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Dynamic Elements and Aspects of Neural Circuitry in Relation to Developmental Psychopathology in Youth

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Abstract

The journey from youth to adulthood involves a dynamic neurodevelopmental agenda which governs a series of intricate molecular and cellular events in the brain that ultimately affect the maturation of neural circuitry and cognitive properties. These neurobiological changes confer the ability to transition from parental guidance or guardianship to self-sufficiency. Adolescence represents an important inflection point on this journey: each person's unique experience during this distinct neurodevelopmental period is linked to positive and negative gradients of mental health as well as to vulnerability to mental illness. Despite significant technical achievements and advances in neuroscience, gaps still remain in our understanding and knowledge of the mechanisms that guide brain development and their relevance to the onset of psychiatric disease in youth. To contextualize the emergence of psychopathology in youth, this chapter outlines the neurobiological mechanisms underlying the development and maturation of neural circuitry in the brain during this critical period of life. Emphasis is placed on examining neural circuitry reorganization in response to physiological and pathological influences in relation to the emergence of developmental psychopathology. Controversial and open questions are discussed regarding developmental psychopathology in relation to youth. Unsolved problems, knowledge gaps, and the neurobiologically inspired notion of preventing psychopathology during this delicate period of neurodevelopment are also addressed.

Introduction

Youth is a phase of the life span that includes puberty, adolescence, and young adulthood. It is a distinct period of life when important neuronal developments

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and maturational refinements take place in the brain. Some of the key maturational processes known to occur in the brain during this period include synaptic pruning and myelination (Barnea-Goraly et al. 2005; Huttenlocher 2002). These neurodevelopmental changes lay the cognitive and emotional foundations for the individual to make the transition from parental guidance or guardianship to social and personal responsibilities associated with adulthood, such as starting a family, working, and contributing to one's community (Dahl et al. 2018).

While the brain maturation process has long been tied to hormonal fluctuations during puberty and adolescence (Sisk and Foster 2004; Vigil et al. 2016), genetic, environmental, and experiential phenomena are also known to provoke neuroplastic changes, which in turn can modulate the connectivity and communication between neurons and within and between individual neural circuits and brain regions (Tau and Peterson 2010). Notably, youth marks a critical period of life when the brain is particularly vulnerable to environmental, psychological, and physiological stressors that may disrupt the neural circuit architecture of the developing brain, culminating in the emergence of psychopathology (Lockhart et al. 2018; Paus et al. 2008). Indeed, it has been estimated that approximately 50% of all mental disorders emerge before the age of 15 yr and 75% before the age of 18 yr (Kessler et al. 2005). Hence, successful diagnosis and early intervention of major mental disorders in young people (e.g., schizophrenia, bipolar disorder, anxiety disorders, depression) will alleviate and perhaps even prevent lifelong detrimental consequences in terms of personal, family, economic, and societal cost (Holmes et al. 2018; Merikangas et al. 2009).

Here, we outline the key neurobiological mechanisms that govern the postnatal maturation of neural circuits in the developing brain. We also examine circuit reorganization in response to physiological and pathological influences in relation to the emergence of developmental psychopathology. Beyond the onset of psychopathology in youth, we discuss controversial and open questions as well as unsolved problems regarding the neurobiologically inspired notion of preventing psychopathology during this distinct period of neurodevelopment.

A Narrow Glimpse into Neural Circuitry Development in the Brain

Human brain development is a protracted, highly complex, and metabolically expensive process that begins during the second week of gestation and spans throughout adolescence and into adulthood (Kuzawa et al. 2014; Stiles and Jernigan 2010) (Figure 7.1). At birth and during early postnatal development, the brain is comprised of a surplus number of neuronal connections. As the brain develops during infancy and childhood, these connections afford benefits that are formed and strengthened; those that are "noisy" are eliminated

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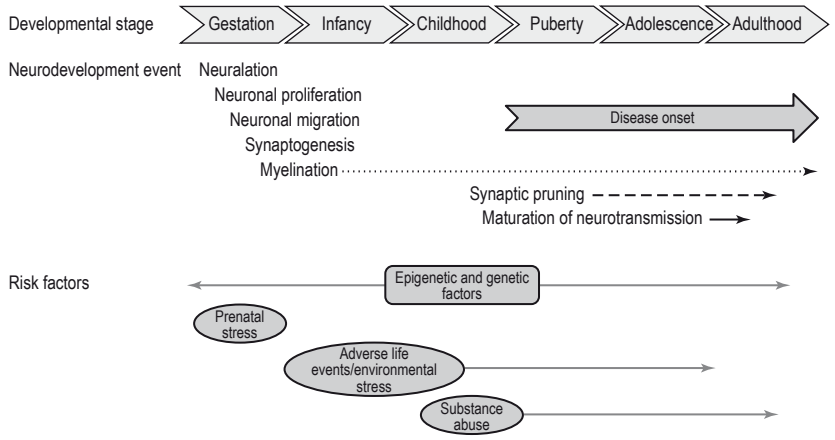

Figure 7.1 Timeline of neurodevelopmental processes involved in brain maturation in relation to onset of psychopathology in youth.

(Budday et al. 2015). The specificity of synapse connections involves a series of neurodevelopmental processes, including dendritic growth, axonal guidance, synaptogenesis, and synaptic elimination, which all ultimately contribute to the generation of a blueprint for neural circuits (Colon-Ramos 2009). Through the dynamic process of synaptic reorganization, which results in a net loss of the number of synapses, as well as the myelination of axonal fibers linking these cortical circuits and the maturation of neurotransmitter systems (e.g., the inhibitory circuitry within the cerebral cortex and dopaminergic innervation of the cerebral cortex), this blueprint is eventually sculpted into mature networks of functional neural circuits during the period of adolescence and early adulthood. This blueprint provides the neurobiological substrates that support higher-order cognitive and emotional abilities: decision making, executive planning, reasoning, problem solving, impulse control, and affective regulation, all of which are vital for an individual to navigate adulthood (Barnea-Goraly et al. 2005; Greiff et al. 2015; Stiles and Jernigan 2010; Tau and Peterson 2010).

Indeed, it is speculated that the pathophysiological underpinnings of major mental disorders stem from aberrations from the normal trajectories of maturation that take place during youth (Giedd et al. 1999; Paus et al. 2008). Here, we consider and summarize these dynamic neurobiological processes as they are thought to be particularly susceptible to both intrinsic (e.g., increased oxidative stress due to genetic vulnerability) and extrinsic (e.g., stress) perturbations that could derail their trajectories of maturation, and hence lead to psychopathology.

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Maturation of Cortical Excitatory Circuits through Synaptic Pruning

During adolescence and early adulthood, the densities of glutamatergic synapses and dendritic spines on pyramidal neurons in the prefrontal cortex (PFC), in both humans and nonhuman primates, decrease by ~50% (Anderson et al. 1995; Goldman-Rakic et al. 1997; Huttenlocher 2002). Synaptic pruning can extend into the third decade of life in the human PFC (Petanjek et al. 2011). Other evidence has shown that in the monkey PFC, neural circuits furnished by layer 3 pyramidal neurons undergo large-scale pruning of axonal arbors (Woo et al. 1997). In contrast, the density of inhibitory synapses of γ-aminobutyric acid (GABA)ergic terminals is believed to be largely unaffected during this period of development (Kuzirian and Paradis 2011).

Imaging studies have shown that gray matter in prefrontal, parietal, and temporal cortices undergoes volumetric reductions through the period of late adolescence and early adulthood (Gogtay et al. 2004; Shaw et al. 2008; Sowell et al. 2001). This finding is generally thought to reflect, at least in part, the pruning of synapses, dendritic spines, and axonal terminals. Functionally, the establishment of the mature, large-scale neural networks of pyramidal neuronal circuits within and between brain regions is a prerequisite for the maturation and emergence of the highest level of cognitive and emotive regulations that, in many cases, are uniquely human.

Dysregulation in this developmental process has been associated with a number of neuropsychiatric conditions, perhaps most notably in schizophrenia and autism spectrum disorders (ASDs). While children with ASD have been posited to possess an excess number of synapses due to a deficit in pruning (Hutsler and Zhang 2010; Neniskyte and Gross 2017), patients with schizophrenia are thought to exhibit reduced synaptic connections as a result of exaggerated pruning (Feinberg 1982; Keshavan et al. 1994; McGlashan and Hoffman 2000; Woo and Crowell 2005).

Consistent with these hypotheses, the temporal window for synaptic overproduction commences around the age of onset for ASD. Although the onset of the synaptic pruning process temporally coincides with the decline in the prevalence of these disorders, the conclusion of this pruning process occurs at around the typical age range of onset for schizophrenia. In the case of schizophrenia, an alternative but not necessarily mutually exclusive hypothesis, is that pathophysiological events or insults (e.g., infection or hypoxia) which occur during the earlier stages of brain development (e.g., *in utero* or perinatal development) may result in "subthreshold" synaptic deficits, whereas the peri-adolescent synaptic pruning process magnifies these preexisting deficits, resulting in an alteration of synaptic numbers beyond the critical threshold. As such, the functional integrity of neural circuitry becomes compromised and ultimately contributes to the expression of the psychiatric phenotypes (Lewis and Lieberman 2000; McGlashan and Hoffman 2000; Weinberger 1987). Regardless, understanding the neurobiological mechanisms that govern

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synaptic pruning and dendritic and axonal remodeling during adolescence is likely to provide important insight into the pathophysiology of several neuropsychiatric conditions (Forrest et al. 2018).

Maturation of Cortical Inhibitory Circuits Mediated by Parvalbumin-Containing Neurons

Converging evidence of recent preclinical studies suggests that the maturation of inhibitory neural circuits regulates the onset and possibly the duration of the critical period for synaptic plasticity of excitatory pyramidal neurons (Berardi et al. 2000; Di Cristo 2007; Hensch 2003; Huang et al. 1999; Jiang et al. 2005; Kirkwood et al. 1995). For example, evoked GABA currents gradually increase postnatally, which temporally coincides with the critical period for synaptic plasticity (Berardi et al. 2000). In addition, the $GABA_A$ alpha 1 subunit, which is preferentially localized to synapses formed by basket cells—a subset of inhibitory neurons that express the calcium-binding protein parvalbumin (PV) (Gao and Fritschy 1994; Gao et al. 1993; Klausberger et al. 2002)—is necessary to initiate the critical period (Fagiolini et al. 2004). The notion that PV cells play a key role in regulating the critical period is also supported by the observation that dark rearing, which prolongs the duration of the critical period and delays the functional maturation of the visual cortex, is associated with a downregulation of the expression of the mRNA for PV (Tropea et al. 2006). Interestingly, these effects of dark rearing can be rescued by the overexpression of brain-derived neurotrophic factor, or BDNF (Gianfranceschi et al. 2003). Furthermore, in transgenic mice in which BDNF is overexpressed, the functional maturation of PV neurons is accelerated and accompanied by the precocious termination of the critical period (Hanover et al. 1999; Huang et al. 1999). Likewise, in the mouse barrel cortex, the maturation of PV neurons coincides with the time course of critical period and their maturation is arrested in BDNF (-/-) animals (Itami et al. 2007). Finally, it has been directly demonstrated that optimization of somatic inhibition provided by basket cells, many of which are PV-containing cells, is essential for critical period onset (Katagiri et al. 2007). Altogether, these observations indicate that inhibitory circuits mediated by PV neurons play a central role in the postnatal maturation of pyramidal neuronal circuits in the rodent cerebral cortex by regulating developmental synaptic plasticity, which subsequently affects excitatory/inhibitory synaptic balance.

At present, virtually nothing is known about the neurobiological mechanisms that govern adolescent synaptic pruning in the primate cortex; however, it appears that mechanisms similar to those identified in rodents may be involved. For instance, in both monkeys and humans, expression of BDNF in the PFC increases during postnatal development and peaks during the adolescent period (Huntley et al. 1992; Webster et al. 2002), when PV neurons gradually achieve maturation (Anderson et al. 1995). In addition, the expression

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of the $GABA_A$ receptor alpha 1 and 2 subunits, which are preferentially localized to synapses formed by PV-containing basket and chandelier neurons, respectively, undergo significant changes during adolescence (Cruz et al. 2003; Hashimoto et al. 2009). Together these observations suggest that similar inhibitory mechanisms that underlie the critical period for synaptic plasticity in the rodent cerebral cortex may also regulate the final maturation of the primate PFC during adolescence until young adulthood.

One aspect of the functional properties of PV neurons that is of particular interest is their preferential expression of the N-methyl-D-aspartate (NMDA) class of glutamate receptors: activation of these receptors plays an essential role in sustained neuronal activation during working memory (Durstewitz and Gabriel 2007; Wang 1999, 2001, 2002). Conversely, ablation of NMDA receptors on PV neurons impairs oscillatory synchrony of excitatory circuits in the gamma frequency band and working memory (Korotkova et al. 2010), which is an emergent property of gamma. Furthermore, in the rodent PFC, NMDA neurotransmission on PV neurons undergoes maturation during adolescence (Wang and Gao 2009), providing a physiological foundation for the maturation of working memory. Disturbances involving PV neurons at either the pre- or postsynaptic end are known to affect excitation-inhibition balance and have the potential to disrupt synaptic homeostasis, synaptic plasticity, and the maturation of gamma-band oscillations. These neurophysiological changes are known to lead to information processing and working memory deficits, in addition to other impairments in cognitive operations that require gamma, hence contributing to some aspects of psychopathology.

Microglia and the Complement System Sculpt the Maturation of Cortical Circuits

Increasing evidence implicates components of the neuroimmune system (e.g., certain proteins and microglia) as major players in the elimination of synapses during normal brain development (Paolicelli and Ferretti 2017; Schafer and Stevens 2010). While complement proteins play a role in the recognition and opsonization of pathogens, microglia serve as sentinels of the central nervous system (CNS). In contrast to all other elements of the brain, including other types of glial cells, which are derived from the neuroectoderm, microglia arise from the embryonic endoderm, which gives rise to cells of the blood and immune system.

Over the past few years, there has been a steady growth in knowledge about microglia and the complement system in the physiology of the CNS (Aguzzi et al. 2013; Kettenmann et al. 2013; Paolicelli and Ferretti 2017). Indeed, a burgeoning body of evidence indicates that these immunomodulatory components play a central role in many aspects of neurodevelopment (Mallya et al. 2018; Paolicelli and Ferretti 2017; Reemst et al. 2016; Tay et al. 2017). Specifically, in the context of the current discussion, microglia and

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the complement cascade have been shown to be involved in synaptic formation, elimination, and maturation (Hoshiko et al. 2012; Miyamoto et al. 2016; Ueno et al. 2013). Notably, a recent study of the PFC in rats during critical periods of postnatal development has found microglia to engulf glutamatergic elements on both the presynaptic end—identified by vesicular glutamate transporter 1 (vGlut1) immunoreactivity—and the postsynaptic end—identified by postsynaptic density-95 (PSD-95) immunoreactivity (Mallya et al. 2018). Thus, in conjunction with other processes discussed in this chapter, it appears that the immune system plays a key role in the final maturation of cortical circuits (Mallya et al. 2018).

Given the apparent roles of microglia and the complement cascade in the critical processes of circuitry refinements that sculpt the eventual maturation of the cerebral cortex, one may speculate that any deviation from the functional homeostasis of either of these immunoregulatory systems during brain development could contribute to the onset of neuropsychiatric disorders as a result of dysmaturation of synaptic connectivities. Indeed, Sekar et al. (2016) recently reported that diverse alleles of the *complement component 4* gene promote altered expression of the *complement component 4* gene in the brain of patients with schizophrenia. Given that the complement 4 protein is located at neuronal synapses, dendrites, axons, and cell bodies, anomalies in *complement component 4* expression may influence synaptic pruning and stability, thus contributing to the synaptic and neural circuit deficits observed in schizophrenia patients (Sekar et al. 2016). Similarly, published evidence suggests that microglial dysfunction exists along with deficits in synaptic connectivity reported in schizophrenia and ASD (Monji et al. 2009; Morgan et al. 2010). Findings using animal models have mechanistically linked microglia to some of the behavioral phenotypes that resemble deficits associated with these conditions (Bilbo and Schwarz 2012; Blank and Prinz 2013). For example, in mouse models of maternal immune activation, in which animals are subjected to infection *in utero*, offspring are observed to develop a constellation of behavioral deficits, such as deficits in prepulse inhibition and social interactions as well as cognitive impairments associated with schizophrenia (Bitanihirwe et al. 2010b, 2010c; Meyer 2014; Vuillermot et al. 2010). Beyond the changes in cognition and behavior observed in these animal models, the number and the activational state of these cells in the brains of these animals are also drastically altered (Bilbo et al. 2007; Giovanoli et al. 2013; Williamson et al. 2011). Perhaps most interestingly, these effects are especially prominent in those animals that are further exposed to stress later in life (Giovanoli et al. 2013). These findings, therefore, support the concept that *in utero* insults, such as maternal infection, can "prime" microglia such that exposure to subsequent challenges later in life elicits an exaggerated neuroinflammatory response mediated by these cells; this may then lead to aberrant maturation of brain circuits and thereby contribute to the onset of neuropsychiatric disorders in youth.

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Perineuronal Nets Consolidate the Maturation of Cortical Circuits

Perineuronal nets (PNNs) are lattice-like structures comprised of extracellular matrix molecules, including chondroitin sulfate proteoglycans, hyaluronan, tenascin-R, and link proteins (Wang and Fawcett 2012). These structures are commonly found ensheathing various neuronal and neuritic elements, including the soma and proximal dendrites of PV neurons (Hockfield et al. 1990; McDonald et al. 2018). Although the exact functions of the PNN remain to be elucidated, a number of studies suggest that they may play a contributory role in neuroprotection (Cabungcal et al. 2013b), ion homeostasis (Morawski et al. 2015), synaptic plasticity (Pizzorusso et al. 2002), as well as regulating the excitatory-inhibitory balance of neural circuits (Cabungcal et al. 2013b; Donato et al. 2013; Liu et al. 2013a).

Together with the maturation of inhibitory neural circuits involving PV neurons, as described above, the progressive formation of PNNs during the postnatal developmental period increasingly restricts cortical plasticity, hence marking the end of the critical period of adolescent neurodevelopment (Sorg et al. 2016). Notably, enzymatic removal of PNNs in the adult brain, such as by chondroitinase ABC, is known (a) to reinstate a juvenile state of experience-dependent plasticity, such as restoring ocular dominance plasticity in the visual system (Pizzorusso et al. 2002) or reestablishing auditory relearning capacity that is normally lost after the adolescent period (Happel et al. 2014) and (b) to erase fear memory, which is normally only possible in the juvenile brain within a critical period during postnatal development (Gogolla et al. 2009). Further, PNN removal resets neural network activity to the juvenile state by readjusting excitatory-inhibitory balance (Lensjo et al. 2017), hence providing a neurophysiological mechanism for enhanced plasticity that is otherwise not possible in the adult brain.

Expression of PNN components around PV neurons is modulated by the homeoprotein orthodenticle homeobox 2 (OTX2) (Sugiyama et al. 2008), which is produced and secreted by epithelial cells of the choroid plexus (Spatazza et al. 2013a, 2013b). OTX2 is then taken up by PV neurons and subsequently promotes their functional maturation. Recent research has shown that OTX2 uptake into PV neurons is dependent on the structural maturity of PNNs in terms of the sulfation pattern of chondroitin sulfate proteoglycans, resulting in a positive feedback loop (Beurdeley et al. 2012; Lee et al. 2017; Miyata et al. 2012).

Given the integral role of PNNs in the regulation of postnatal experience-dependent maturation of brain circuits and the maintenance of their functional integrity in the mature brain, aberrant formation of PNNs during development can, in theory, contribute to developmental neuropsychiatric disorders by disturbing these processes. Indeed, deficits in structural components of PNNs have been reported in postmortem entorhinal cortex, thalamic reticular nucleus, amygdale, and PFC in people affected by schizophrenia and bipolar

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disorder (Mauney et al. 2013; Pantazopoulos et al. 2010; Steullet et al. 2017). In addition to the postmortem evidence linking PNN disruption to developmental psychopathology, evidence from preclinical work using a rat model of prenatal immune activation, which captures some aspects of the pathophysiology of schizophrenia, found a reduction of PNNs in the PFC and amygdala in offspring exposed to maternal immune activation during pregnancy (Paylor et al. 2016). Other research has shown that mice lacking the NR2A subunit of the NMDA receptor exhibit alterations in redox status that results in the delayed maturation of PNNs (Cardis et al. 2018). Interestingly, a reduction in NR2A mRNA expression was previously observed in the cerebral cortex of subjects with schizophrenia (Woo et al. 2004), and this reduction occurs preferentially, if not selectively, in PV neurons (Bitanihirwe et al. 2010a). Furthermore, redox regulation is increasingly recognized to be altered in this disorder (Do et al. 2009, 2015). Thus, it appears that NR2A reduction together with redox dysregulation may represent one of the possible mechanisms that underlie PNN deficits in schizophrenia.

Ventral Tegmental Area Dopaminergic Projections Sculpt the Maturation of Cortical Circuits

A number of specific and unique brain connections that are established during early to mid-adolescence may influence a variety of behaviors (e.g., such as risk taking) as well as affective and cognitive abilities (Crone and Dahl 2012). For example, dopaminergic projections from the ventral tegmental area (VTA) to the cortex exhibit marked postnatal maturation (Goto and Grace 2007; Rosenberg and Lewis 1995; Tseng and O'Donnell 2007). Until young adulthood, the concentration of dopamine and the density of fibers immunoreactive for tyrosine hydroxylase (the rate-limiting enzyme in the synthesis of dopamine from tyrosine) continue to increase in the PFC (Lambe et al. 2000; Rosenberg and Lewis 1995). Aside from the PFC, dopaminergic neurons within the VTA also project to the medial and ventral parts of the caudate putamen, nucleus accumbens, hippocampus, and amygdala (Goto and Grace 2007). These projections from the mesolimbic dopaminergic system are not fully mature until after adolescence. The late maturation of these dopaminergic connections has been proposed to influence the development and integration of normal and abnormal emotional behavior and cognition during adolescence (Goto and Grace 2007). Consistent with the observations of adolescent maturation of dopaminergic fibers, distinct developmental trajectories have also been reported in other components of the dopamine system, including dopamine receptors (D1, D2 short and D2 long isoforms, D4, D5), catechol-*O*-methyltransferase, and monoamine oxidase (A and B) (Roudi and Moser 2014).

PV neurons are a principal recipient of dopaminergic inputs to the PFC (Sesack et al. 1998). In monkeys, PV neurons preferentially express the dopamine D1 receptor (Muly et al. 1998). Furthermore, dopaminergic innervation

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of the monkey PFC undergoes a process of overproduction followed by pruning during adolescence (Rosenberg and Lewis 1995). The expression of the D1 receptor follows a very similar time course of postnatal maturation (Lidow and Rakic 1992), although how the neuronal localization of the D1 receptor is developmentally regulated is unknown. As the D1 receptor plays a critical role in working memory by mediating sustained neuronal firing (Williams and Castner 2006), the maturation of D1 expression in PV cells may be one of the key players in the emergent ability of PFC circuitry to engage in gamma oscillatory synchrony during postnatal development (Uhlhaas et al. 2009, 2010), which may provide the temporal structure within which experience-dependent synaptic pruning is possible (Woo et al. 2010). Disturbances in gamma-band oscillations may therefore interfere with developmental synaptic reorganization processes. Such disturbances may, in turn, contribute to the behavioral symptoms and cognitive deficits observed in neurodevelopmental conditions such as schizophrenia and ASD (Uhlhaas 2013; Uhlhaas and Singer 2015; van Diessen et al. 2015).

Myelination Consolidates the Maturation of Cortical Networks

One of the final steps involved in brain maturation is myelination. Within and between brain regions, it facilitates neural circuit communication by allowing myelinated axons to transmit electrical signals much more rapidly than unmyelinated axons, hence maximizing the fidelity and efficiency of information processing and cementing the final functional maturation of the entire cerebral cortex (Picton and Taylor 2007; Weil et al. 2016). The timing of myelination is dependent upon the region of the brain. For instance, while sensory and motor regions tend to be myelinated during brain development in childhood, myelination of the PFC is not completed until early adulthood (Sousa et al. 2017). Interestingly, the period in which the normal maturation of myelinated pathways involving the PFC takes place coincides with the common age of onset of many neuropsychiatric conditions, such as psychotic disorders (Kroken et al. 2014; Mighdoll et al. 2015). It is of interest to note that in metachromatic leukodystrophy, a dysmyelination disorder with a wide range of ages of onset, patients who develop the disease during the adolescent period, but not during childhood or adulthood, are most prone to develop psychosis (Hyde et al. 1992). Perhaps because myelination is a temporally discordant process in which different brain regions follow specific temporal trajectories of myelination, dysmyelination that occurs at different developmental times may lead to the emergence of distinct constellations of clinical symptoms and cognitive deficits by disturbing information processing mediated by different brain circuits and networks. Thus, unraveling the pathophysiological basis that explains the propensity of adolescent dysmyelination for the emergence of psychosis would be instructive in deepening our understanding of the neurobiological substrate of psychosis.

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Normally there is an age-related increase in the numerical density of oligodendrocytes, consistent with greater myelination of the major fiber tracts that link areas of the associative cortex, such as the PFC and the anterior cingulate cortex, with the temporal regions throughout adolescence (Benes 1989). Beyond the neuroimaging studies that have played an integral role in delineating the developmental trajectories of white matter (Lebel and Deoni 2018), further evidence supporting the progressive increase of myelin observed during neurodevelopment comes from protein and mRNA studies evaluating 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) and myelin-associated glycoprotein (MAG), markers for mature oligodendrocytyes. Indeed, it has been found that both MAG and CNP expression appear to increase with age (Miller et al. 2012).

In addition to the genetic program that dictates the developmental time course of myelination, neuronal activity has also been shown to play an important role in fine-tuning the myelination process and thus axonal conduction velocity, which can directly affect the precision of information-processing dynamics within neural circuits (de Faria et al. 2018; Tomlinson et al. 2016). Aberrant oligodendrocyte differentiation has been suggested to underlie myelin deficiencies in schizophrenia (Mauney et al. 2015) and may also contribute to the development of other neuropsychiatric conditions, such as depression, bipolar disorder, or obsessive-compulsive disorder (Marlinge et al. 2014; Miyata et al. 2016; Nissen et al. 2016).

Hormonal Changes

The surge in hormones that takes place during puberty is known to play an influential role in neurodevelopmental changes (Blakemore et al. 2010; Peper and Dahl 2013; Sisk and Foster 2004; Sisk and Zehr 2005; Vigil et al. 2016). These have been linked to risk taking as well as social and exploratory behavior (Crone and Dahl 2012). While the exact endocrine mechanisms underlying the onset of puberty continue to be unraveled, it is widely appreciated that a key event that signals the beginning of this transitional period is the activation of the hypothalamic–hypophyseal–gonadal axis, which is maintained in a dormant state during prepubertal years through what has been defined as an "intrinsic CNS inhibitory mechanism" (Vigil et al. 2016). The "release" of the hypothalamic–hypophyseal–gonadal system from the dormant state involves gonadotropin-releasing hormone secretion, which leads to gonadal maturation and the awakening of the reproductive system through the production of sex steroids (testosterone in boys and estradiol in girls).

These hormonal influences have been categorized as either activational or organizational (Arnold and Breedlove 1985). Activational effects are transient, occur throughout life, and can facilitate sex-typical physiological processes or behavior. Organizational effects are permanent and are believed to occur during early development. For instance, when testosterone is transiently elevated

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in males, it is believed to masculinize the brain (Celec et al. 2015). Similarly, when ovarian hormones are released into the system, they are believed to program sex-typical physiology and behavior (Arnold and Breedlove 1985). Interestingly, brain developmental studies applying imaging techniques have reported the effects of sex steroids on cerebral gray matter morphology, and these differences are believed to underlie the risk for sex-biased psychopathologies. Indeed, a recent study by Koolschijn et al. (2014) reported that sex-specific differences in testosterone can influence the volume of the anterior cingulate cortex. This cortical region, which has been linked to developmental psychopathology (Lichenstein et al. 2016), is a neural hub that integrates cognitive, affective, and social information so as to guide self-regulation across domains and support adaptive development of self-regulation during adolescence. In another study, ovarian hormones at the onset of puberty were shown to exert organizational effects in the PFC via increased GABAergic neurotransmission, thus contributing to its functional maturation (Piekarski et al. 2017a). While the inhibitory neuronal cell type mediating this observation was not identified, Piekarski et al. speculate that PV neurons are the likely candidate by virtue of the preferential expression of the estrogen β receptor in these cells, compared to any other neuronal types. Furthermore, manipulating puberty onset by altering the levels of ovarian hormones can directly influence the maturation of PFC-mediated functions, providing a possible link between sex hormones, maturation of inhibitory circuits mediated by PV neurons, and the onset and emergence of psychopathology in youth.

Effects of the Microbiome on the Maturation of Cortical Circuits

The human microbiome represents an ecosystem comprised of bacteria, archaea, viruses, and eukaryotic microbes that reside in and on our bodies, resulting in a unique symbiotic relationship (Eloe-Fadrosh and Rasko 2013). These microbes have tremendous potential to impact physiology, and their composition is now known to change throughout life in response to physiological and environmental cues (Rodriguez et al. 2015). Increasing research has shown the microbiome to modulate a number of key metabolic aspects, such as the immune and endocrine systems (Dickerson et al. 2017; Zeevi et al. 2016). Beyond these aspects, increasing and provocative evidence has linked the microbiome to processes related to the development of brain circuits, including myelination, neuronal maturation, and neuromodulation, such as that mediated by GABAergic, glutamatergic, serotonergic, or dopaminergic pathways (Lu et al. 2018). Additional evidence suggests that a plethora of external challenges and events to which adolescents are exposed (e.g., diet changes, sleep patterns, psychological stress, alcohol and drug use) have all been suggested to result in alterations to the composition of the intestinal microbiota (Shreiner et al. 2015). These changes in microbiome homeostasis may affect neural pathways and circuits and contribute to the emergence of neuropsychiatric disorders (Dickerson

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et al. 2017; McVey Neufeld et al. 2016; Tognini 2017). Using mouse models and intervention studies involving fecal microbiota transplantation, a series of recent translational studies, for instance, have linked a dysfunction in the microbiome with neuropsychiatric conditions such as ASD (De Angelis et al. 2015; Li et al. 2017; Williams et al. 2012), schizophrenia (Castro-Nallar et al. 2015; Olde Loohuis et al. 2018; Yolken et al. 2015), and affective disorders (Castro-Nallar et al. 2015; De Angelis et al. 2015).

Other evidence linking the microbiome to psychopathology stems from studies that evaluate the effects of antibiotic treatment and intestinal microbial dysbiosis in germ-free animals. These studies not only identified alterations in brain neurochemistry typically associated with psychopathology, they report changes in behavioral phenotypes relevant to psychiatric illness, including increased anxiety- and depression-like phenotypic traits (Clarke et al. 2013; Desbonnet et al. 2014; Moloney et al. 2014; Neufeld et al. 2011). Against this background, targeting the microbiota–gut–brain axis during adolescence in individuals at high risk for psychopathology may represent a preventative approach to protect the brain from undue physiological stress and improve mental health outcome (McVey Neufeld et al. 2016).

Aberrant Maturation of Cortical Circuits in Youth

Impact of Neuroinflammation on Emerging Psychopathology

The CNS had long been considered to be "immune privileged," neither susceptible nor contributing to inflammation (Klein and Hunter 2017). Increasingly, however, it has been appreciated that the immune system and its associated inflammatory processes may play a crucial role in various aspects of normal and aberrant brain development, such as synaptic organization and function. Neuroinflammation can be broadly defined as a complex set of orchestrated biochemical processes in the brain in response to a wide variety of intrinsic (e.g., oxidative stress, autoimmune condition) or extrinsic (e.g., infection, environmental stress) events or insults involving the activation of microglia and the increased release of many molecular signals (e.g., cytokines, chemokines, growth factors, and immune components such as complements) by microglia as well as other cell types (e.g., astrocytes, neurons).

Pre- or perinatal insults (e.g., infection, poor maternal health, malnutrition) can trigger inflammatory and immune responses, which may compromise or alter the course of *in utero* brain development. These insults have been associated with an increased incidence of developmental neuropsychiatric disorders, the onset of which occurs during childhood (e.g., ASD, obsessive-compulsive disorder) or youth (e.g., schizophrenia, bipolar disorder, borderline personality disorder) long after the occurrence of the insults.

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What mechanisms account for the delay between the occurrence of these insults and the actual onset of psychopathology a decade or two later? It has been hypothesized that the immune system is "primed" or "sensitized," especially in individuals who may be genetically predisposed, by the initial inflammatory events, and that subsequent exposure to insults (e.g., psychological stress, infection), during postnatal brain development, triggers the same or an exaggerated response at a lower threshold—the second hit. In other words, the individual becomes more vulnerable to developing psychopathology at the second hit because these insults nonlinearly magnify the resultant neuroinflammatory response, thus disturbing the brain circuits that are undergoing maturation at the time of the second hit. This leads to impairment in cognitive, emotive, or perceptual functions that are normally supported by these circuits.

Immune proteins and cytokines, such as IL-1 β and IL-6, have been found to be elevated in the serum of patients suffering from various neuropsychiatric conditions, including depression, schizophrenia, or bipolar disorder (Goldsmith et al. 2016). Moreover, postmortem studies in schizophrenia and depression implicate immune cell activation in the disease process (Shelton et al. 2011; Trepanier et al. 2016). These findings, however, are inconclusive due to the wide variability in results and factors associated with death. Recently, a series of positron emission tomography studies evaluated neuroinflammation in psychopathology by using a ligand for translocator protein (TSPO), which is greatly induced in activated microglial cells (Albrecht et al. 2016). Studies conducted in schizophrenia and depression, for example, revealed differences in the levels of TSPO in distinct neuroanatomical regions of the brain known to be associated with the clinical symptoms of these disorders (Hafizi et al. 2017a, 2017b; Holmes et al. 2018) and support the role of neuroinflammation in psychopathology.

Within the concept of neuroinflammation contributing to psychopathology onset, the potential roles of oxidative stress have attracted increasing attention (Do et al. 2009, 2015; Mahadik and Scheffer 1996). Neuroinflammation and oxidative stress are inextricably linked to one another, with events such as infection or stress inducing proinflammatory cytokines, which in turn evoke free radical formation that result in oxidative damage to DNA, proteins, and lipids, possibly contributing to the pathophysiology of a number of psychiatric disorders, such as depression, anxiety, and schizophrenia (Edlow 2017; Najjar et al. 2014; Neier et al. 2015; Xanthos and Sandkuhler 2014). In fact, oxidative stress is thought to lead to an increase in the expression of the matrix metalloproteinase MMP-9, which in turn promotes the proteolysis of receptors for advanced glycation end products (RAGE) 55-kDa type I membrane glycoprotein of the immunoglobulin superfamily, resulting in the shedding of a soluble ectodomain, which then promotes neuroinflammation (Dwir et al. 2017). In addition, MMP-9 was shown to be involved in brain structural and functional plasticity (Murase et al. 2017). For instance, increased expression of MMP-9 during neuroinflammation and oxidative stress may disrupt the postnatal

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maturation of brain circuitry in part through the degradation of PNNs (Gray et al. 2008; Wen et al. 2017). Given that PNNs play an integral role in capturing OTX2 (Beurdeley et al. 2012), the availability of which is necessary for modulating cortical plasticity by promoting and sustaining the functional integrity of PV neurons, MMP-9-mediated degradation of PNNs would negatively impact, if not overtly derail, the maturation of brain circuits in youth by disrupting excitatory-inhibitory balance (Takesian and Hensch 2013), hence contributing to the developmental pathophysiology of neuropsychiatric disorders (Chauhan et al. 2010; Lepeta and Kaczmarek 2015; Vafadari et al. 2016; Wen et al. 2017).

Impact of Stress on Emerging Psychopathology

The dopamine system is known to undergo remodeling and maturation during adolescence (Wahlstrom et al. 2010). Exposure to stress during early life has been hypothesized to interfere with the maturation of the dopamine circuitry in the brain, with subsequent implications for adolescent onset of psychiatric disorders (Syed and Nemeroff 2017). Indeed, synaptic perturbations within dopaminergic circuitry of the nucleus accumbens have been suggested to provide the neural substrate for the altered hedonic state often observed in depression (Russo et al. 2012; Russo and Nestler 2013). Recent work has found an elevation of dendritic spine density and increased glutamatergic postsynaptic currents on nucleus accumbens medium spiny neurons in mice following chronic social defeat stress—a paradigm that induces a depression-like phenotype (Christoffel et al. 2011; Golden et al. 2013). It is also known that medium spiny neurons within the nucleus accumbens contain both D1 and D2 type receptors, which play distinctive roles in stress-induced depression-like behavior. Thus, mice which display depression-like behavior following the chronic social defeat stress paradigm exhibit a decrease in excitatory synaptic input to medium spiny neurons expressing the D1 receptor and an increase in medium spiny neurons that express the D2 receptor. Furthermore, using cell-specific optogenetic techniques, it has been directly demonstrated that activation of D1 neurons can promote resilience, whereas activation of D2 neurons promotes susceptibility (Francis et al. 2015). These findings are consistent with other recent studies which suggest that similar circuit mechanisms may play a role in depression-like phenotypes (Bruns et al. 2018; Heshmati et al. 2018; Hodes et al. 2015). Further work is necessary to establish and understand the specific circuitry that undergoes plasticity after stress, as well as to test their functional role in regulating depression-like behavior.

In addition to the nucleus accumbens, the VTA represents a key dopaminergic region involved in affective regulation. Utilizing a two-hit stress mouse model, which combines early life stress from maternal separation with chronic social defeat stress later in life, Pena et al. (2017) recently showed that stress during an early postnatal sensitive window can increase susceptibility to depression in adulthood via long lasting transcriptional programming in the VTA

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in an OTX2-dependent fashion. Thus, OTX2 may be a key regulator of developmental neural circuit plasticity that transcends sensory and functional domains.

Impact of Cannabis on Emerging Psychopathology

Based on the increasing literature linking exposure to cannabis with psychotic illness (Murray et al. 2017a, 2017b; Sami and Bhattacharyya 2018), this psychoactive drug remains an integral model for understanding the neurobiology of psychosis (Burns 2013; Shrivastava et al. 2014). Given recent activities to legalize recreational use of cannabis in the United States and Canada, this is a most relevant issue. These studies suggest that several factors moderate the link between cannabis and psychosis, including age of exposure, amount of cannabis use, potency of the substance, and a family history of psychotic illness (Murray et al. 2017b). However, because of a lack of clear information in the published studies regarding the potency of the cannabis evaluated, recall bias in the individual's pattern of cannabis consumption, as well as a clear definition of the cannabis consumer in terms of frequency and duration of use, straightforward conclusions are difficult (Burns 2013).

Neurobiologically, the potential mechanistic link between cannabis and psychosis remains unclear, although research studies do point toward alterations in dopamine neurotransmission. Preclinical evidence has revealed that tetrahydrocannabinol, one of the main psychoactive constituents of cannabis, increases dopamine levels and dopamine firing in the VTA, nucleus accumbens, and striatum (Cheer et al. 2004; Ginovart et al. 2012; Tanda et al. 1997), which in turn can modulate striatal endocannabinoid release (Giuffrida et al. 1999). In the cerebral cortex, the cannabinoid 1 receptor (CB1), the principal cannabinoid receptor expressed in the brain, is widely distributed across layers especially in the upper layers (i.e., 2–4), which furnish corticocortical and thalamocortical connections (Eggan et al. 2010b). Furthermore, the CB1 receptor appears to be preferentially localized to the presynaptic terminals of the population of basket cells that express the neuropeptide cholecystokinin (CCK) which, along with those basket cells that contain PV, regulate perisomatic inhibition of pyramidal neurons (Soltesz 2005).

Activation of CB1 is thought to suppress GABA neurotransmission between CCK and pyramidal neurons. In schizophrenia, the density of the mRNA for CB1 receptor and that of CB1-immunoreactive profiles have been found to be decreased, which may represent a compensatory mechanism to restore the perisomatic inhibition that is diminished as a result of a deficit of PV neurons (Eggan et al. 2008, 2010b). These findings provide a neurobiological pathway through which cannabis can affect perisomatic inhibition of pyramidal neurons via their binding to the CB1 receptor and, through this mechanism, may influence higher cortical functions by affecting gamma synchrony.

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Can the Emergence of Psychopathology in Youth Be Prevented?

Youth represents a distinct developmental period of brain circuitry associated with resilience and vulnerability. It is also a period during which many mental disorders tend to emerge. We have provided a conceptual framework derived from the latest understanding of the neurobiology of aspects of postnatal brain maturation. Specifically, many elements of the brain undergo profound changes during postnatal development: the excitatory circuits furnished by pyramidal neurons, the inhibitory circuits involving PV neurons, which regulate the maturation of the excitatory circuits, and the PNN which, in turn, regulates and consolidates the maturation of both the PV inhibitory and pyramidal neuronal circuits. Additionally, hormonal changes, neurotransmitter systems (e.g., the dopamine and the cannabinoid systems), and the microbiome can further modify the maturation of these circuits. Finally, myelination represents perhaps one of the last steps to solidify the functional maturation of the brain by "insulating" the communication between and within neural circuits to ensure the efficiency and fidelity of information processing. It is important to note, however, that all of these processes are developmentally and mechanistically intertwined. Thus, any perturbation at any point in time in development can affect one, some, or all of these processes.

Within this framework, it may be possible to begin to develop theoretical models that may explain the developmental pathophysiology of psychopathology. Nevertheless, there are many unanswered questions. For example, neuroinflammation appears to be one of the possible mechanisms that can affect all aspects of the entire developmental processes—from prenatal development to the final maturation of the cerebral cortex during youth and early adulthood—although the precise molecular pathways that mediate these pathophysiological mechanisms are poorly defined. How and why can the same mechanisms (e.g., stress) influence the pathophysiology of a wide range of clinically distinct neuropsychiatric disorders? Is this due to the timing of the occurrence of the specific events or the nature of the events themselves? What determines whether (and if so how) some individuals are more or less vulnerable (or susceptible) to identical insults? What are the protective mechanisms that mitigate the potential detrimental effects of these insults? In other words, which neurobiological elements confer resilience? Perhaps the most provocative question is: Can psychopathology be prevented?

The goal of preventive interventions is to reduce the impact of established causal risk factors, affect the availability and/or influence of known protective factors, and reduce the likelihood that adolescents will develop or progress toward psychopathology (Costello 2016). Realizing this goal requires a multipronged approach to identify the pathogenetic variables at the genetic, epigenetic, genomic, molecular, cellular, circuit, physiological, behavioral, and even psychosocial levels, and to understand how these variables may drive the onset of psychopathology in youth by causing aberrant or maladaptive neural circuit

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development. Despite the knowledge outlined in this chapter, substantial gaps remain as many of these variables have yet to be identified and elucidated. Ultimately, to understand how these variables may lead to psychopathology onset, a systems-level approach is likely to be essential, given the extremely large number of variables involved in various combinatorial fashions, the fact that the interactions of these variables are likely to be nonlinear, and the complexity of defining how these variables derail the trajectories of brain development. The emerging field of prediction modeling, which applies concepts such as dynamic systems theory, network theory, catastrophe theory, as well as instability mechanisms may hold the promise of determining what and how specific variables may influence and trigger the onset of specific psychopathology (Nelson et al. 2017; Rosenberg et al. 2018). Thus, effective early intervention and prevention strategies requires the development of strategies that can modify or ideally normalize the pathogenetic effects of these variables at specific point in time during brain maturation.

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