptic density peaks at around 5 years of age, and then many synapses are pruned throughout childhood, and into the third decade of life (Silbereis et al., 2016). Through this process, efficient and effective connections are established in the brain. While overproduction of synapses followed by selective stabilization and elimination is associated principally with excitatory synapses in the cortex (Giedd et al., 1999; Lee et al., 2014), maturation of inhibitory neurons depends on the inputs from excitatory neurons, (Caballero et al., 2016). As a result, local circuitries with the appropriate excitatory/inhibitory (E/I) balance are established in the brain. Disrupted E/I balance is predicted to be responsible for many psychiatric disorders (Penzes et al., 2013).

While many synapses are eliminated, there is an increase in white matter during adolescence (Konrad et al., 2013). This change is partly mediated by "white matter plasticity" due to the formation of myelin and growth in axon diameter (Almeida and Lyons, 2017). Changes in white matter during adolescence likely influence the conduction of electrical impulses across the brain, and axonal transport of cargoes essential for neural transmission, cell metabolism, and neuronal survival (Lee et al., 2014). It has been shown that myelination is an activity-dependent process (Almeida and Lyons, 2017): more active axons lead to more myelin formation, and as a result, better and faster conduction through those axons. Abnormalities in white matter plasticity are also predicted to be important for psychiatric disorders associated with altered cognition (Mount and Monje, 2017; Pajevic et al., 2014; Takahashi et al., 2011).

Cognitive function is regulated by many neuromodulatory systems that show changes during adolescence (Murrin et al., 2007; Wahlstrom et al., 2010). For example, acetylcholine, dopamine, and norepinephrine regulate working memory, while dopamine is important for top-down control and attention (Arnsten, 2011; Gomes et al., 2016; Thiele and Bellgrove, 2018). Serotonin modulates attention, cognitive flexibility, and reversal learning, and is also involved in aggression, fear, and anxiety (Suri et al., 2015; Teissier et al., 2017). All these systems control the degree of neural activity in broad areas of the brain, as well as motivation and affective processing, all of which can affect cognition (Kennedy et al., 2014). Each neuromodulatory system shows a different developmental trajectory, and some of the processes may be activity-dependent (Suri et al., 2015). For example, serotonergic innervation of PFC develops during the perinatal period, whereas dopaminergic innervation develops extensively during adolescence (Gomes et al., 2016; Hoops and Flores, 2017). Therefore, changes in the dopamine system can affect many aspects of cognitive maturation during adolescence (Padmanabhan and Luna, 2014). Notably, altered dopamine signaling has been repeatedly implicated in schizophrenia (Fusar-Poli et al., 2011; Howes et al., 2017; Kesby et al., 2018; Yildirim and Derksen, 2015).

3.1.4. Sensitive period?

In the visual system, there is a time window during development called the "sensitive/critical period," in which the plastic brain can respond to inputs from the environment and change accordingly (Takesian and Hensch, 2013). This ability depends on neuronal activity, and molecular mechanisms for opening and closing the time window of plasticity have been characterized (Nabel and Morishita, 2013). This critical period can be modulated by several different mechanisms including neuromodulation (Suri et al., 2015). An intriguing question is whether the development of PFC and cognitive function possesses a critical period. MRI studies have shown that the human brain reaches approximately 90% of its adult size by age six, but that the gray and white matters in the brain continue to undergo dynamic changes throughout adolescence (Giedd, 2004; Gogtay et al., 2004; Riccomagno and Kolodkin, 2015; Sowell et al., 2003). While the refinement of the primary cortices is observed mainly during childhood, the remodeling of higher-order association cortices such as PFC takes place during adolescence (Riccomagno and Kolodkin, 2015). There are many examples of developmental processes in PFC that are sensitive to external inputs, such as autobiographical memory, executive function, and response to stress (Piekarski et al., 2017). Whether or not these are indicative of the presence of the critical period in PFC, it is fair to say that maturation of brain networks involving PFC and other regions extends beyond adolescence. These processes perhaps ensure that the brain can continue to improve its ability for information processing and adapt to its environment.

Assuming that adolescence is an extended time period for the brain to respond to the environment, another intriguing question is whether this increased plasticity makes the system sensitive to environmental insults during adolescence. Selemon and Zecevic (Selemon and Zecevic, 2015) suggested two major vulnerable periods for insults that lead to schizophrenia, one prenatal/perinatal and the other during adolescence. The prenatal/perinatal period can be affected by both genetic and environmental insults, the latter including exposure to

inflammation *in utero*, obstetric complications, and early life stress (Brown, 2011; Cameron et al., 2017). Meanwhile, challenges during adolescence include changes in physical and social environments (e.g., Davis et al., 2016; Sakurai et al., 2015) that, while providing us with mental and physical stress, would also provide us with positive and negative experiences, memories, and opportunities to develop value perspectives and skills, such as problem solving, and strategic planning (Lourenco and Casey, 2013). These experiences would in turn establish an individual's own way of utilizing cognitive networks for tasks, leading to either harmful or beneficial behaviors (Foulkes and Blakemore, 2018). Thus, it is plausible that PFC may have a longer time window to be modified by environmental inputs than other brain regions like the sensory cortex.

The social brain areas including PFC are also extensively matured during adolescence (Blakemore, 2012). Adolescence is typically associated with increased motivation to approach peers to gain social affiliation (Kilford et al., 2016). By sorting through social cues, a process requiring a fair amount of attention, people attempt to predict other people's thoughts to judge the appropriateness of their actions and predict consequences. These situations can create stress and sometimes even anxiety and depression due to unexpected outcomes. It is interesting that Foulkes *et al.* have suggested that individual differences in brain development are derived from socioeconomic status, peer environment, and cultural background (Foulkes and Blakemore, 2018). Tougher social environments during adolescence, e.g., chronic social stress, lead to functional reorganization of the social brain in animals (e.g., Burke et al., 2017; Niwa et al., 2013; Tielbeek et al., 2018). In brain imaging studies, the ACC appears to be most affected by social stress in humans (Akdeniz et al., 2014). Interestingly, the prodromal period of schizophrenia shows changes in ACC (Bhojraj et al., 2011).

Therefore, the social environment is regarded as a crucial factor that can impose either benefits or damages on vulnerable brain circuitry during adolescence (Davis et al., 2016; Millan et al., 2016), which may be relevant to the onset of schizophrenia.

3.2. What is vulnerability?

Since the circuitry is very adaptive during adolescence, it can be affected drastically by many forms of stress during this period. In the prodromal period of schizophrenia, the brain circuitry seems more vulnerable to the stress during adolescence, but what makes the circuitry more vulnerable? One feature consistently observed in prodromal schizophrenia is lower cognitive function at earlier time points during adolescence compared to normal controls (Seidman et al., 2016). This finding suggests that people with prodromal schizophrenia may already have functional weakness in PFC, which may confer vulnerability in the brain to further insults in the maturation processes during the already vulnerable adolescence period as described in the previous section. What are the biological phenomena underlying impaired cognitive functions?

Genetic and environmental factors are likely responsible for the fragility of the brain in those predisposed to psychiatric disorders (O'Donnell, 2011). Epidemiological studies as well as genetic analyses in humans have implicated many biological events in the pathogenesis of schizophrenia. Animal studies have shown that some of those events predispose the circuit to vulnerability, as described below (Table 3).

Genetic analysis has implicated alterations of many synaptic molecules in schizophrenia (Fromer et al., 2014). Knockout mice for synaptic proteins such as Kalirin and Shank3 have shown synaptic changes associated with behavioral phenotypes relevant to schizophrenia (Remmers et al., 2014; Zhou et al., 2016). The dynamic nature of synaptic functions can be affected by even subtle expression changes in synaptic molecules since synaptic functions depend on the fine balance of these structural proteins. Therefore, changes in structural synaptic molecules like cell adhesion molecules, intracellular trafficking of synaptic molecules (such as those mediated by DISC1), and glial cells involved in the synapses, can affect the local circuitry activity (Sakurai, 2017; Takahashi and Sakurai, 2013; Tomoda et al., 2017) (Fig. 2). Furthermore, autophagy may also be involved in the turnover of synaptic molecules that are important for synaptic homeostasis (Hernandez et al., 2012) (Fig. 2), and its alteration has been implicated in autism spectrum disorder (ASD) and schizophrenia (review, Gozes, 2016; Hui et al., 2018). We recently showed that autophagy defects affect the pyramidal neurons in PFC and can lead to behavioral phenotypes relevant to schizophrenia (Sumitomo et al., 2018b). All these changes at the synapses would affect information processing capability in neurons in the local circuits as well as reduce synaptic transmission in and among the local circuits.

Prenatal inflammation *in utero* caused by microbial infections seems to increase the incidence of schizophrenia in human offspring (Miller et al., 2013), and is implicated in altering the circuitry of GABAergic neurons in animal studies (Canetta et al., 2016; Corradini et al., 2018). Neuroinflammation during the pregnancy (Steullet et al., 2016) as well as obstetric complications can induce oxidative stress, and it has been shown that reduced CSF levels of superoxide dismutase-1, an enzyme involved in reducing oxidative stress, may be correlated with clinical features of early psychosis (Coughlin et al., 2017). Animal studies have shown that the stress can affect the formation of the local circuitry (e.g., Khan et al., 2017; Steullet et al., 2017a), leading to behavioral phenotypes (Johnson et al., 2013). In particular, fast-firing neurons, namely GABAergic interneurons, are more vulnerable to oxidative stress due to their high energy demands (Do et al., 2015). Furthermore, hypersensitivity of these cells to stress predisposed by their initial exposure to oxidative stress may also contribute to the vulnerability later in life (Steullet et al., 2017b).

Prenatal inflammation can also prime microglia, macrophage-like cells that are a major player in inflammation in the brain, to induce exaggerated inflammatory responses by converting them into the inflammatory populations and other inflammatory cells when these cells encounter "a second hit" (Calcia et al., 2016; Takahashi and Sakurai, 2013). This priming may be mediated by epigenetic mechanisms supporting cellular memory (Tay et al., 2017; Wendeln et al., 2018). Brain imaging studies in humans using PET ligands have shown the involvement of neuroinflammation in the onset of schizophrenia (Pasternak et al., 2016). Moreover, it has been shown that blood samples from schizophrenia patients contain increased levels of CD14, which is expressed in macrophages and are involved in innate immune responses (Tanaka et al., 2017). Microglia are also involved in synaptic maturation and pruning (Hammond et al., 2018) (Fig. 2). Altered synaptic maturation and pruning may also be responsible for vulnerability to schizophrenia (Riccomagno and Kolodkin, 2015; Sekar et al., 2016). Interestingly, in postmortem brains of patients with schizophrenia, fewer dendritic spines were observed in pyramidal cells in layers 2/3 of PFC (Glantz and Lewis, 2000), indicating that either impaired development or hyper-pruning of spines may be associated with schizophrenia.

These events affecting synapses are summarized in Fig. 2. Genetic and environmental insults can impact many processes within synapses. Dynamic aspects of synaptic function can be modulated by alterations in the expression, recycling, targeting, and degradation of synaptic molecules. Altered autophagy involved in the turnover of the molecules may also be a possibility. These changes can affect homeostatic plasticity that is crucial for proper synaptic function. Microglia that are involved in pruning dendritic spines can affect vulnerability of synaptic function. These changes around synapses lead to reduced maturation of local circuitry, affecting function of the circuitry.

Perinatal stress affects expression levels of molecules involved in the HPA axis, causing persistent changes throughout the body (Meaney et al., 1996). Maturation processes of PFC can be affected by expression levels of both stress hormones and their receptors (McEwen and Morrison, 2013). For example, dopaminergic neurons have been shown to be a target of stress hormones in animal studies (Niwa et al., 2013;

Table 3
Possible effects of events predisposing vulnerability to the brain

Events	Molecular and cellular changes	Effects on circuitry	References
Perinatal inflammatory response, microglial activation and priming	Cellular damage Exaggerated response on a second hit HPA axis, gene expression changes	Changes in neural activities Disrupted E/I balance	(Calcia et al., 2016; Canetta et al., 2016; Corradini et al., 2018; Takahashi and Sakurai, 2013)
Oxidative stress	Cellular damage (GABAergic interneurons, oligodendrocytes)	Decreased activity in GABAergic neurons White matter abnormalities	(Do et al., 2015; Khan et al., 2017; Maas et al., 2017; Steullet et al., 2017b)
Perinatal stress hormone	HPA axis, gene expression changes Exaggerated response on a second hit	Decrease in dopamine signaling Changes in GABAergic neurons	(McEwen and Morrison, 2013; Meaney et al., 1996; Niwa et al., 2013)
Altered synaptic homeostasis, synaptic molecules, synaptic recycling	Synaptic overload Changes in synaptic transmission	Altered information processing Altered transmission speed	(Remmers et al., 2014; Sakurai, 2017; Sumitomo et al., 2018b; Tomoda et al., 2017; Zhou et al., 2016)
Altered synaptic pruning	Too many/too few dendritic spines	Synaptic alterations	(Riccomagno and Kolodkin, 2015)
Changes in neuromodulation	Too much/too little innervation Changes in gene expression Changes in synaptic modulation Changes in GABAergic interneurons	Altered top-down control Altered sensory gating Altered S/N ratio Altered information processing Alterations in speed of information processing Altered motivation	(Howes et al., 2017; Teissier et al., 2017; Tseng and O'Donnell, 2007)
Altered oligodendrocyte/myelin	Lower conduction speed, less transmission	Altered information processing Altered information integration	(Nave and Ehrenreich, 2014; Takahashi et al., 2011)

Niwa et al., 2016; Gomes and Grace, 2018; Lodge and Grace, 2011; Valenti et al., 2012; Valenti et al., 2011). The NAPLS study mentioned above has shown that there may be changes in stress hormone levels in blood from people with prodromal schizophrenia (Moskow et al., 2016). Interestingly, there may be sex differences in the correlation between stress hormone levels and clinical signs (Moskow et al., 2016; Owens et al., 2018; Walder et al., 2013), suggesting that responsiveness to stress may be sexually dimorphic.

Changes in neuromodulatory systems such as for dopamine can affect maturation and integration of inhibitory neurons in the local circuitry of PFC (Tseng and O'Donnell, 2007) (Fig. 2). Changes in inhibitory local networks would affect neural ensembles in the network activity of PFC (Gonzalez-Burgos et al., 2015). Neuromodulatory systems can also affect the sensory threshold and signal-to-noise ratio (S/N ratio) in the circuitry as well (Arnsten et al., 2012), whose disruption may be associated with schizophrenia. Furthermore, it would affect top-down control of behavior and motivation (Howes et al., 2017). Since the dopamine system develops significantly during adolescence as described above, it can have major impact on any of these events. In contrast, the serotonin system develops mainly during the perinatal period, and may set the tone of the circuitry early in life, which can have significant impact on later maturation processes (Teissier et al., 2017).

In addition to changes in neurons, alterations in oligodendrocytes and myelination can affect connectivity and synchrony among brain areas (Takahashi et al., 2011) (Fig. 2). In humans with schizophrenia, white matter abnormalities have been identified by both brain imaging and postmortem studies (Takahashi et al., 2011). These white matter changes may be introduced by both genetic and environmental factors. Oligodendrocytes may also be a target for oxidative stress (Maas et al.,

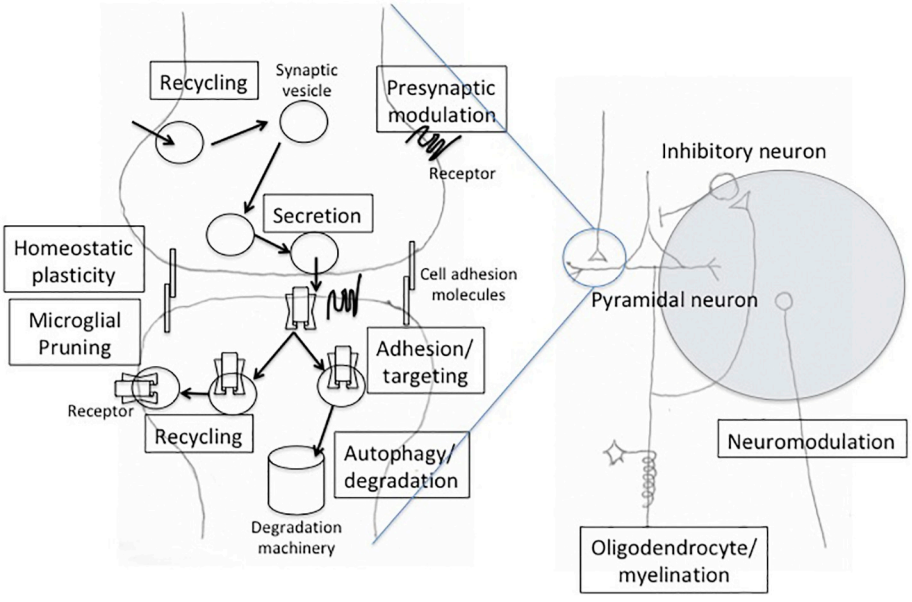

Fig. 2. Vulnerability imposed on synapses of neurons in the local circuits
Genetic and environmental insults can impact many processes within synapses of neurons. Dynamic aspects of synaptic functions can be modulated by alterations in the expression, recycling, targeting, and degradation of synaptic molecules. Autophagy involved in the turnover of these molecules may also be altered. These changes can affect homeostatic plasticity that is crucial for proper synaptic functions. In addition, activity of microglia that are involved in pruning of dendritic spines can be exaggerated, and psychoactive drugs such as cannabis can affect presynaptic modulation. Furthermore, synaptic function can be altered by neuromodulatory systems. Outputs from the excitatory neurons can also be modulated by changes in oligodendrocytes/myelin. All these can alter the activity of local circuitry composed of combinations of excitatory and inhibitory neurons, making circuits vulnerable to further insults during network maturation. Note that any of these processes may be a target for treatment (see text).

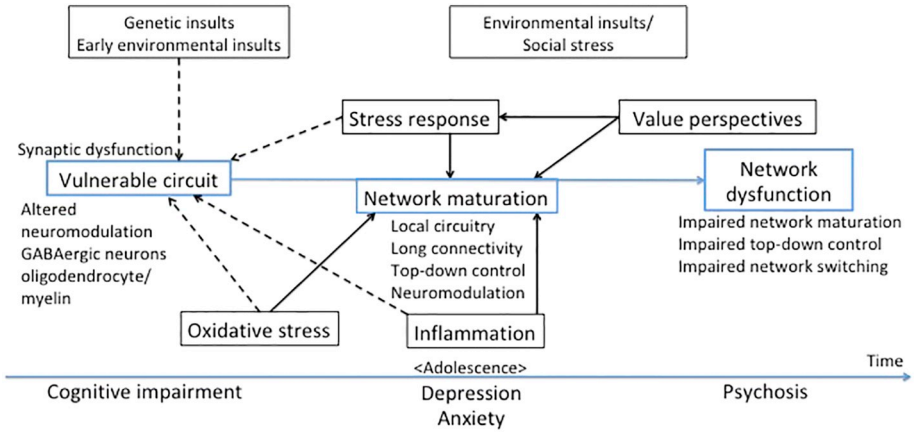

Fig. 3. Transition of prodromal state into full-blown schizophrenia
Genetic variations, as well as stress response, inflammation, and oxidative stress by perinatal environmental insults (dotted arrows) affect synapses, GABAergic neurons, oligodendrocytes/myelin, and neuromodulatory systems, prediposing vulnerability to circuits (see Fig. 2). These vulnerable circuits manifest as cognitive impairment. During adolescence, further environmental insults such as social stress impact maturation of brain networks and functions through stress response, oxidative stress, and inflammation (arrows), resulting in network dysfunction involving impairment in brain network maturation, top-down control, and network switching. Psychoactive drugs such as cannabis alter synaptic activities and neuromodulation. Value perspectives can also affect network maturation (see text). All these may result in manifestation of psychosis.

2017). Impaired neuromodulation as well as oligodendrocyte/myelin can also affect local circuitry.

Any of these scenarios may be responsible for reduced cognitive function that is observed in prodromal schizophrenia. Understanding how the cellular phenotypes described above affect the brain circuitry is crucial in characterizing the prodromal stage of schizophrenia at the cellular and molecular levels (Table 3).

3.3. What makes prodromal schizophrenia convert to full-blown schizophrenia during adolescence?

How would people who are predisposed to schizophrenia develop the full-blown disease during the “vulnerable” adolescent period?

During adolescence, by responding to external stimuli, brain networks achieve 1) strengthening and weakening of networks, such that functional connectivity among brain areas is refined (this would lead to better synchronization and hub formation in the networks), 2) better top-down control from cortices over other cortical and subcortical brain areas, 3) better neuromodulation for functional network engagement, and 4) value determination for individuals through perspectives based on experiences, reinforcement learning, and motivation. Individuals with vulnerable circuitry may not be able to sufficiently achieve all of these processes (Fig. 3). Changes in the HPA axis, inflammation, oxidative stress, neuromodulation, etc., described above, can all lead to synaptic alterations involving GABAergic neurons, which may lead to network alterations responsible for predisposition to schizophrenia. When vulnerable networks receive a fair amount of stimuli from the environment, they may be easily overloaded due to their reduced information processing capacity caused by altered synaptic function and/or interneurons in the circuitry. In addition, reduced synaptic transmission and processing speed due to changes in the connectivity and oligodendrocytes/myelin may lead to alterations in information processing capacity at the levels of local circuitry as well as in long-range connectivity (Nave and Ehrenreich, 2014). These changes may result in reduced ability of brain networks to integrate information.

Alternatively, PFC in those predisposed to schizophrenia may not be able to suppress cortical (e.g., top-down control of behavior) and subcortical (e.g., regulation of emotional responses by amygdala or top-down control over the neuromodulatory systems) responses, due to altered connections or mismatched development of connected areas (Casey et al., 2015). This would in turn affect their ability to process information through the networks involving the cortical and subcortical regions.

Changes in the neuromodulatory systems, either in the projection patterns or responsiveness, can affect both local and long-range information processing. Furthermore, reduced motivation due to altered neuromodulatory systems may affect cognition and other functions in the brain (Howes et al., 2017). It is also possible that appropriate network switching to allocate available brain resources to particular tasks, which is necessary for efficient cognitive functions, may not work well due to less developed circuitry and altered neuromodulatory systems (Anticevic et al., 2012).

Furthermore, such vulnerable individuals may go through rather emotional experiences and different learning processes from those with less vulnerable brains due to their lower cognitive skills. These experiences may affect the adolescent brain in multiple ways. First, as described above, stress can activate the HPA axis, leading to different maturation processes in brain networks (Niwa et al., 2016). In addition, since the circuitry becomes more susceptible to stress hormones, subsequent stress would induce more exaggerated responses in the brain, further damaging the circuitry. Second, reinforcement learning involving dopamine is crucial for prediction and reward learning in the brain (Walker et al., 2017). Different outcomes of these learning processes, both positive and negative, may be established in the vulnerable brain. For example, people with increased risk for social anxiety disorders may experience an approach-avoidance conflict in situations normally regarded as socially rewarding, due to their high investment in what their peers think of them (Caouette and Guyer, 2014; Davey et al., 2008; Kilford et al., 2016). These situations may eventually lead to adolescent depression. Different perspectives lead to different behavioral choices in these individuals’ decision-making. Third, if brain networks cannot handle the salient stimuli properly due to their intrinsic vulnerability as described above, the individuals would not only experience stress and altered learning outcomes, but these experiences would alter the course of brain maturation, further compounding the effects on the functional development of PFC that requires proper activation of the circuitry. All these effects would accumulate in network alterations that lead to deficits in the local connectivity, long-range connections, top-down control, and neuromodulation, contributing to different perspectives and outcome expectancy, misunderstanding, improper reasoning, and altered motivation in the affected individuals (Fig. 3).

Since the maturation of cognition is crucial for social behaviors (Blakemore and Mills, 2014), any delay in cognitive maturation would further affect the development of social cognition, which may be considered as a risk for developing schizophrenia (Davis et al., 2016). When social cognition of people who are vulnerable to developing schizophrenia is not matured properly, these people will experience more stress during social encounters, which may lead to further activation of the HPA axis. If their social cognition, including theory of mind and mentalizing is not matured properly, many instances of unsuccessful learning and bad experiences may lead to different expectations of these people from those of others, leading them to social

isolation. In fact, immigration is linked to such situations (Akdeniz et al., 2014) and has been shown to be a risk factor for schizophrenia by epidemiological studies (van Os et al., 2010). Anxiety and negative symptoms observed in prodromal schizophrenia (Jones et al., 2016) may also be associated with social isolation. Another risk factor for schizophrenia as shown by epidemiological studies is urban upbringing (e.g., Paksarian et al., 2017), and it would be reasonable to assume that living in urban areas demands more social encounters compared to living in rural areas (but see also DeVylder et al., 2018).

Usage of cannabis and other psychoactive drugs is known to change synaptic activity during adolescence more than during any other time period in life (Swendsen et al., 2012). These drugs can alter the neuromodulatory systems, leading to changes in network-switching ability, motivation, top-down control, and cognitive modulation (Aguilar et al., 2018), such that if used, they would compound harm on already vulnerable networks (Davis et al., 2016) (Fig. 2 and Fig. 3).

All these changes may converge to eventually push individuals with vulnerable brain circuitry to develop profound network alterations responsible for psychotic episodes, contributing to the onset of schizophrenia (Fig. 3). However, we currently do not know whether the onset of the disorder is associated with shutting down of functional networks, i.e., no longer responding properly to the outside world, or with the loss of brain plasticity. As stated above, males develop psychotic symptoms earlier than females despite their somewhat slower time course of PFC functional maturation. While estrogen has been implicated in the protective effects against the emergence of psychosis (Riecher-Rossler, 2017), it seems that males develop schizophrenia when brain plasticity is still high, whereas females do so when the plasticity gets lower, suggesting that there may be sex differences in the mechanisms underlying the onset of schizophrenia.

In schizophrenia, even during its prodromal state, many PFC functions are affected. Thus, one may think that the primary defect would be altered PFC function. But in principle, any brain regions within networks associated with PFC can be involved in the disease state. Kellendonk's group showed that both reduction of activity in the thalamic mediodorsal nuclei and overexpression of the dopamine type 2 receptor in the striatum affected PFC function in mice (Kellendonk et al., 2006; Li et al., 2011; Parnaudeau et al., 2013). Therefore, changes in the maturation process of any such brain region may be sufficient to affect the entire circuitry/system, putting constraints on network activity involving PFC, and leading to functional deficits associated with the networks.

4. How can we study the trajectory of schizophrenia in animal models?

4.1. Why do we need animal models?

Animal models have been used extensively to understand the neurobiology of disease phenotypes. In particular, animal models with construct validity share the same pathogenic causes with human cases, and are predicted to be particularly suitable for study (Nestler and Hyman, 2010). Since genetic contribution in schizophrenia is quite high, human genetic studies have been performed at a large scale, resulting in a list of many genetic variants associated with schizophrenia. These include rare copy number variations (CNVs) that increase the disease risk by four- to 70-fold (Marshall et al., 2017). Several animal models mimicking the CNVs in humans have been characterized to study the pathogenesis of schizophrenia associated with these variants (Hiroi et al., 2013; Nomura and Takumi, 2012). Since CNVs may account for only about 2% of these cases, other forms of genetic variants must be responsible for most of the heritability observed in schizophrenia (Birnbaum and Weinberger, 2017). Similarly, other rare variants like single nucleotide variants (SNVs) with large effects have been clarified only for about 1% of cases (Fromer et al., 2014; Genovese et al., 2016; Purcell et al., 2014). Unlike the situation with autism, in which whole genome/exome sequencing techniques have identified many rare SNVs responsible for the disorder (De Rubeis et al., 2014), more than a hundred common SNVs spread all over the chromosomes are associated with schizophrenia, whose individual odds ratios are marginal (< 1.3) at best (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Nevertheless, combinatorial effects of common SNVs estimated by polygenic risk scores support their involvement in the schizophrenia pathogenesis (Schizophrenia Working Group of the Psychiatric Genomics, 2014). But since almost all these SNVs are intergenic, the effects of variants may or may not be directly related to genes that are in close proximity to those SNVs. Therefore, so far no "cardinal schizophrenia genes" have been identified that would allow the identification of pathways responsible for schizophrenia. As a result, it has been difficult to establish genetics-based precision medicine approaches that target the responsible pathways for schizophrenia, unlike for other developmental disorders of the nervous system (e.g., epilepsy, Dhindsa and Goldstein, 2015). In light of the findings that multiple genetic variants with small effects seem to be major factors responsible for the disease, Hyman recently expressed a rather pessimistic view on the usage of even animal models with construct validity in developing new therapeutic approaches for schizophrenia (Hyman, 2018). He also implied that, instead of mouse models, brain organoids mimicking the human brain in 3D form may be better suited for this purpose (Hyman, 2018). In contrast, Canetta and Kellendonk presented a more optimistic view on animal models for schizophrenia research (Canetta and Kellendonk, 2018).

Schizophrenia is a disorder of brain circuitry, but many genes identified by human genetics studies are not directly associated with specific circuitries that are affected in schizophrenia. Using recent iPS cell-based approaches, we may be able to identify cellular phenotypes associated with these genetic variants in neurons (Jacobs, 2015). However, even if we can identify the cellular phenotypes, we still need to understand them in the context of brain circuitry to clarify the mechanisms by which altered genes/molecules lead to behavioral phenotypes. For this purpose, we need to use animal models to understand network alterations caused by the genetic variants (Sigurdsson, 2016).

In addition to the circuitry issue, developmental aspects of networks can also be characterized using animal models. For example, fear extinction learning changes markedly across development especially during the transition through the juvenile period (Pattwell et al., 2012). Moreover, both learning and retention of fear extinction are attenuated during adolescence (Pattwell et al., 2016). In this transition, a shift of fear learning circuitry is observed, from a juvenile form that is a fairly restricted subcortical circuitry, to an adult form that is more flexible and expansive to involve PFC in fear regulation. This transition may be initiated by changes in the connectivity between the amygdala, hippocampus, and ventromedial PFC during adolescence (Arruda-Carvalho et al., 2017; Casey et al., 2015). Animal models are powerful in clarifying causal relationships involving temporal changes in brain-wide networks.

4.2. What do animal models really model?

In order to understand the mechanisms underlying pathogenic processes in humans, it would be ideal to have animal models that mimic the disease trajectory observed in humans. There are some reports of prodromal animal models for schizophrenia (Featherstone et al., 2015; Pinault, 2017). Although it is fair to say that mice never develop schizophrenia like humans, almost all animal models currently available are in fact models for the prodromal status of the disorder based on their behavioral phenotypes. There are several points that we need to consider in order to develop better animal models for schizophrenia.

First, animal models with construct validity, namely developmental animal models involving either genetic or perinatal environmental insults, may be suitable for characterizing the neurobiological basis of

vulnerable brains. Those animal models may be useful to clarify how other insults modulate those prodromal states. Two-hit models are an example (Giovanoli et al., 2016) and described below.

Second, in the context of the schizophrenia trajectory, we would like to understand how the vulnerability in the brain and social environment during adolescence would contribute together to the disruption in the circuitries and networks. As stated in the previous section, a key source of stress during adolescence may come from the social environment. Effects of social environments have been characterized in animal models. For example, the social defeat model has been used extensively to characterize the neurobiological basis of depression in humans (Hammels et al., 2015). Juvenile social plays are known to increase dopamine levels in PFC (Vanderschuren et al., 2016). Since both serotonin and dopamine are shown to alter circuitry maturation (Suri et al., 2015; Teissier et al., 2017), their changes induced by social behaviors may affect circuitry maturation. Furthermore, male rats exposed to chronic social instability stress during adolescence are more anxious and less socially interactive than control animals, and show deficits across many sexual behaviors in adulthood (Green et al., 2013; McCormick et al., 2013), suggesting that social environment during adolescence can alter maturation of rodent brains, leading to behavioral phenotypes in adulthood. Social isolation during adolescence has been shown to affect the dopamine system (Burke et al., 2017), and has also been shown to induce alterations in brain structures in fMRI studies, including functional connectivity of the frontal brain, as observed in people with schizophrenia (Reinwald et al., 2017). Moreover, chronic stress during adolescence results in a hyperdopaminergic PFC, leading to blunted PFC development in adulthood and aggressive behaviors (Tielbeek et al., 2018).

Therefore, prodromal animal models can be combined with situations like social stress, social isolation, and social defeat to mimic the disease trajectory of schizophrenia in humans. It has been shown that adolescent social isolation of *Disc1* mice, a genetic model of major psychiatric illnesses, changes the dopaminergic innervation of PFC through stress responses, and induces behavioral alterations in adulthood (Niwa et al., 2013). Interestingly, social isolation of wild type mice during pre-adolescence affects oligodendrocyte/myelin formation in PFC instead of the dopaminergic system, and induces different sets of behavioral alterations in adulthood (Makinodan et al., 2012), supporting the idea that there may be differences in biological processes even from the similar social stress, depending on the timing and/or vulnerability of the animals (Sakurai et al., 2015).

Third, prodromal animal models should display cognitive impairment like ones observed in human cases. A variety of cognitive tests has been developed for rodents, some of which are correlated with those for humans (e.g., Kellendonk et al., 2009). Developmental aspects of cognitive function may also be tested (e.g., fear learning, Pattwell et al., 2012; reversal learning, Johnson and Wilbrecht, 2011), although some domains, especially executive functions that require extensive training, may be hard to test during earlier developmental stages in rodents. In addition, since rodents are social animals, social behavioral tests have also been established covering a wide range of behaviors across the lifespan including attachment, affection, juvenile play, social motivation, social recognition, social memory, and pair bonding (Crawley, 2007). However, more complex social cognitive functions are difficult to model in rodents, like ethical thoughts, empathy, and theory of mind/mentalization, which require higher levels of cognitive function (Blakemore and Mills, 2014). There are some reports on behavioral testing for, e.g., empathy (Langford et al., 2006; Ueno et al., 2018) and observational learning of socially derived signals in rodents (Allsop et al., 2018), however (see below).

As described above, developmental processes of cognition and social cognition are inter-related. Therefore, instead of studying higher social cognition per se, we may be able to study developmental aspects of its interaction with cognition in rodents, namely effects of social skill development on cognitive development as well as effects of cognitive development on social behavioral development. We can study the former by adding social situations into cognitive tasks, like working memory, flexibility, and strategic behavior learning, by testing animals in a group-housed situation during adolescence and adulthood. This can be performed by, e.g., using the Intellicage (Krackow et al., 2010). Risk-taking behavior induced by social peer pressure observed in humans can also be evaluated in the rodent models as well. Adolescents tend to engage in more reward-seeking behaviors when they are with friends than when they are alone (Foulkes and Blakemore, 2016). Similarly, adolescent mice also consume more alcohol in the presence of conspecifics than in their absence, while adult mice do not show any differences between these two conditions (Chein et al., 2011; Logue et al., 2014). Fear learning in adolescence is also affected in a group-housing situation (Panksepp and Lahvis, 2016). Finally, social hierarchy which is determined by many factors involving social cognitive skills may also be analyzed in similar situations (Bicks et al., 2015).

Group housing is also known to affect some aspects of social behaviors. For example, when *Neuroligin 3* knockout and wild type mice are group housed, the wild type mice show deficits in sociability, normally observed with knockout mice, which may be associated with changes in parvalbumin-positive neurons (Kalbassi et al., 2017). Interestingly, this effect was observed only in males (Kalbassi et al., 2017). Social animals like rodents can also detect the affective states of conspecifics, and utilize this information to orchestrate social interactions (Rogers-Carter et al., 2018; Sterley et al., 2018). Some have suggested that this observation may be related to empathy in humans (Levy and Yizhar, 2018). Interestingly, the pattern of this response is different between adolescents and adults: rats approached the stressed juveniles but avoided stressed adults (Rogers-Carter et al., 2018). Nevertheless, social environments require a lot of attention, strategic moves, negotiation with others etc., and prior cognitive training may affect the animals' behavior in such environments. Therefore, many ideas are being explored to mimic social situations in humans, and study the development of cognitive behaviors in prodromal animal models.

In sum, genetic as well as environmental animal models for prodromal schizophrenia, which can be further exposed to social stress that is relevant to that during human adolescence, may be a better model following the trajectory of schizophrenia (Lockhart et al., 2018). By using those models, it is hoped that clarifying the biological processes underlying the onset of schizophrenia and their association with social stress will help us to devise strategies for new therapeutics. However, we can never emphasize too much that we need to have a clear understanding of what we can and cannot model in animals and which aspects are clinically-relevant, in order to translate findings to humans without unnecessary over-interpretation.

5. Can we use prodromal animal models to develop new therapeutics?

An ultimate goal of translational research is to develop potential new therapeutics. In the above mentioned article, Hyman has stated that we should separate animal models for constructing basic science from disease models when we consider usage of animal models for the disease research (Hyman, 2018). Since the effects of individual common SNVs are not remarkable, even animal models with construct validity may not be useful to predict the efficacy of therapeutics for the disorder (Hyman, 2018). However, using mouse models, it should still be possible to understand basic neurobiology and explore new therapeutic approaches based on this understanding (Canetta and Kellendonk, 2018; Gomes et al., 2016; Millan et al., 2016).

As mentioned above, one third of the population with increased risk for schizophrenia converts to full-blown schizophrenia during adolescence and early adulthood. Although it is possible that this third and the remaining population are different (e.g., in the severity of the damage and/or specificity of the damaged areas of the brain), it is also possible that those non-converters, even those individuals with a vulnerable

circuitry, have been able to develop their cognitive function sufficiently to live through adolescence without further damage from environmental stimuli. If we can identify high-risk individuals early and perform proper interventions, we may be able to reduce the incidence of schizophrenia to less than one third in this population (Millan et al., 2016).

Adolescence may be equivalent to the sensitive/critical period for the visual system for PFC function, including social cognition (Piekarski et al., 2017; Suri et al., 2015). It has been shown that effects of early adversity, namely early rearing condition, can have long-term consequences for cognitive behaviors in rodents (Sabatini et al., 2007). For example, social isolation during the juvenile period can induce specific behavioral phenotypes in adulthood (Makinodan et al., 2012). Interestingly, re-socialization of animals that had been socially isolated earlier can rescue the alterations in PFC and attentive behavioral phenotypes (Makinodan et al., 2017), supporting the idea that 1) there may be a sensitive period for social effects on PFC function, and 2) appropriate intervention may be possible for individuals socially isolated earlier in life. This does not mean, however, that effects of early rearing, namely adverse social experiences during infancy, can be completely erased later in life. Institutionalization early in life has been shown to have persistent effects on psychological development, namely social attachment (Lionetti et al., 2015). Immigrants who are in a foreign country at a younger age have a significantly higher risk for schizophrenia (Pedersen and Cantor-Graae, 2012). Therefore, we may not be able to remove the vulnerability itself. But it is still possible to use the sensitive period for intervention, during which the social environment can affect PFC maturation.

In order to ensure that the early intervention is successful, we would ideally modulate the brain during the possible sensitive period to support vulnerable circuitries, and prevent them from further damage. For that, we can utilize the intrinsic plasticity of the circuitry, and nurture it during development by setting up appropriate environmental situations. Importantly, however, the plastic period should cease at some point, and it is crucial to clarify this timing, and perform any interventions and prophylactic prevention before it ends. Expression of perineural nets (PNN), which are extracellular matrices surrounding interneurons, has been found to correlate with the ending of the sensitive period in the visual (Hou et al., 2017) and other (Steullet et al., 2017b) systems. Since PFC seems to possess cellular heterogeneity in the timing of maturation depending on the networks (e.g., Kim et al., 2017; Ye et al., 2016), there may also be molecular heterogeneity in the mechanisms mediated by PNN in restricting the sensitive period (TS unpublished).

Another intriguing point is that early life stress, one of the risk factors for schizophrenia, can affect the length and degree of the critical period (Cameron et al., 2017). If that is the case, the critical period itself becomes an additional target for early intervention by aiming to extend it to maximize the effects of any modifications (Nabel and Morishita, 2013). To clarify the critical period for each behavioral domain, it is crucial to establish better cognitive and social cognition tests that can be monitored during development in rodents. We will also need molecular markers to evaluate the degree of maturation of PFC and other brain areas (biomarkers). As described, we will need to keep in mind the heterogeneity of neurons in the PFC (Parnaudeau et al., 2018; Ye et al., 2016).

Using animal models with vulnerable circuitry based on neurobiology behind the disease trajectory observed in humans, we can explore novel therapeutic options with a variety of strategies to improve cognitive function. These strategies can be categorized into two groups: those that improve the vulnerable brain to support better cognitive function and those that protect the vulnerable brain from further adverse effects.

5.1. Stimulation and training

The vulnerable brain may show differences from control animals at many levels, such as local circuitry, long-range connections, and the neuromodulatory systems including their regulation by cortical regions. We can try to improve circuitry function by stimulating appropriate brain areas/circuitries to help their maturation, and in turn allow them to better support PFC function.

5.1.1. Cognitive training

A study using the neonatal ventral hippocampal lesion model of rats, a well studied neurodevelopmental model of schizophrenia, showed that cognitive training during adolescence prevented the cognitive impairments in adults, normalized brain function, and enhanced the cognition-associated synchrony of neural oscillations between the hippocampi (Lee et al., 2012). In humans, extensive cognitive training in patients with schizophrenia appears to be effective in some cases (Fisher et al., 2016). Higher motivation of the patients seems to be crucial in order to maximize the effects of this training (Saperstein and Medalia, 2016). This may be due to relatively less damaged neuromodulatory systems in those with higher motivation.

5.1.2. Deep brain stimulation/circuitry modulation/neuromodulation

Using a maternal immune stimulation model of rats, another well studied neurodevelopmental model of schizophrenia, deep brain stimulation (DBS) to the medial PFC during adolescence has been shown to prevent the emergence of deficits in sensorimotor gating, attention selectivity, and executive function in adulthood, as well as enlarged lateral ventricles and mal-development of dopaminergic and serotonergic transmission (Hadar et al., 2018). This result supports the idea that targeting the medial PFC before the onset of psychosis via less invasive neuromodulatory approaches may be a viable strategy to prevent schizophrenia (Hadar et al., 2018). In humans, if we can identify the circuitry/brain areas responsible for particular phenotypes, we may be able to use transcranial magnetic stimulation (TMS) instead of DBS (Ferenczi and Deisseroth, 2016).

5.1.3. Unknown mechanisms (omega-3 polyunsaturated fatty acids)

It has been shown that levels of polyunsaturated fatty acids are reduced in schizophrenia patients (Hoen et al., 2013). Administration of omega-3 polyunsaturated fatty acids may be effective in preventing the emergence of adult phenotypes such as increased anxiety and impaired prepulse inhibition in the maternal immune activation model (Li et al., 2015). Several potential mechanisms have been proposed, including enhanced neurogenesis (Janssen et al., 2015), anti-inflammatory and antioxidant properties, improved membrane fluidity, mitochondrial performance and synaptic plasticity, inhibition of phospholipase A2, normalization of dopaminergic pathways, and promotion of white matter integrity (Millan et al., 2016). Clinical trials testing omega-3 polyunsaturated fatty acids in patients with schizophrenia seem to be somewhat effective (Millan et al., 2016). The course-altering effects of omega-3 polyunsaturated fatty acids may depend on the precise regimen, conditions of treatment, and stratification of patients for whom the treatment may be effective (Millan et al., 2016).

5.2. Protection from stress

We can protect vulnerable brain circuits by modulating various biological events that may underlie the vulnerability imposed on the circuitry, and prevent them from further damage.

5.2.1. The HPA axis

Inhibition of glucocorticoid signaling during adolescent social isolation of *Disc1* mice prevents dopaminergic changes in these animals, as well as the appearance of behavioral symptoms in adulthood (Niwa et al., 2013). In human studies, the severity of symptoms of the first episode of psychosis correlates with blood levels of cortisol and its metabolite in the patients (Garner et al., 2011). Therefore, prophylactic administration of drugs modifying stress signaling may be effective for prodromal populations with enhanced activation of the HPA axis.

5.2.2. Atypical antipsychotics treatment

It has been debated whether preventive administration of atypical antipsychotics for people at high risk for schizophrenia is beneficial (Murray et al., 2016). The idea behind this approach is to preemptively treat potentially altered neuromodulatory systems using antipsychotics. How we should identify high-risk individuals for whom manipulating the neuromodulatory systems would be appropriate is an issue. In addition, since the majority of available antipsychotics is effective for psychotic episodes but not proven to improve cognitive function (Young and Geyer, 2015), we would need to carefully consider which phenotypes should be targeted for treatment and how we would evaluate the outcome, e.g., psychotic episodes or cognitive impairment etc.

5.2.3. Oxidative stress

Using the neonatal ventral hippocampal lesion model, Cabungcal *et al.* showed that juvenile and adolescent treatment with the antioxidant, N-acetyl cysteine, prevented the reduction of parvalbumin interneuron activity in PFC, defects in electrophysiology, and behavioral phenotypes observed in adulthood (Cabungcal et al., 2014). They also showed that adolescent treatment with a glutathione peroxidase-mimicking agent reversed behavioral deficits (Cabungcal et al., 2014). These studies suggest that when vulnerable brain circuitries are under stress during adolescence, they can be damaged further by oxidative stress, which may be tolerated under normal circumstances (Emiliani et al., 2014; Hardingham and Do, 2016). These anti-oxidative approaches are now in clinical trials (Retsa et al., 2018).

5.2.4. Inflammation

Using a two-hit model in mice in which prenatal maternal administration of a viral mimetic served as the first hit and exposure to subchronic unpredictable stress during the peripubertal period served as the second hit, Giovanoli *et al.* showed that minocycline treatment during stress exposure prevented the emergence of behavioral dysfunctions in adulthood such as prepulse inhibition and increased sensitivity to the psychotomimetic drugs, amphetamine and dizocilpine (Giovanoli et al., 2016). The treatment also blocked microglial activation and interleukin-1β expression in the hippocampus and PFC (Giovanoli et al., 2016). Interestingly, the treatment did not prevent anxiety-like behavior induced by exposure to peripubertal stress with and without prenatal inflammation, supporting the idea that minocycline treatment is not simply associated with general protective effects against stress-induced behavioral abnormalities. Rather, it seems to be particularly effective in preventing pathological effects that require the combination of two environmental adversities (Giovanoli et al., 2016). These findings suggest that vulnerable circuitries may be more susceptible to inflammation during adolescence, which may be rescued by minocycline and other methods to prevent further damage caused by other stressors.

5.2.5. Synaptic overload

If vulnerability is associated with the brain circuitries' inability to process an overwhelming volume of information, enhancing the ability to process incoming stimuli may serve as a preventive approach. One idea would be to reduce the volume of incoming information and to allocate available resources to the most relevant stimuli by enhancing attention through training and/or the neuromodulatory systems, e.g., enhancing sensory gating ability (Thiele and Bellgrove, 2018). We can also try to improve processing ability in the local circuitry. For example, if recycling of synaptic molecules is affected by defects in autophagy, we may be able to rescue it by enhancing autophagy to facilitate the turnover of synaptic molecules (Fig. 2) (Vijayan and Verstreken, 2017). We have recently demonstrated this in mouse models including behavioral rescue (Sumitomo et al., 2018a; Sumitomo et al., 2018b). Autophagy enhancers have been tried for neurodegenerative disorders (Kovacs et al., 2017), and may be applicable for a subpopulation of neuropsychiatric disorders associated with autophagy deficits (Atkin and Kittler, 2012; Merenlender-Wagner et al., 2015). Reducing synaptic overload may also be achieved through the neuromodulatory systems (Fig. 2). Arnsten's group has been taking a lead on testing several drugs as potential cognitive enhancers by tweaking the neuromodulatory systems in PFC, such as dopamine type 1 receptor agonists and alpha 2A adrenergic receptor agonists (Arnsten et al., 2017; Arnsten and Wang, 2016). In addition, we can prevent hyper-pruning of dendritic spines by inhibiting the associated signaling cascade (Hayashi-Takagi et al., 2014), if hyper-pruning is associated with the onset of schizophrenia.

5.2.6. Mental support systems

Since social and affective situations can influence the development of cognition, it would be beneficial to place vulnerable adolescents in a supportive social environment to reduce social stress. It is interesting that even for ASD patients, feeling understood while growing up is important in determining their fate in society (Thompson et al., 2018). Supportive groups in the community for youth at risk, e.g., "headspace" in Australia, are an example for this kind of approach (McGorry et al., 2014). It may be difficult to mimic this situation in animal studies, however.

6. Issues to be considered

As described above, many promising therapeutic approaches for schizophrenia have been tested in animal models, and in some cases in humans. In order to advance preclinical studies to successful clinical trials in humans, several points should be considered.

First, we need methods to identify and evaluate vulnerable brain circuitries in humans before the onset of schizophrenia. Brain imaging and other methods assessing brain function may be used for this purpose (Ferenczi et al., 2016). It has been shown that abnormal brain connections analyzed with the aid of machine learning can be used as a predictive tool for ASD (Yahata et al., 2016). Furthermore, functional neuroimaging of high-risk six-month-old infants can accurately predict a diagnosis of ASD at 24 months of age (Emerson et al., 2017). This finding supports the feasibility of early risk assessment by brain imaging and developing early preventive interventions for ASD. Similar strategies can be developed for schizophrenia (Chung et al., 2018). To be able to compare results from animal models and humans side by side, we need to develop better analytical methods for measuring the functional states of brain circuitries in animal models, e.g., technologies for measuring oscillation and synchrony among brain areas with multiple recordings (Padilla-Coreano et al., 2016) and for imaging of both connectivity and function in developing animal brains (Ferenczi et al., 2016). In addition, cognitive measurements in animal models focusing on developmental profiles will be necessary to test potential therapeutic approaches that manage cognitive function during development. It is also necessary to establish biomarkers to assess circuitry functions to evaluate the efficacy of treatments in both humans and animals.

Second, we will need to be able to identify populations at high risk of developing schizophrenia who may benefit from early intervention. For this purpose, reliable and cost-effective biomarkers are essential for selecting appropriate populations and assessing the effectiveness of intervention. For the former, a combination of approaches for patient evaluation including genetic data may be useful (Millan et al., 2016). Nevertheless, in order to use genetic data effectively, we need to connect genetic variants with specific circuit vulnerability, so that we can move one step closer to precision medicine in psychiatry based on human genetics (Birnbaum and Weinberger, 2017). For the latter, it would be important to have methods to evaluate individuals' plasticity and internal mental states, such as motivation, which would be determining factors for the effectiveness of intervention. Gender may also be a critical factor, in light of the fact that mechanisms underlying the onset of schizophrenia may be different between males and females.

Third, it is crucial to understand how we can modulate circuitry development. For this, we will need to clarify how alterations in

particular molecules/genes may lead to circuitry changes that manifest as behavioral phenotypes in animal studies, and compare them to phenotyping data from genetically stratified human studies. Then, using animal models, we will need to identify the proper brain regions involved in modulating the development of the circuitry activity, while understanding connectivity and their working principles.

Fourth, it is important to consider individual variations of brain development and circuitries in humans. There is no clear boundary between normal and disease situations, and there are many different ways to respond to external and internal stimuli during adolescence even in normal situations (Volkow et al., 2017). Considering individual differences may be critical when we try to integrate knowledge in cognitive neuroscience in humans into neurobiology using animal models. In particular, social cognition, which is a result of a combination of different brain functions, affects how to respond to social environments, determining individuals' behavioral trends in certain situations (Foulkes and Blakemore, 2018). Social behaviors can be dissected into components, as shown in Fig. 1, and it will be important to consider how to integrate individual differences in value perspectives based on their own experiences as variables in the principle of computation and how to translate the principle into animal models.

Finally, we will need to establish a public consensus on prophylactic treatment of schizophrenia in high-risk populations. Critical risk-benefit assessments, including potential costs (Davis et al., 2016) and available support systems for patients are key factors in order to convince the public.

To do all these, an understanding of the developmental trajectory of disease in humans is crucial.

Concluding remarks

Schizophrenia is a heterogeneous disorder, and better-personalized management of the disorder based on its pathogenic mechanisms has long been awaited. By translating characteristic clinical features in humans into animal studies, it should become possible to understand the complex neurobiology underlying schizophrenia. Through multidisciplinary approaches involving both human and animal studies and by devising therapeutic strategies that target neurobiological changes for at-risk populations, it is hoped that precision medicine for schizophrenia will become a reality in the near future (Breen et al., 2016).

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