12

Modifications in Brain Coordination and the Emergence of Brain Disorders during Late Adolescence

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Abstract

Late adolescence is associated with the emergence of major brain disorders, such as schizophrenia and affective disorders, thus raising the question of the underlying biological vulnerability and mechanisms that confer risk for psychopathology. This chapter presents evidence which shows that during late adolescence, dynamic brain coordination undergoes major modifications in specific circuits involved in cognition and affective regulation. These data are consistent with emerging findings from physiology and anatomy that physiological and anatomical underpinnings of brain coordination are characterized by profound changes during the transition from adolescence to adulthood. This chapter posits that the expression of psychopathology may be intimately linked to ongoing modifications in brain coordination, which occur during adolescence, and that these could confer a biological vulnerability for disturbances in affect and cognition.

Introduction

Until recently, an essential dogma of developmental neuroscience was the assumption that fundamental properties of cortical networks were formed mainly *in utero* as well as in the early postnatal years. From this perspective, later developmental stages, such as adolescence, were viewed as having little or virtually no effect on the functional characteristics and anatomical layout of cortical and subcortical networks. Only scant systematic evidence existed on the fundamental properties of neural circuits and their associated neuronal dynamics during later developmental periods. This position has recently been overturned by evidence, from a range of disciplines, showing that brain coordination

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undergoes profound reorganization; many important features of large-scale networks, such as rhythmic activity and functional integration of distributed neural responses, mature only fully during late brain development.

In this chapter, I outline evidence which suggests that the reorganization of circuit properties during late adolescence constitutes a critical period for development and confers crucial vulnerability for the emergence of major brain disorders. I summarize studies that implicate the transition of adolescence to adulthood in the expression of schizophrenia and disorders involving affective dysregulation. I also review data from developmental cognitive neuroscience that reveal important changes in oscillatory dynamics and functional connectivity during brain maturation. In conclusion, I discuss candidate mechanisms for changes in brain coordination, such as changes in neurotransmitter systems, that have been involved in the generation of fast neuronal dynamics as well as modifications in the layout of anatomical connections.

Adolescence and Brain Disorders

Adolescence represents a paradoxical stage of human development whereby increased mental and physical fitness is accompanied by vulnerability for severe and enduring mental disorders (Kessler et al. 2005; see also Figure 12.1). Although the troubling nature of adolescence has been described since antiquity, cognitive neuroscience and clinical psychology have only recently started to investigate systematically the changes in brain function during adolescence that are likely to constitute the vulnerable developmental window from which adult mental disorders emerge (Paus et al. 2008; Lee et al. 2014). The fundamental question of which biological and psychological mechanisms give rise to this phenomenon still remains to be answered. The hypothesis that I would like to advance here is that the expression of psychopathology is intimately linked to ongoing modifications in brain coordination, especially during adolescence, that confer a biological vulnerability for disturbances in affect and cognition.

The expression of psychopathology is of paramount importance for current health systems, as the onset of 75% of all mental disorders can be traced to this age period (Kessler et al. 2005) and of these, one in four to five adolescents develops a mental disorder with severe impairment across their lifetime (Lee et al. 2014). If we are ultimately to improve mental health, research and treatment approaches require a fundamental reframing. We need to move beyond the current focus on adulthood—the stage at which mental disorders are already established, symptoms fully expressed, and associated disabilities clearly visible. Indeed, a paradigm shift is emerging that highlights the importance of early intervention in adolescents at risk for psychosis and affective disorders (McGorry 2010). However, a crucial prerequisite for the implementation of the early intervention paradigm is a coherent understanding of the trajectory

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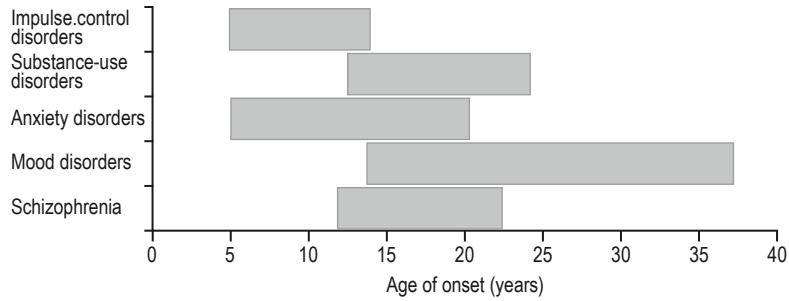

Figure 12.1 Emergence and duration of mental disorders during adolescence. Mood disorders, anxiety, substance abuse, and schizophrenia typically begin in adolescence (after Paus et al. 2008 with permission).

and mechanisms of adolescent brain development that could support an improved understanding of developmental vulnerabilities and novel treatment approaches. As Lee et al. (2014:547) state: "…understanding neurodevelopmental changes and their roles in both emergence of mental disorders and how they affect treatment efficacy is imperative."

Schizophrenia

Brain disorders closely associated with adolescence include disturbances in reality testing and affective regulation. Psychotic disorders, such as schizophrenia, typically emerge during the transition from adolescence to adulthood. In schizophrenia research, analysis of the biological mechanisms that underlie clinical symptoms and cognitive deficits has focused for a long time on the contribution of circumscribed brain regions, such as the prefrontal cortex (PFC). Contrasting this view, which was largely inspired by findings from clinical neuropsychology, current research indicates that anatomical alterations involve a large number of cortical and subcortical regions; this suggests that schizophrenia, and perhaps other mental disorders, are likely to constitute systemic disturbances involving essentially a disruption of brain coordination (Uhlhaas and Singer 2012). This position is supported by extensive evidence from electro- and magnetoencephalography (EEG/MEG) studies which show impairment of the amplitude and synchronization of oscillatory activity, in particular at gamma-band frequencies (Uhlhaas and Singer 2010). Significantly, these dysfunctions are present prior to illness onset and independent of medication status, suggesting that readouts of neural oscillation could be used as biomarkers for early intervention and diagnosis.

Importantly, this fundamental disruption of large-scale neuronal dynamics is supported by data that has consistently implicated disturbances in excitation–inhibition (E–I) balance parameters, especially in disturbances of gamma-aminobutyric acid (GABA)ergic interneurons and N-methyl-D-aspartate (NMDA)

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receptors (Uhlhaas and Singer 2012). This has important implications for the development of novel treatments. From this perspective, disturbances in E–I balance parameters during brain development give rise to abnormal dynamics and disturbed coordination which, in turn, lead to cognitive deficits that provide the underlying vulnerability from which the more complex manifestations of the disorder emerge. Currently, however, it is not known at which point disturbances in E–I balance emerge during development, and whether they are causally involved in the expression of aberrant neural dynamics. Testing such relationships requires careful manipulations of circuit properties during development in animal models and could eventually provide more mechanistic insights into these relationships.

Cognitive impairments across several domains are detectable several years before the onset of psychosis, which typically emerges during late adolescence or early adulthood (Insel 2010). The onset of clinically manifested symptoms during this developmental period may thus be due to the ongoing changes in oscillatory dynamics and the underlying neurobiological mechanisms responsible for coherent mental states. This perspective is consistent with current thinking that perceptual and cognitive impairments are the earliest indicators for an at-risk mental state, although subthreshold and full psychotic symptoms emerge only later during development (Fusar-Poli et al. 2013).

The development of certain positive symptoms, such as delusions and hallucinations, could represent an adaptive response aimed at attributing significance to the abnormal states that result from disturbed dynamic coordination of distributed networks. One of the functions of the dopaminergic system is to reward consistent brain states, such as those likely to be associated with the eureka effect that accompanies solutions of perceptual tasks and the confirmation of predictions. One might expect an upregulation of dopaminergic signaling if such states are rare. This, in turn, could cause normally neutral external and internal experiences to be judged as meaningful or salient, which is a hallmark of positive symptoms. The transition from adolescence to adulthood could constitute a critical period for such a scenario, since it is only during this late developmental phase that dopamine signaling is fully matured (Tseng and O'Donnell 2007).

Affective Dysregulation

In addition to the emergence of impaired reality testing and cognitive deficits, adolescence is also associated with the emergence of affective dysregulation. Intense and frequent emotions are common during the early adolescent years and are likely to constitute the earliest indications for the emergence of a pathological state of mood in adulthood. Indeed, evidence has emerged that mood disorders and anxiety peak in prevalence during adolescence (see Figure 12.1). More recently, borderline personality disorder, which involves profound affective dysregulation and instability of emotional experience, has

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been conceptualized as a life-span developmental disorder which has its roots in adolescence. As a result, diagnostic criteria have been developed that are similar to risk symptoms of psychosis and could potentially identify adolescents at risk for the development of disorders involving altered states of mood and affective regulation (Chanen et al. 2007; Bechdolf et al. 2014).

Vulnerability for psychosis and affective dysregulation during adolescence, however, should not be considered separately, since evidence suggests that a large percentage of at-risk participants for psychosis develop a range of affective disorders (Lin et al. 2015). This highlights the importance of developing novel approaches for risk prediction and stratification for diverse health outcomes.

One potential mechanism that could underlie the changes in affective experiences and the emergence of its disorders during adolescence is emotion regulation. In this context, emotion regulation can be broadly defined as conscious or unconscious strategies to start, stop, or otherwise modulate the trajectory of an emotion. These two forms of emotion regulation depend on interactions between prefrontal and cingulate control systems and cortical and subcortical emotion-generative systems. In recent years, deficits in emotion regulation have emerged as a putative maintaining factor and promising treatment target for a broad range of mental disorders in adulthood, such as depression, bipolar disorder, and borderline personality disorder (Berking and Wupperman 2012).

Recent fMRI/MRI and behavioral studies indicate profound modifications in the ability to regulate emotional states during adolescence (Heller and Casey 2016). This could explain the high prevalence of mood disorders and instability of emotional experience during this period. Accordingly, understanding the mechanisms of emotion regulation, its developmental modifications as well as its impairments in adolescence may have wide-ranging consequences for mental health and brain development.

Do Modifications in Brain Coordination Increase Vulnerability for Emerging Brain Disorders?

The evidence outlined above suggests that adolescence is associated with (a) the expression of dysfunctions in both cognitive processes and emotion regulation and (b) important windows of vulnerability for the development of brain disorders. This hypothesis is supported by recent evidence (discussed below) that brain coordination undergoes important modifications during the transition from adolescence to adulthood.

Neural Oscillations and E–I Balance Parameters

Developmental findings on neural oscillations indicate that cortical circuits during late brain maturation are accompanied by profound modifications in

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the amplitude and synchrony at theta, beta, and gamma frequencies (Uhlhaas et al. 2010). Uhlhaas et al. (2009b) examined the development of induced oscillations in the 4–80 Hz frequency range in children, adolescent participants, and young adults during the perception of Mooney faces (Figure 12.2). During

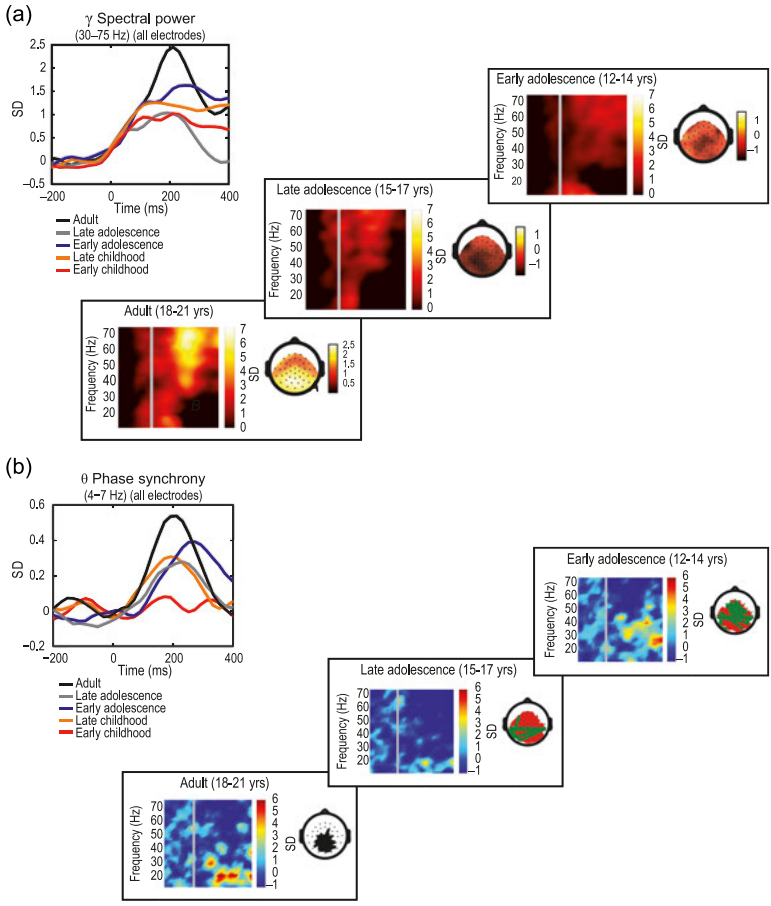

Figure 12.2 Development of induced oscillations and emergence of high-frequency oscillations and synchrony during the transition from adolescence to adulthood. (a) Spectral power in the beta- and gamma-frequency bands during the perception of Mooney faces across all electrodes in the 13–75 Hz frequency range for adult (18–21 years), late adolescence (15–17 years), early adolescence (12–14 years), late childhood (9–11 years), and early childhood (6–8 years). Topography for the 30–75 Hz frequency band lies between 100–300 ms. All values are expressed in standard deviations in reference to the baseline. Group comparison across all electrodes of spectral power in the 30–75 Hz range between 100–300 ms. (b) Phase synchrony in the beta and gamma bands in the face condition averaged across all electrode pairs in the 13–75 Hz frequency range. Group comparison for all electrodes of phase synchrony in the 13–30 Hz frequency range between 100–300 ms. Modified after Uhlhaas et al. (2009b).

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adolescence, important changes in the amplitude and synchrony of theta- and/or gamma-band oscillations occurred that correlated with improved detection rates and reaction times. In particular, phase synchrony in the beta and gamma bands increased until age 14, followed by a reduction during late adolescence (15–17 years) before synchrony increased again sharply in 18- to 21-year-olds. This nonlinear development of phase synchrony was accompanied by a reorganization in the topography of phase-synchrony patterns in the beta band. Finally, phase synchrony between frontal and parietal circuits was significantly increased during adolescence.

Developmental modifications during adolescence in rhythmic activity are supported by several studies that have investigated the maturation of basic sensory-evoked oscillations, revealing improved phase consistency and amplitude of gamma-band activity during auditory and visual stimulation (Uhlhaas et al. 2010; see also Figure 12.3). These preliminary data suggest that changes in stimulus-locked activity frequently follow a linear trajectory: earlier maturation is associated with power and phase values of oscillatory activity, not with

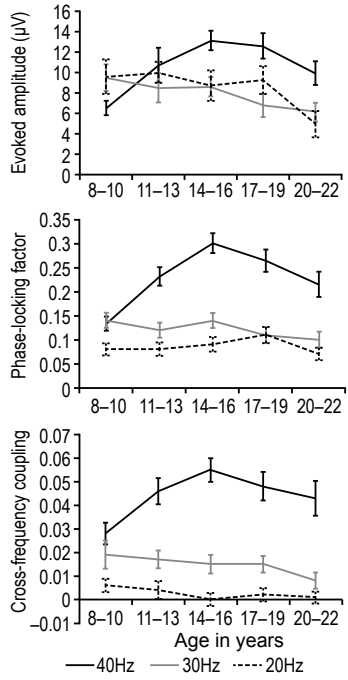

Figure 12.3 Maturation of sensory-evoked oscillations show improved phase consistency and amplitude of gamma-band activity during auditory stimulation. Age-related changes are shown in evoked amplitude, phase-locking factor, and cross-frequency coupling during auditory steady-state stimulation: 20, 30, and 40 Hz. All measures for the 40 Hz condition follow an inverted U trajectory. Responses to 30 and 20 Hz stimuli show a flat or decreasing trend with age. Used with permission from Cho et al. (2013).

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nonphase-locked, induced oscillations. The reason for this is that the latter correspond more closely to the internal, self-generated dynamics characteristic of large-scale networks that govern higher cognitive functions. Accordingly, one hypothesis is that brain coordination processes that give rise to these phenomena are more likely to reveal developmentally sensitive signatures of developmental processes during the transition from adolescence to adulthood which, in turn, can be disrupted by aberrant brain development and existing pathophysiological events.

One possibility is that maturational changes in oscillatory activity are closely linked to the development of circuit properties that are linked to the emergence of neural oscillation and their synchronization. While the number of GABAergic cells undergoes only small modifications during adolescence, axons of parvalbumin-containing basket and chandelier neurons seem to undergo more extensive modifications (Hoftman and Lewis 2011). Changes in GABAergic neurotransmission also comprise modifications in the subunit composition of GABA receptors. Hashimoto et al. (2009) described a decrease of $GABA_A$ receptor α2 subunits and an increase of α1 subunits with age in the monkey dorsolateral PFC. This change is accompanied by marked alterations in the kinetics of induced pluripotent stem cells (iPSCs), including a significant reduction in the duration of miniature iPSCs in pyramidal neurons. The shift in GABAergic subunit expression could lead to an increase in the precision of temporal patterning, as the time course of iPSCs is an important determinant for the frequency at which a network can oscillate.

In addition, there are changes in excitatory and modulatory systems that lead to a modification of inhibitory processes, such as alterations of the dopaminergic modulation of prefrontal interneurons (Tseng and O'Donnell 2007) and the reconfiguration of NMDA and AMPA receptors in fast-spiking interneurons (Wang and Gao 2009). Together, these data suggest that the transition from adolescence to adulthood is accompanied by circuit modification that supports the emergence of high-frequency activity and precise synchronization and will likely have an important impact on the functional properties of large-scale networks. It should be noted, however, that such relationships are exceedingly complex: the different types of oscillation parameters (evoked vs. induced) and distinct frequencies most likely involve different generating mechanisms whose detailed developmental modifications remain to be elucidated.

These modifications also allow for the impact of environmental factors, such as cannabis, to exert detrimental effects on brain development. Previous work has indicated that tetrahydrocannabinol (THC)—the principal psychoactive constituent of cannabis—dysregulates the E–I balance of cortical circuits through its impact on cannabinoid 1 receptors (Robbe et al. 2006). Because E–I balance parameters are important for rhythmic activity, THC leads to a disruption of neural oscillations (Morrison et al. 2011), constituting a potential candidate mechanism for the generation of cannabis-induced cognitive deficits and possibly psychosis. This is supported by emerging evidence in mice,

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where chronic THC administration during adolescence, but not in adulthood, was found to reduce the strength of *in vitro* oscillations in PFC circuits (Raver et al. 2013).

Maturation of Emotion Regulation Circuits

Studies that have looked at changes in circuits involved in emotion regulation during adolescence have found similar modifications in brain coordination that point to crucial modifications in the properties of large-scale networks. In the adult brain, functional and anatomical studies indicate that interactions between the PFC, in particular the ventromedial PFC, and the amygdala are fundamentally involved in emotion regulation (Hare et al. 2008). In adolescent participants, converging evidence indicates heightened amygdala activity in response to threat-related stimuli; this correlates with levels of trait anxiety when modulatory feedback from the ventromedial PFC is decreased. Resting-state fMRI data also provide support for a developmental switch in this pathway (Gee et al. 2013), thus suggesting the existence of positive connectivity between the amygdala and PFC in early childhood and a switch to negative functional connectivity during the transition to adolescence.

Moreover, studies in rodents have shown that fear extinction learning is attenuated during adolescence relative to preadolescent and adult animals (Pattwell et al. 2011), indicating a sensitive window for the development of affective disorders during adolescence. Together with evidence for increased risk-taking and neural signatures of elevated activity in reward structures (Galván et al. 2006), these findings suggest a unique nonlinear developmental trajectory of adolescent brain networks, characterized by a transient destabilization involving elevated activity in subcortical versus cortical regions (Heller and Casey 2016).

These modifications in brain coordination can be linked to ongoing development in anatomical pathways that are critical for the corticolimbic interactions. Although *in vivo* anatomical studies in humans are relatively scarce, tracing studies suggest that amygdala-to-PFC projections emerge earlier than PFC-to-amygdala projections, and that these connections continue to develop through adolescence in rodents (Cunningham et al. 2002).

Summary and Perspective

Current data suggest that important modifications in brain coordination occur during the transition from adolescence to adulthood: improved generation of rhythmic activity and its synchronization at low and high frequencies as well as changes in the functional interactions between brain regions that underlie emotion regulation. Because of the coincidence of these changes with the emergence of brain disorders that are characterized by profound disruption of

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reality testing and emotional experience, it is likely that these maturational changes provide windows of vulnerability during which favorable conditions give way to the expression of dysfunctions that then lead to behavioral anomalies. Here I have applied this framework of understanding to schizophrenia and affective disorders but suggest that it can also be applied to other mental disorders that emerge during the transitional period from adolescence to adulthood, such as substance abuse and anxiety disorders (Lee et al. 2014). Moreover, developmental modifications of circuits involved in major mental disorders are also vulnerable to the effects of stress and its epigenetic regulation (Niwa et al. 2013), thus providing an important link to environmental factors.

Important characteristics of these modifications in brain coordination are (a) the nonlinear trajectory of developmental changes, supported by EEG and fMRI studies, and (b) the close relations shown with the underlying neurobiological parameters (Heller and Casey 2016). This indicates that brain coordination during the late adolescent period is characterized by unique properties that transiently disrupt large-scale brain dynamics and are possibly required for the emergence of fully mature brain coordination. From a dynamical systems perspective, the nonlinear developmental trajectory of functional networks during adolescence is consistent with the idea that phase transitions between different states of a system are characterized by critical fluctuations. In the adolescent brain, the transient reduction in large-scale synchronization of cortical networks and the concomitant increase of subcortical input could be a condition that favors critical fluctuations. If these become supracritical when the developing system undergoes the phase transition toward the adult state, the brain could remain in a faulty bifurcation and fail to accomplish the final development steps:

1. Increase in the precision of synchronized, high-frequency oscillations
2. Integration of frontal and subcortical activity patterns
3. Shift in the balance between local and global coordinated brain states

These insights have implications for the development of interventions designed to target large networks and brain coordination mechanisms. In view of the converging evidence for a disturbed E–I balance and the resulting changes in brain dynamics caused by alterations in GABAergic and glutamatergic neurotransmission, we need to intensify the search for drug targets to restore E–I balance. Consideration should be given to interventions that modulate brain dynamics. There is increasing evidence that transcranial magnetic stimulation and transcranial direct-current stimulation could be used to modulate neuronal oscillations and large-scale synchrony in a frequency-specific fashion (Thut et al. 2011). Finally, to correct and improve central psychological processes, such as reality testing and affect regulation, we should consider using psychological interventions, such as cognitive behavioral therapy and cognitive remediation. Such applications could play an important role in early intervention and prevention of mental disorders that emerge during adolescence.

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