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The Development of Brain Circuits during Youth

A Framework for Understanding Emerging Mental Disorders and Early Intervention

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Abstract

Given the disease burden of mental health in youth, the development of age-appropriate treatments and effective prevention strategies needs to be prioritized. This, however, requires a better understanding of how and why mental disorders emerge. The clustering of the onset of mental disorders in youth suggests that there may be identifiable underlying brain circuit changes during this period, and that examination of normal and abnormal circuit development can improve our understanding of emerging mental disorders. This chapter synthesizes evidence related to multiscale changes in large-scale networks that occur during youth and highlights their relevance to emerging psychopathology. The impact of environmental risk factors is explored and strategies for future research proposed.

Introduction

Three-quarters of all mental disorders emerge before the age of 24 yr (Kessler et al. 2005, 2015; Paus et al. 2008). They lead to more years lost to disability in youth than any other group of illnesses—more than twice as many as the next

Group photos (top left to bottom right) Chris Davey, Matcheri Keshavan, Beatriz Luna, Sophia Frangou, Peter Uhlhaas, Wilson Woo, Francis Lee, Matcheri Keshavan, Andreas Meyer-Lindenberg, Peter Uhlhaas, Akira Sawa, Chris Davey, Andreas Meyer-Lindenberg, Sophia Frangou, Beatriz Luna, Francis Lee, Peter Uhlhaas, Wilson Woo, Sophia Frangou, Akira Sawa, Matcheri Keshavan

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two leading causes combined (unintentional injuries and infectious diseases) (Gore et al. 2011). There is evidence that the burden might be increasing, driven by increased rates of affective disorders in young women (Collishaw 2015).

We need to better understand the underlying causes of emerging mental disorders during youth so that we can develop age-appropriate treatments and effective prevention strategies. We refer to "youth" as a period that encompasses development from puberty to about the age of 25 years, extending beyond what has traditionally been referred to as "adolescence" on the basis of evidence of continuous brain development over the extended period (Gogtay et al. 2004; Lebel and Beaulieu 2011). Here, we use the terms interchangeably to refer to the same period. The major disorders that emerge in youth are schizophrenia (and other psychotic spectrum disorders), bipolar disorder, depression, and substance use disorders (Kessler et al. 2005, 2007). We will also include anxiety disorders in our discussion: while they begin to emerge in childhood, many anxiety disorders do not develop until adolescence, and they are risk factors for, and frequently comorbid with, other youth-onset disorders (Lewinsohn et al. 1997).

The clustering of the onset of mental disorders in youth suggests that there may be identifiable underlying brain circuit changes during this period, and that examination of normal and abnormal circuit development can improve our understanding of emerging mental disorders. Importantly, this period is marked by heightened plasticity, and the development of brain circuits that support important cognitive processes; thus, it affords an opportunity for early intervention that can potentially change developmental trajectories (Larsen and Luna 2018). A deeper understanding of the relationship between brain development and psychopathology can lead to the identification of developmentally targeted treatments. Since the large majority of treatments for mental disorders have been developed in adult patients, it is often unclear how effective they are for emerging mental disorders in youth.

In this chapter we synthesize the evidence related to the multiscale changes in large-scale networks that occur during youth with the goal of highlighting their relevance to emerging psychopathology. We explore how these interact with environmental risk factors, and propose key strategies for future research that can inform early intervention efforts.

Plasticity and Brain Organization

Molecular and Cellular Plasticity

Brain development is influenced by multiple molecular and cellular processes, which, if impaired, can disrupt maturation and confer increased risk of mental illness. Histological and animal models provide evidence for maturational processes specific to the adolescent period, which show critical period plasticity

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in association cortices and, in particular, in the prefrontal cortex (PFC). One of the most significant developmental changes that occurs during youth is the pruning of synaptic connections that have not been strengthened by environmental inputs or by internal experiences (Bourgeois et al. 1994; Huttenlocher 2002; Petanjek et al. 2011). Long-term potentiation and depression, and their influence on excitatory-inhibitory (E-I) balance, are key features of the process.

The E-I balance in youth is influenced by changes in the relative dominance of GABAergic compared to glutamatergic neurotransmission, associated with the maturation of fast-spiking parvalbumin (PV) interneurons (Larsen and Luna 2018). These neurons are particularly enriched in prefrontal regions and act to regulate perisomatic inhibition levels (Freund 2003; Sohal et al. 2009; Soltesz et al. 2005; Tukker et al. 2007). PV interneurons are important for the generation of high-frequency oscillations that support the development in youth of higher cognitive processes such as working memory (Sohal et al. 2009; Wang and Buzsáki 1996).

From puberty, there is an increase in inhibitory tone mediated by an increase in alpha-1and gamma-2 subunits of the GABA receptor in layer 3, coupled with a decrease in alpha-2 and -5 subunits in the same layer (Cruz et al. 2003; Datta et al. 2015; Duncan et al. 2010; Hashimoto et al. 2009). Subunits of glutamate receptors are largely unchanged (Datta et al. 2015). The increased inhibitory tone affects E-I balance and changes the way neuronal activity is sculpted via the effects of PV interneurons on high-frequency oscillatory brain activity.

Recent research has shown that glial cells, such as astrocytes and microglia, also have important roles in the regulation of E-I balance. Glial cells contribute to oxidation–reduction (redox) homeostasis (Ogundele et al. 2014) and the mediation of inflammatory responses (Colombo and Farina 2016). These processes are particularly relevant to neurons, especially the highly energy-dependent PV interneurons (Steullet et al. 2016). In addition, NMDA signaling and receptor concentration as well as increasing levels of brain-derived neurotrophic factor (BDNF) precipitate neuronal plasticity, especially experience-dependent plasticity (Malenka and Bear 2004).

Large-Scale Plasticity

Structural magnetic resonance imaging studies have been consistent in describing anatomical changes during youth. Gray matter (GM) development follows an inverted U-shaped developmental trajectory, increasing in volume during childhood, reaching a peak in adolescence, and declining steadily thereafter (Giedd et al. 1996a; Lenroot et al. 2007). By contrast, white matter (WM) volume increases linearly from childhood to the middle of the third decade, with boys showing a steeper rate of increase during adolescence (Giedd et al. 1996a; Lenroot et al. 2007). Total cerebral volume and the GM volumes of the frontal and parietal lobes seem to attain their peak at age 11 yr in girls and 12–14 yr in boys (Giedd et al. 1996b; Gogtay et al. 2004; Lenroot et al. 2007; Raznahan

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et al. 2014). Diffusion tensor imaging (DTI) studies show significant developmental enhancements in WM integrity during youth development, confirming histological studies of increased myelination in frontal, temporal, and parietal cortical regions as well as in striatum and hippocampal-cingulate relays (Benes 1989; Yakovlev and Lecours 1967). Among the subcortical brain tracts, the uncinate fasciculus and cingulum show particularly protracted maturation into young adulthood (Lebel et al. 2012; Simmonds et al. 2014). In contrast to this pattern of increased integrity, there is also evidence for normative decreases in WM integrity in circuits relevant to psychopathology, including WM connections from the PFC to basal ganglia (Larsen et al. 2018) and to amygdala (Jalbrzikowski et al. 2017).

Gonadal Hormones and Plasticity

Puberty marks the beginning of adolescence and is a major driver of plasticity. Peaks in GM and WM volume correspond to the sexually dimorphic ages of gonadarche onset and suggest possible interactions between sex hormones and brain development, although correlations do not necessarily imply causal relationships (Giedd et al. 1996a, 1999). Limbic and primary sensory cortices increase in thickness with increased testosterone in boys, whereas higher testosterone levels appear to accelerate frontal cortical thinning; the latter effect is more pronounced in girls than in boys (Bramen et al. 2012).

Early pubertal changes in subcortical regions include increases in amygdala volume in males and increases in striatal and hippocampal volume in females (Lenroot et al. 2007; Neufang et al. 2009). Positive associations have been observed between circulating estrogen levels and parahippocampal GM volumes, as well as between testosterone levels and diencephalic brain structures (Neufang et al. 2009). Pubertal timing is a factor for the onset of mental illness: early life stresses can precipitate premature puberty (Braithwaite et al. 2009; Sun et al. 2017), and early puberty is a risk factor for later mental disorders (Graber et al. 2004; Tremblay and Frigon 2005).

Developmental Changes in Specific Brain Circuits

Above, our discussion focused on molecular and global changes in brain reorganization during youth. Here we examine developmental changes in specific brain circuits, an approach that is compatible with frameworks that seek to understand the relationship between circuit function and psychopathology, such as the Research Domain Criteria (RDoC) (Casey et al. 2014; Insel et al. 2010). Mental disorders are not likely, however, to be defined by abnormalities of particular circuits in isolation; instead, abnormalities in one circuit will affect another. In the complex interactions that result, symptoms of mental illness emerge.

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Fronto-Amygdala Circuit

Development of fronto-amygdala circuitry in youth plays a significant role in fear-related disorders (Baker et al. 2014), as well as in depression (Carballedo et al. 2011), schizophrenia (Liu et al. 2014b), and bipolar disorder (Anticevic et al. 2013).

In the infant-juvenile period, amygdala projections to PFC precede the development of reciprocal connectivity from the PFC to the amygdala. In rodents, significant PFC projections to the basolateral amygdala (BLA) are not seen until postnatal days 10 to 15, which is delayed relative to PFC projections to the thalamus and striatum (Arruda-Carvalho et al. 2017; Bouwmeester et al. 2002). Around the time of adolescence, there is another surge in BLA connectivity to the PFC—selectively to the prelimbic PFC—that leads to a transient increase in PFC dendritic spine formation (Pattwell et al. 2016).

Parallel behavioral studies have linked development changes of this circuit to attenuated extinction learning during adolescence. Rodent studies suggest that a lack of synaptic plasticity in prefrontal regions during adolescence is associated with blunted regulation of fear extinction (Pattwell et al. 2012). The selective surge in BLA–PFC connectivity during adolescence (Pattwell et al. 2016) could support a cyclic loop of BLA–PFC and PFC–BLA activity that correlates with resistance to cued fear extinction at this age.

In humans, PFC–amygdala functional connectivity exhibits specialization during adolescent development. This involves a reduction in structural and functional connectivity between PFC and amygdala, with differences in the timing of these processes associated with anxiety and depressive symptoms (Jalbrzikowski et al. 2017). Based on functional MRI studies, immature connections between amygdala and medial PFC in childhood reach adult-like patterns in adolescence (Gee et al. 2013). This developmental switch represents a potential neurobiological basis for the improvements in emotion regulation observed across development.

Frontostriatal Circuit

The development of frontostriatal circuits plays a role in adolescent peaks in sensation seeking (Chambers et al. 2003; Spear 2000) and improved cognitive control (Luna et al. 2015). Aberrant function is implicated in schizophrenia (Eisenberg and Berman 2010), depression (Forbes and Dahl 2011), and substance use disorders (Casey and Jones 2010).

Frontostriatal circuits are composed of distinct efferent cortical connections to the striatum, proceeding to the thalamus, and then projecting back to PFC (Alexander et al. 1986). The frontostriatal circuit most relevant to psychopathology is the reward circuit, composed of connections from ventral striatum to orbitofrontal cortex and amygdala (Alexander et al. 1986; Choi et al. 2012; Fudge et al. 2004; Haber and Knutson 2010).

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The striatum is the main target of dopaminergic projections from the ventral tegmental area (VTA), which then project to the PFC. Dopaminergic innervation of the PFC is one of the drivers of PFC maturation. The density of dopaminergic innervation of supragranular layers progressively increases and then plateaus before decreasing to adult levels by early adulthood (Rosenberg and Lewis 1995). Dopaminergic activity accelerates the development of PV interneurons (Porter et al. 1999), and dopamine shows an increased ability to excite PV interneurons during puberty (Tseng and O'Donnell 2007). This facilitates inhibitory circuit function and decreases the E-I balance (O'Donnell 2010), playing a role in triggering critical period dynamics (Takesian and Hensch 2013; Toyoizumi et al. 2013). In rodent models, adolescent social stresses can disturb this dopaminergic maturation, causing disordered behaviors (Niwa et al. 2013).

Ventral striatal regions show hyperactivity in the presence of impending rewards during youth, which moderates with the emergence of adulthood (Galvan et al. 2005; Geier et al. 2010; Luna et al. 2013; Van Leijenhorst et al. 2010). Related to this, functional connectivity between VTA and ventral striatum during reward states is greater in adolescents than in adults, although there is no difference in resting state connectivity (Murty et al. 2018).

Functional connectivity between PFC and striatum declines during youth (Dosenbach et al. 2010; Porter et al. 2015; Supekar et al. 2009). Consistent with this, the recruitment of prefrontal systems in the service of cognitive control decreases as executive function improves through childhood, showing more stability in adolescence (Ordaz et al. 2013; Simmonds et al. 2017), but not stabilizing completely until adulthood (Montez et al. 2017). There is also evidence that striatal systems exert less influence on prefrontal systems. While WM fiber integrity from cognitive networks that feed into convergence zones in the basal ganglia to determine action have been shown to be stable through adolescence, fibers that come from limbic regions decrease, resulting in greater relative input from cortical regions (Larsen et al. 2018). These findings suggest that executive frontal processing is available by adolescence, but striatal reward processing decreases. This specialization indicates that during adolescence there is access to prefrontal executive control, but behavior is driven by reward systems (Luna et al. 2015), which is relevant to the peak incidence of substance use disorders during the period.

Hippocampal-Prefrontal Circuit

The projection of neurons from the hippocampus (HPC) to the PFC has an important role in cognitive and affective processes. Dysfunction of the HPC-PFC circuit is particularly implicated in schizophrenia, depression, and anxiety disorders (Godsil et al. 2013).

Accumulating genetic and connectivity evidence suggests that the HPC is best understood along an anterior-posterior gradient. The anterior HPC is

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more closely linked to subcortical structures such as the amygdala and the hypothalamic-pituitary-adrenal axis, whereas the posterior HPC has reciprocal connections primarily with the PFC (Bannerman et al. 2014). Consistent with this connectivity pattern, the anterior HPC is more involved in contextually dependent emotional processing, including fear extinction and stress responsivity (Bannerman et al. 2003, 2004, 2014; McHugh et al. 2011), whereas the posterior HPC is primarily involved in cognitive processing, particularly episodic memory and spatial learning (Bannerman et al. 2014; Kim and Fanselow 1992; McHugh et al. 2011; Moser et al. 1993; Moser and Moser 1998).

While PFC shows protracted development (Gogtay et al. 2004), the HPC may have an even later timetable for maturation, with synaptogenesis peaking at approximately 10 years of age in PFC, compared to 13 years of age in the HPC (Ghetti and Bunge 2012; Petanjek et al. 2011). In particular, the anterior HPC has been found to show volumetric increases into early adolescence before volumes decrease (Abrahám et al. 2010; Daugherty et al. 2016; DeMaster et al. 2014; Gogtay et al. 2006; Lee et al. 2014b; Tamnes et al. 2014). The relatively extended period of volume increase is also a consequence of ongoing myelination (Benes 1989, 1994).

The HPC-PFC circuit does not fully myelinate until puberty in rodents, monkeys (Benes 1989), and humans (Simmonds et al. 2014). This might explain the delayed emergence of prefrontal abnormalities subsequent to hippocampal damage, such as in the neonatal ventral hippocampal lesion (NVHL) model of schizophrenia (Lipska et al. 1993). In humans, DTI studies have shown that WM integrity of the uncinate fasciculus, which provides major connections between PFC and HPC, continues to increase through young adulthood (Lebel et al. 2012; Simmonds et al. 2014). Activation of this part of the circuitry via contextual elements has been shown to ameliorate observations of diminished cued and contextual fear extinction observed during adolescence (Pattwell et al. 2016). Importantly, increased dopamine activity during the pubertal period has been shown in rodent models to enhance circuit integration across the HPC and PFC (Tseng and O'Donnell 2005, 2007). These findings indicate that developmentally informed treatments which engage this developing HPC-PFC circuit (e.g., contextually based extinction learning) might help to prevent the emergence of anxiety disorders following stressful or traumatic events.

Developmental Integration and Specialization

Distributed Functional Brain Networks

It is well established that the brain is organized into distributed functional networks that support multiple mental operations (Doucet et al. 2011; Power et al. 2011). The most replicable networks include the default mode network (Raichle et al. 2001), the central executive network (Corbetta and Shulman

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2002), and the salience network (Seeley et al. 2007), all of which support diverse and mostly internally guided processes. Other networks, particularly the auditory, visual, and sensorimotor networks, are known to support more specialized and mostly externally driven functions. Despite the robust and reproducible description of these brain networks in adults, there is less information about their maturation during adolescence.

While initial studies suggested possible changes in local to distributed function during development (Fair et al. 2009; Gu et al. 2015; Supekar et al. 2009), these studies were found to be undermined by greater motion in younger subjects (Power et al. 2012). Recent studies have demonstrated that the organization of networks is established by childhood (Fair et al. 2013; Marek et al. 2015), with changes in network integration, particularly involving cognitive networks, increasing into adulthood (Marek et al. 2015). Similarly, hub architecture (i.e., the organization of critical regions that provides high-level integration) is in place by childhood, while cortico-subcortical connections strengthen into adolescence (Hwang et al. 2013). This foundational network organization establishes divergent specialized information streams that are core to cognition and behavior (Grayson and Fair 2017). The anatomical extent of network modules, however, may become more variable into adulthood, suggesting that there is ongoing specialization (Gu et al. 2015).

A hallmark of youth is a change in the way we understand ourselves and others; this is underpinned by developmental changes in the "social brain," a widely distributed network that supports social cognition (Blakemore 2008). Task fMRI has established a social brain network that incorporates medial PFC, superior temporal sulcus, inferior parietal lobule, amygdala, anterior cingulate cortex, and anterior insula (Blakemore 2008; Mars et al. 2012). Social processes are strongly bound to affective processes, and the integration of cortical regions with subcortically based circuits is core to adolescent development (Simmonds et al. 2014; Spear 2000). The social brain becomes more influenced by motivational drives, particularly in relation to sex, drug use, and other peer-influenced behaviors (Davey et al. 2008). These are moderated by the maturation of top-down cortical influences, with improvements in the regulation of affective processes as this circuitry diminishes its influence over established cognitive systems through adolescence (Steinberg 2005).

Developmental Specialization of Brain Function

Taken together, developmental changes in circuitry and network dynamics during adolescence indicate a process of specialization as adult trajectories become established. PFC connectivity with critical regions that support affect (particularly the fronto-amygdala and frontostriatal circuits) demonstrate a transition from heightened affective influence on prefrontal systems during adolescence, which decreases with the emergence of adulthood. This allows cognitive systems to provide better control and hippocampal systems

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to establish contextual flexibility. In particular, adolescence is a time when network organization becomes more firmly established and PFC systems are available at adult levels. This supports the ability of young people to make complex decisions, but in the context of affective influences that drive adaptive information-seeking abilities needed for specialization (Larsen and Luna 2018).

The process of specialization in adolescence proceeds in a "use it or lose it" manner, as brain processes identify the systems that have been in high use and that are therefore relatively strengthened. In this light, psychiatric disorders can be viewed as resulting from processes that integrate genetic predispositions with experience-dependent use. If the disadvantageous function influenced by genetic predisposition has been the developmental norm for a young person, the brain will fortify this norm and an adult trajectory of psychiatric illness can ensue.

Alternatively, the process of specialization itself can become impaired, as happens in schizophrenia. There is evidence of aberrant maturation of perineuronal nets in schizophrenia, which prolongs the development of neural sculpting to the detriment of PFC functioning (Enwright et al. 2016). These impairments are likely to impact established network and circuit processing, further undermining normative trajectories. For example, the modularity of networks has been found to be reduced in schizophrenia, which might lead to aberrant activity of self-oriented task-negative circuits and the development of psychotic symptoms (Collin and Keshavan 2018).

Environmental Risk Factors for Abnormal Adolescent Brain Development

Adolescent brain reorganization can be influenced by environmental exposures that are present earlier in development (e.g., perinatal complications) as well as risk factors that occur during adolescence (e.g., substance abuse, psychosocial stress). It is understood that these exposures interact with genetic predisposition and epigenetic influences to increase the risk of psychopathology (Figure 9.1).

Early Risk Factors

Early risk factors include intrauterine exposures and those experienced during childhood. Maternal infection is an important risk factor for psychopathology, as it can elicit immune disturbances in the fetus, influencing the initial priming of long-lasting microglia (Bilbo and Schwarz 2009). The affected microglia show aberrant responses to stressors postnatally, including in their regulation of synaptic maintenance processes (such as pruning), thereby influencing E-I balance (Mottahedin et al. 2017). Childhood adversity (e.g., maltreatment, abuse) is a particularly potent distal risk factor for adolescent and adult

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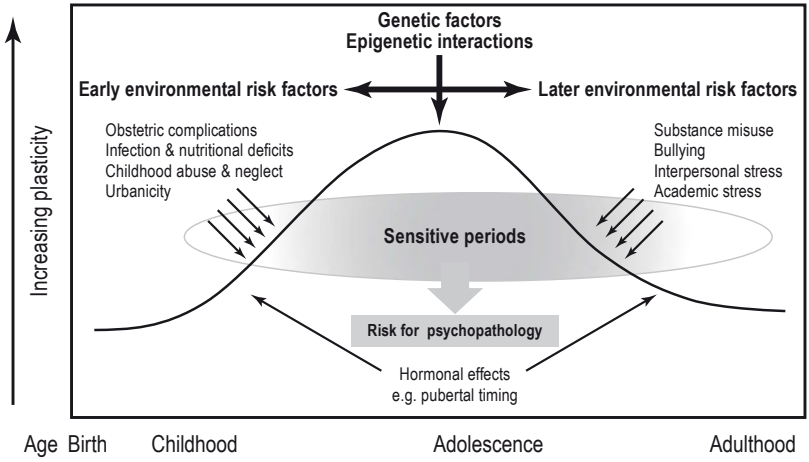

Figure 9.1 Brain reorganization is influenced by environmental exposures, present early in development, and risk factors that occur during adolescence. These exposures interact with genetic and epigenetic factors to increase the risk of psychopathology.

psychopathology. The effects of adversity might partly be mediated through functional and structural changes in the HPC (Dannlowski et al. 2012).

Late Risk Factors

Late risk factors act on brain development after the onset of puberty and can interact with early risk factors to amplify risk further. Cannabis use, which emerges as a significant environmental exposure during adolescence, provides a good example of a late risk factor. The particular culprit is tetrahydrocannabinol (THC), the major physiologically active component in cannabis preparations. Previous work indicates that THC can dysregulate the E-I balance of cortical circuits by affecting cannabinoid 1 receptors (CB1R) (Robbe et al. 2006), which are highly expressed on GABAergic interneurons and astrocytes, thus leading to disruption of neural oscillations (Renard et al. 2017; Skosnik et al. 2012). Importantly, the expression of CB1Rs in the PFC increases until adulthood, thus contributing to developmental modifications in network inhibition (Eggan et al. 2010a). The influence of THC on these processes constitutes a potential candidate mechanism for the generation of cannabis-induced cognitive deficits and possibly for the development of psychosis. This is supported by recent evidence that THC exposure during adolescence is associated with poor visuospatial working memory (Verrico et al. 2014) and highlights the importance of developmental timing for the effects of risk factors on circuits.

It is important to note that human studies have predominantly been retrospective. This makes it difficult to assess whether working memory impairments

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precede use and might, in fact, be a risk factor for it. A recent study found that working memory impairments and associated aberrations in frontoparietal activation in early adolescence were risk factors for later cannabis use (Tervo-Clemmens et al. 2018). Adolescence is a period when rates of experimentation with cannabis are high, which mostly does not result in mental illness. Those who do develop mental disorders are likely to have other risk factors that make them more sensitive to the effects of cannabis. The interactions between brain developmental processes and environmental exposures are complex.

Treatment Implications

We argue that understanding circuit modifications during youth can provide a neuroscientifically informed platform for refining or developing interventions for emergent psychopathology. Specifically, the efficacy of treatments might be increased if they map selectively to the specific relevant brain circuits at the appropriate developmental period. In particular, an understanding of heightened plasticity during critical period specialization can identify the period where interventions may be most effective. A neuroscience-informed platform for early intervention needs to consider

1. the developmental timing of brain circuits relevant to psychopathology,
2. the selection and development of appropriate therapies (neurobiological, pharmacological, and psychological) to target these circuits, and
3. the testing of the efficacy and side effects of treatments in relation to the developmental stage of the brain circuits.

One example of such an approach comes from a study of developmental timing of alterations in fear circuits (Pattwell et al. 2011). Diminished cue-based fear extinction during peri-adolescence, compared to earlier and later periods, significantly reduced the effectiveness of treatments for anxiety disorders that relied on extinction mechanisms during this period. Conversely, context-based extinction learning was specifically *enhanced* during peri-adolescence (Pattwell et al. 2016). These data suggest that treatment response to standard cue exposure-based cognitive behavioral therapy varies nonlinearly with age, with the poorest response in adolescents (Drysdale et al. 2014). This highlights the importance of optimizing treatment strategies based on age as well as the potential importance of developing contextual extinction-based therapies and related preventive interventions for youth.

Evidence from preclinical research indicates that early circuit impairments can be reversed during youth. A study that examined oxidative stress in NVHL rats, an established neurodevelopmental model of schizophrenia, provides a pertinent example (Cabungcal et al. 2014). The administration of the antioxidant N-acetyl cysteine to juvenile and adolescent rats prevented the expected reduction of prefrontal PV interneuron activity as well as anticipated

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electrophysiological and behavioral deficits. This suggests that presymptomatic oxidative stress yields abnormal adult brain function in a developmentally compromised brain and highlights redox modulation as a potential target for early intervention (Do et al. 2015). Redox imbalance is reproducibly reported in patients with psychosis from early disease stages, and the use of safe antioxidants such as sulforaphane might be potential therapies (Shiina et al. 2015).

Similarly, intervening to correct E-I imbalances in adolescence using cognitive approaches might ameliorate the emergence of aberrant behaviors. For example, in NVHL rats, adolescent cognitive training was shown to prevent adult cognitive control impairment (Lee et al. 2012). The findings suggest that cognitive training during the adolescent period might (a) tune compromised neural circuits to develop in the service of adult cognition and (b) attenuate schizophrenia-related cognitive impairments that manifest in adulthood.

Strategic Research Priorities for Early Intervention

In the preceding sections we proposed that the unfolding of psychopathology across stages of mental disorders might parallel the development of relevant brain circuits. While our knowledge of brain development during youth has significantly expanded in recent years, highly significant knowledge gaps still exist. Addressing these gaps will be necessary if we are to develop a developmentally sensitive, neuroscience-informed, circuit-based framework for implementing effective interventions during youth. These gaps can be addressed by attending to the following strategic priorities.

Resolving Conceptual Frameworks for Youth Mental Health

Adolescence is described as a "sensitive period," implying that there are unique developmental events that occur during this period, and that alterations in the normal developmental trajectory will lead to vulnerabilities to mental illnesses. However, there are alternative views. It might be that the accumulation of risks, which are causally linked, better explains the emergence of mental illnesses. Models that integrate sensitive periods with risk models might provide insights that more directly inform treatment strategies by identifying systems underlying risk and the peak timing for intervention.

Critical period and *sensitive period models* assume that there are stages in human development during which the influence of external agents have particularly potent effects on subsequent development and vulnerability to illness. Implicit in the critical period model is the notion that the influence of external agents, when they occur during youth, alter the function or structure of biological tissues or systems through processes of "biological programming" (Kuh et al. 2003; Papachristou et al. 2013). Conversely, the influence of the same agents during other developmental stages will be minimal or absent.

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Less strictly defined than critical periods, sensitive periods refer to stages in development when the influence of external agents may have strong effects on disease risk, but which can be modified by subsequent experiences or exposures (Kuh et al. 2003; Papachristou et al. 2013). Understanding the molecular mechanisms underlying periods of heightened plasticity can help us identify circuits that might be particularly susceptible at particular points in time (Larsen and Luna 2018).

Different insights can also be gained by considering the *accumulation of risk model*, which emphasizes that exposures or insults act in a cumulative fashion to increase gradually the risk of disease or mortality. The model postulates that cumulative differential lifetime exposure is the main explanation for observed individual differences in disease risk (Kuh et al. 2003; Papachristou et al. 2013). An extension of this is the *chain of risk model*, which proposes that factors may be linked in chains (or cascades), whereby each exposure leads to further adverse exposures or experiences. Each link in the chain may have an independent effect on disease risk, otherwise disease onset may be predicated only by the final link (Kuh et al. 2003; Papachristou et al. 2013). Support for these models can be determined by modeling and testing pathways to show how risk factors relate to adolescent development, by assessing the cumulative effects of prolonged exposure or clustering of factors, and by identifying chains of risk that have not yet been fully described.

Building Global Data Repositories to Determine Normative Centile Curves

While our knowledge of circuit development has advanced, the field lacks robust evidence for the age-related trajectories of brain, cognitive, and behavioral phenotypes. In most fields of medicine, age-related trajectories derived from healthy individuals are used as references to identify deviations from the expected range, which are then used to trigger further investigations or interventions. An important example is the age trajectory of body mass index, which has been instrumental in informing public health policies relating to cardiometabolic health (Johnson et al. 2015). To move forward, the field requires international initiatives to pool data, already acquired in population-based adolescent samples, and enable us to derive age-related trajectories of key phenotypes. That is, there is a wealth of "big data" available that provides the power, individual variability, and unique contextual and genetic information to advance our understanding significantly. We also need to harmonize brain, cognitive, and behavioral phenotypes to minimize interstudy differences in terminology and methodology. This would benefit from prospective large-scale longitudinal studies that can clarify factors associated with risk and resilience to mental health outcomes (Feldstein Ewing et al. 2018; Frangou 2011).

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Detailed Mapping of Brain Circuits to Psychopathology and Cognition

Above, we highlighted several brain circuits that show age-related changes in activity and connectivity during youth. This circuit-based approach has been promoted by the RDoC initiative (Insel et al. 2010), where the focus is on shared dimensions of impairment that may be particularly relevant to understanding developmental specialization of trajectories. This is particularly valuable given that it is often difficult to diagnose psychiatric illness early in development, when adult brain and cognitive trajectories have not yet been established. With the possible exception of the fronto-amygdala circuit, our knowledge of the age-related trajectories of these circuits lacks detail. Although there is a degree of face validity in linking different circuits to cognitive and behavioral phenotypes, a principled and comprehensive characterization of the link between adolescent changes in these circuits with psychopathology is still missing. This area of research is best addressed by integrating animal and human studies. Human studies could highlight phenotypes of key relevance to adolescent psychopathology and systems-level brain processing, which could then be examined in preclinical designs that allow for more detailed mechanistic dissection of the neural underpinning of these phenotypes and effects of treatments.

Multivariate Models of Risk, Disease, and Resilience in Youth

Previous research has identified multiple risk factors for adolescent psychopathology, including polygenic instruments of genetic risk, polyenvironmental risk (comprising biological factors, such as obstetric trauma and infections, and nonbiological exposures, such as psychosocial trauma as well as social and family adversity), and epigenetic markers linking exposures to molecular changes. It is widely accepted that adolescent mental health problems arise from complex interactions between these factors. However, examination of these interacting "omic" influences requires advanced multivariate modeling, large samples, and significant computing power to handle simultaneously high-dimensional data sets. This is an emerging field with multiple groups endeavoring to define optimal statistical algorithms and test their external validity (e.g., Nymberg et al. 2013; Xia et al. 2018).

Clarifying the Role of Sex and Pubertal Changes for Youth Mental Health

We have outlined what is known about the molecular factors that are involved in the initiation of puberty. With the onset of puberty, significant changes in brain circuits begin, including the sexual dimorphism of brain regions. It is also from puberty that most serious mental illnesses start to emerge and become diagnosable. Significant gaps in our knowledge remain, however, about

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how pubertal processes exert their influence on brain development. Few studies have examined the association between gonadal steroid levels and measures of brain processes, such as white matter integrity, brain function (including resting-state fMRI), and neurochemistry (MRS) in adolescence. Similarly, the relationship between gonadal steroid levels and functional brain changes are limited to a small number of tasks (e.g., Braams et al. 2015; Fareri et al. 2015). Even fewer studies have focused on the association between gonadal hormones and adolescent changes in the intrinsic architecture of the brain functional connectome.

Integrative Systems Neuroscience of Large-Scale Network Development

While considerable evidence has been obtained for neuroanatomical development in youth, there remains a substantial knowledge gap in understanding the relationship to fundamental systems neuroscience parameters, important for large-scale brain activity. These include systematic studies into maturation of neural oscillations as well as circuit motifs that are involved in the sculpting of neuronal dynamics, such as E-I balance parameters. In addition, there remains only circumscribed evidence for neurotransmitter systems changes during youth, despite evidence for late-occurring changes in dopamine-NMDA receptor interactions, for example (Tseng and O'Donnell 2005). Extending these data and establishing links with large-scale network measures (EEG, MEG, fMRI) will be critical for understanding more fully the emergence of psychiatric disorders and their relationship to ongoing brain maturation during youth.

Conclusion

We propose that the sequential unfolding of psychopathology across stages of mental disorders parallels the hierarchical development of brain circuitries, and that emerging psychopathology is related to different risk factors to which the brain is exposed during sensitive periods of circuit development (Table 9.1). Importantly, we hold that unique opportunities exist to provide a developmental lens of the precursors of mental illness by understanding development—and in particular adolescent development—as a period when adult trajectories become established that can lead to lifelong psychiatric diagnoses. While there are many gaps in our knowledge of these brain–behavior relationships, they offer a framework for further research. Fine-grained studies of developmental neurobiology and their psychopathologic correlates are needed, using state-of-the-art tools from cognitive and affective neuroscience, imaging, and molecular biomarker research. From this, we hope that new treatment approaches

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Table 9.1 Brain development processes and their relevance to emerging psychopathology: prefrontal cortex (PFC), posttraumatic stress disorder (PTSD), ventral tegmental area (VTA).

	Behavior/Cognition	Developmental Modifications	Relevance for Emerging Psychopathology
Fronto-Amygdala Circuit	Fear extinction, anxiety	Early amygdala influence on medial PFC, reverses direction	Anxiety, depression, bipolar disorder, schizophrenia
Frontostriatal Circuit	Sensation seeking, reward processing, cognitive control	Increased dopamine projections from VTA to PFC, reduced PFC-striatal connectivity	Substance use disorders, schizophrenia, bipolar disorder, depression
HPC-PFC Circuit	Memory, contextual encoding, learning	Increasing hippocampal (CA1) innervation of PFC	Schizophrenia, anxiety (including PTSD), depression
Distributed Brain Networks	Mentalizing, cognitive control	Network integration and specialization, increasing top-down cortical control	Schizophrenia, depression, substance use disorders

can be developed to address circuit abnormalities, which might ameliorate the experience of youth-onset mental ill-health into adulthood.

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