From “Emergent Brain Dynamics: Prebirth to Adolescence,”
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

11

Understanding Effects of Experience on Neurocognitive Development through the Lens of Early Adolescence

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Abstract

How does lifetime experience shape cognitive and neural development? This chapter considers this question from the perspective of early adolescence. Plasticity in the adolescent brain may occur on three possible time courses: adolescent brains may be no more plastic than adult brains; adolescence could mark the end of critical periods which began in infancy; or adolescence might constitute its own, distinct critical period. In humans, all these time courses likely coexist. Many functional properties of the brain continue to change well into adolescence (e.g., regional cortical information selectivity, neural network correlations, oscillatory activity). Determining how these developmental changes are influenced by genes and/or experience in humans is challenging. Some insight comes from studies with individuals who have different developmental histories (e.g., individuals who grow up blind). These investigations suggest that experience plays a fundamental role in determining the functional specialization of cortical networks and patterns of functional connectivity. Studies with animal models provide crucial insight into the causal factors that drive brain development because they allow

Group photos (top left to bottom right) Marina Bedny; Tomáš Paus; Sam Doesburg; Bryan Kolb; Pasko Rakic; Cheryl Sisk; Jay Giedd; Patrick Purdon; Tomáš Paus; Sam Doesburg; Cheryl Sisk; Bryan Kolb; Pasko Rakic; Marina Bedny; Row Hashemiyoon; Row Hashemiyoon; Patrick Purdon, Jay Giedd, and Bryan Kolb; Tomáš Paus; Marina Bedny; Jay Giedd; Patrick Purdon

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direct manipulation of experience and genetics as well as more direct measurements of neural function. However, work is needed to bridge the gap between measurements of brain function in animals and humans. At present, work with animal models has focused on plasticity in sensory systems, whereas much of the developmental change that occurs in early adolescence is in higher cognitive systems. Bridging these gaps is an important goal for future research.

Introduction

In this chapter, we consider the time course and mechanisms of experience-based plasticity through the lens of early adolescence. Adolescence is of interest in its own right as a developmental phenomenon. It is a time when humans and other animals undergo profound changes in social behavior, transitioning from a focus on social relationships within the family to relationships with peers. Many important cognitive functions continue to develop into adolescence, including social cognition, aspects of episodic memory, and abstract thinking (Steinberg 2005; Shing et al. 2008; Dumontheil 2014). Adolescence is also a time when many psychiatric conditions, such as depression and schizophrenia, emerge or become exacerbated (Paus et al. 2008). As such, the clinical significance of this time period cannot be overstated.

The study of adolescence provides an opportunity for us to consider some basic questions regarding the effects of experience on neurocognitive development more generally:

- Why might the potential for learning change across the human life span?
- What are critical periods, and does the term "critical period" refer to the same phenomena in the context of sensory and higher cognitive systems?
- Are critical periods that occur in early childhood qualitatively similar to hypothesized critical periods later in development?

Our goal in this chapter is to highlight insights into experience-based plasticity from the perspective of early adolescence.

Adolescence and the Time Course of Experience-Based Plasticity

Before we consider the time course of experience-based plasticity in adolescence, we must first operationalize the term "plasticity." All learning throughout the life span is associated with some neural change, whether this involves modifying long-range tracts during early postnatal development or long-term potentiation of a single synapse. According to an inclusive definition, all neural changes constitute plasticity. On the other hand, one could take a more restrictive view, where the term plasticity is reserved for more substantial and long-term changes. The line between learning and plasticity could be drawn

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in anatomical terms. For example, changes to individual synapses might not count as plasticity if the overall number of synapses in a particular brain region remains consistent, whereas systemic pruning of large numbers of synapses in a given cortical area would constitute sufficient change to warrant the term.

Here we operationalize the term experience-based plasticity in functional terms, as a substantial change in the representational and processing capacities of a neural system resulting from informational input from the environment. Visual deprivation early in life is a classic example of experience-based plasticity (Hubel and Wiesel 1970). Such deprivation permanently changes the capacity of the visual cortex to support basic visual functions, such as line orientation discrimination, three-dimensional perception, and face recognition (de Heering and Maurer 2012). By contrast, learning a new face would constitute a case of learning without plasticity, according to this definition, since it does not substantially alter the visual system's ability to process or learn other information.

A useful framework for thinking about the time course of plasticity was articulated by Greenough et al. (1987), who distinguished between two broad classes of plasticity with different characteristic time courses: experience-expectant and experience-dependent plasticity. Experience-expectant plasticity occurs in cases where the brain evolved to expect certain types of input from the environment that are nearly ubiquitous for the species (e.g., input from the two eyes, presence of motion, language and social interactions with other agents). Greenough et al. argued that mammalian brains evolved to expect such species-typical experiences during particular temporal windows in development; that is, during critical periods (Figure 11.1a, b). During these windows, such experiences have potent organizing effects on the brain. By

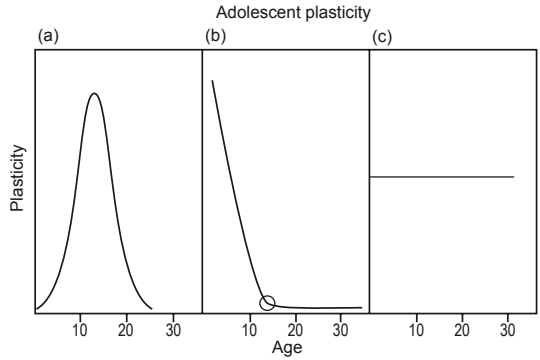

Figure 11.1 Theoretical depiction of how plasticity (i.e., responsivity to experience) changes over the life span: (a) adolescence may be its own independent critical period that is not contiguous with childhood; (b) adolescence could mark the end of a critical period that began in infancy or early childhood; (c) the brain is able to change in response to experiences and is stable over the entire life span.

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contrast, before and after the critical period, the same type of experience has little to no effect on the same neural systems.

In contrast to experience-expectant plasticity, experience-dependent plasticity results from experiences that, in general, vary widely across species members. Only some of us will learn to ride a bicycle or play the piano, and literacy levels vary widely across humans. Evolution could not have prepared the brain to expect such experiences. Greenough et al. (1987) proposed that unlike experience-expectant plasticity, which is restricted to critical periods, the capacity of the brain to change in response to experiences is stable throughout the life span (Figure 11.1c). Thus the organism is capable of this type of learning to a similar degree early and late in life. An example of this kind of learning is the capacity of humans to add words to their vocabulary throughout the life span.

Within this framework, we can ask whether the human brain is intrinsically more plastic during adolescence: Has the brain been prepared by evolution to expect particular experiences during this period of life? If so, we would expect the adolescent brain to be differentially sensitive to the influences of environmental input relative to the adult brain. Consistent with the idea of enhanced sensitivity, humans undergo large-scale behavioral changes during adolescence. However, such changes could be driven by external environmental changes that occur during this time of life (e.g., intensification of interactions with peers), rather than due to enhanced potential for change within the brain (Figure 11.1c) (Fuhrmann et al. 2015). They could also purely be due to maturational factors that do not reflect an enhanced sensitivity to the environment.

Alternatively, adolescence could be a special time of sensitivity to environmental input (i.e., a critical period). Adolescence could mark the end of critical period(s) that began in infancy or early childhood (Figure 11.1b). An example of such an effect has been postulated in the context of acquiring the grammar of language. A seminal study examined the acquisition of a second language by immigrants from China and Korea to the United States. Here, Johnson and Newport (1989) reported that individuals who entered the country before approximately age 7 attained native-like abilities in the use of English sentence-level grammar, with proficiency falling off linearly until at approximately age 15 before it plateaus. The presence and precise timing of such a plateau in second language learning remains controversial. The critical period may be earlier and sharper for the acquisition of the first language (Friedmann and Rusou 2015; Mayberry 1998). Nevertheless, in principle, such a pattern corresponds to a prolonged critical period that terminates in adolescence. There is also evidence that the brain undergoes anatomical changes during the adolescent period. Gray matter volume thins in much of the cortex from early childhood throughout the late teens, and the total amount of white matter in the human brain increases, abating only in young adulthood (Gogtay et al. 2004; Giedd and Rapoport 2010; Walhovd et al. 2017). This long-lasting neural immaturity could be associated with

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sensitivity to environmental influences on the brain. Such temporal trajectories are examples of adolescence marking the end of a very long critical period lasting the first two decades of life (Figure 11.1b).

It is worth noting that the protracted duration of putative critical periods that terminate in adolescence distinguishes them from the classic critical periods that have been described in sensory systems. For example, the period of ocular dominance plasticity in mice is estimated to last 1–2 months (Morishita and Hensch 2008). The critical period for monocular deprivation in humans lasts for the first few years of life, peaking sometime before the second year and ending by approximately year six (Berardi et al. 2000; Maurer and Hensch 2012). In general, animals with longer life spans have longer critical periods. Thus the critical period for monocular deprivation in mice is shorter than that of monkeys, which is in turn shorter than that of humans (Berardi et al. 2000). Nevertheless, even relative to the human life span, critical periods which end in adolescence are protracted. Why might putative critical periods be so long?

One factor that could contribute to long-lasting critical periods in humans is the relatively late maturation of higher cognitive systems as compared with sensory systems. Even within the visual system, visual functions that mature slower (vision for high spatial frequencies) have more prolonged critical periods and mature later (vision for low spatial frequencies) (Maurer and Hensch 2012). Analogously, critical periods in higher cognitive systems may be longer because higher cognitive systems mature more slowly. From an evolutionary perspective, such a protracted period of sensitivity to external information may provide an advantage by enabling humans to achieve maximal adaptation to a variety of changing environments. There may have been a specific evolutionary pressure for the human brain to remain flexible later into development to enhance learning and adaptability (e.g., Thompson-Schill et al. 2009). Whether such long critical periods are mediated by similar neurophysiological mechanisms, as the shorter-lasting critical periods in sensory systems, remains to be determined. Irrespective of the mechanism, however, in humans, adolescence may mark the end of a number of protracted critical periods that began in early childhood.

An alternative nonmutually exclusive possibility is that adolescence is its own independent critical period that is not contiguous with childhood (Figure 11.1a). If so, we might expect the potential for plasticity to begin rising in early adolescence and fall off by adulthood. Consistent with this possibility, there is some evidence from studies with humans and animal models that adolescents are more sensitive than juveniles or adults to experiences of social stress (Fuhrmann et al. 2015). Such enhanced sensitivity to experience could be mediated by adolescence-related hormonal changes. Alternatively, the same or analogous neural mechanisms that render the brain especially sensitive to the influence of hormonal changes in adolescence could independently enhance sensitivity to experience.

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Studies with animal models provide extensive evidence for the idea that hormone exposure during adolescence affects the brain, social behavior, and learning in ways that are distinct from hormonal exposure outside of the adolescent period. In rodents, like in many other species, puberty is associated with a surge in testosterone. If male rodents are gonadectomized prior to puberty, then adolescent brain development proceeds in the absence of the normal influences of testicular hormones. Under these conditions, hamsters fail to acquire a wide range of male social behaviors typically learned during adolescence, and these behaviors are compromised in adulthood. Prepubertally gonadectomized male Syrian hamsters display lower levels of sexual behavior compared with male hamsters that are gonadectomized in adulthood. The deficits resulting from prepubertal gonadectomy are not reversed either by prolonged testosterone replacement therapy or sexual experience in adulthood (Schulz et al. 2004). Other male typical adult behaviors that are organized by pubertal testosterone include aggression, scent marking, play fighting, and nonaggressive social interactions (reviewed in Schulz et al. 2009a; Schulz and Sisk 2016). Thus, the absence of testicular hormones during adolescence results in long-lasting impairments of sociosexual behaviors. Conversely, the presence of testicular hormones during adolescence masculinizes neural circuits underlying sociosexual behaviors and programs enhanced activational responses to testosterone in adulthood.

Research suggests that pubertal testosterone specifically affects social learning—the ability to make behavioral adaptations as a function of social experience (De Lorme et al. 2013; De Lorme and Sisk 2013, 2016). By contrast, pubertal testosterone does not affect performance or motor execution of sociosexual behaviors per se, because males deprived of testosterone during adolescence do display the consummatory components of sexual behavior, aggression, and scent marking, albeit at lower levels compared with males that did experience testosterone during adolescence. For example, normal male hamsters gain social proficiency over the course of repeated encounters with another male in a neutral arena. During the first social encounter between two unfamiliar males, an aggressive interaction occurs initially, and a dominant-subordinate relationship is established within a few minutes. In subsequent encounters, there is little aggression but the dominant–subordinate relationship is maintained through flank marking by both males. This experience-dependent behavioral pattern is disrupted in males deprived of testosterone during adolescence: these males display low overall levels of flank marking, even if they are dominant, and the dominant–subordinate relationship is not maintained by flank marking, but instead is reestablished via aggression in subsequent encounters (De Lorme and Sisk 2013).

Thus, during adolescence, the brain appears to "expect" pubertal testosterone, and this testosterone exposure organizes neural circuits that govern social cognition, the mental processes by which an individual encodes, interprets, and responds to sensory information from a conspecific. Crucially, the adolescent

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brain appears to be specifically sensitive to the influence of testosterone, thus suggesting a critical period of plasticity where hormones have a unique potential to influence the brain. Whether similar sensitive periods exist for the influence of experience on the brain during adolescence, apart from the experience of hormones, remains to be tested. A further interesting possibility is that hormones interact with experience, such that deprivation from specific social experiences during adolescence interferes with the typical hormonal effects.

In sum, the potential for plasticity in the adolescent brain could theoretically follow one of three types of time courses. First, adolescent brains could be no more plastic than adult brains. Second, adolescence could mark the end of critical periods that began in infancy. Third, adolescence could be its own critical period, with a beginning and end that is distinct from critical periods occurring in early childhood. Given the available evidence, it seems probable that all of these time courses coexist in the human brain. As was pointed out by Greenough et al. (1987), the brain does not follow a single sensitive period: each neurocognitive system has its own time course of development. Some neurocognitive systems may be stable in their plasticity throughout the life span, others may begin their sensitive periods early in life and taper off during adolescence, and still others may have a specific critical period of sensitivity spanning adolescence itself (e.g., sensitivity to social stress). Future research is needed to uncover the time course of plasticity across different neurocognitive systems.

Animal Models for the Study of Experience-Based Plasticity

It is not possible to understand the causal variables that drive human brain development based on studies with humans alone. Currently, noninvasive imaging approaches in humans are severely limited in their ability to measure specific neural mechanisms, since the measurements of neural activity in humans are indirect and limited both in their temporal and spatial resolution. Functional magnetic resonance imaging (fMRI) and light-based hemodynamic measures (near infrared spectroscopy) infer neural activity through metabolic markers that are substantially divorced from the biological mechanisms of primary interest. Furthermore, such studies lack temporal precision. While neural events occur on the timescale of milliseconds, hemodynamic responses stretch over seconds. Electroencephalography (EEG) and magnetoencephalography (MEG) provide millisecond timing accuracy but have poor spatial resolution. They are unable to disentangle unambiguously the specific neurophysiological generators of activity even at the level of cortical region and are insensitive to certain neural sources, depending on their depth and orientation in the brain. Even the comparatively "high" spatial resolution of fMRI (millimeters) is far lower than what is required to disentangle the neurophysiological mechanisms that drive developmental change at the level of circuits (e.g., specific neural

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subpopulations, neurotransmitters, receptors, synapses). Thus, at present, studies in humans are limited to measuring coarse network properties. While these measurements are informative in their own right, they represent only a fraction of what we need to know about human brain development.

A further challenge to conducting research with humans is that we are unable to manipulate experimentally genes or experience. This limits our ability to disentangle the contribution of these factors to developmental change. By contrast, the experience of animals can be precisely controlled during specific windows of time. This includes both studies of deprivation (e.g., dark-rearing or monocular deprivation), studies of enrichment, and more fine-grained changes such as exposure to motion in a specific direction and deprivation from occluded objects (e.g., Hubel and Wiesel 1970; Sale et al. 2007; Vallortigara et al. 2009; Arcaro et al. 2017). Such controlled rearing studies continue to be a bedrock of developmental science. Over the past decade, it has become possible to manipulate the genes of animals. This enables not only testing the effects of specific genes, but also dissecting the neurophysiological mechanisms that govern critical period plasticity (Hensch 2005). Studies of animals, therefore, provide crucial insights into the causal factors that drive brain development.

There are some inherent challenges, however, in leveraging insights gained from animal studies to answer questions about development in humans and in adolescents, in particular. At present, most of what we know about the biological mechanisms of experience-based change in animals is circumscribed to early development in primary sensory systems (e.g., effects of monocular deprivation on V1; Hensch 2005). The degree to which similar mechanisms mediate development during early adolescence is not known. A key feature of learning and plasticity in early adolescence is that higher cognitive systems are involved. The neurocognitive systems that continue to develop into early adolescence include those which support language, social cognition, executive function, memory, emotion, and decision making. Analogously, psychiatric disorders that emerge during adolescence implicate these higher cognitive systems (e.g., depression). Since higher cognitive systems are more developed in humans compared to other species, the creation of adequate animal models to study plasticity in higher cognitive domains poses a key challenge.

Most work in animals has concentrated on sensory systems, and comparatively few studies with animals have even attempted to look at experience-based change in higher cognitive systems. One study by Yang et al. (2012) examined the neural basis of music preference learning in juvenile mice. The acquisition of such preference is associated with changes in medial prefrontal cortex, rather than the auditory cortices, consistent with the idea that such learning is mediated by higher cognitive systems. This study found that mice have a critical period for developing music preferences, and this critical period is influenced by neurochemical modulators similar to those which affect visual

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system development (valproic acid). This result is consistent with the possibility that experience-based plasticity in higher cognitive systems is mediated by similar neurophysiological mechanisms as those that govern critical period plasticity in primary sensory systems (e.g., excitatory–inhibitory balance) (Yang et al. 2012).

Notably, although the above study examined neural changes in prefrontal cortices, the nature of the learning experience itself was more similar to the passive sensory-based learning in the visual and auditory systems than to the higher cognitive experiences of human adolescents. In other words, the mice either did or did not experience a type of music. By contrast, higher cognitive learning in humans is more complex, both in terms of the knowledge acquired (e.g., the grammatical structure of sentences or the causal relationship between people's mental states and their behaviors) and the nature of the learning experience itself (e.g., constrained by previous knowledge, self-directed, socially situated).

In this regard, play is a key example of a learning experience that has a complex character representative of the type of learning that occurs in higher cognitive systems. During the first years of life, children spontaneously engage in object-directed and social play. There is evidence that such play provides children with crucial information about how the world works. For example, children actively test hypotheses about the causal mechanisms that govern how toys work (Cook et al. 2011). They systematically seek out evidence both by physically manipulating the objects and seeking out information from other social agents that they perceive to be reliable (Gweon et al. 2014). Although the play behavior of humans is likely to have a distinctive character, other animals, including rodents, also engage in play in the wild. In their studies of the neurobiological mechanisms of social play learning in rats, Kolb and colleagues found that prefrontal cortex plays a central role in play behavior and, conversely, that the development of prefrontal cortex is strongly influenced by play. For example, the complexity of neurons in the medial prefrontal cortex of rats and hamsters is related to the amount of play behavior (Bell et al. 2010; Burleson et al. 2016). Furthermore, the number of conspecifics that an animal plays with during development influences the pruning of the orbitofrontal cortex (Bell et al. 2010). These studies provide an example of how animal models could be used to understand the effects of higher cognitive experience on the developing brain.

For animal model work to inform maximally our understanding of plasticity in humans, further work is needed that examines the neurophysiology of experience-based learning in higher cognitive systems, perhaps using naturalistic behaviors of the species in question, such as play. Nevertheless, since there is a qualitative gulf between the cognitive repertoire of humans and other species, it will ultimately be necessary to measure higher cognitive plasticity directly in humans and to link these measures to markers of experience-based learning in animals. One attempt at such linking is discussed at the end of this chapter.

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Neural Markers of Development and Experience-Based Change in the Human Brain

The human brain continues to change substantially throughout early adolescence and even into young adulthood (e.g., Uhlhaas et al. 2010). Below we highlight some examples of the type of neural markers of human brain development that have been identified, focusing on measurements of functional development. In most cases, directly linking these markers to the influence of experience per se, as opposed to maturation, has remained out of reach. However, some work on cross-modal plasticity provides an in-principle demonstration of how the effects of experience on the brain can be studied in humans (discussed in the following section).

One course of action in the study of development of human cortical functions is to compare the amount of response in a given cortical area during a cognitive task across groups. For example, if we wish to know whether working memory circuits are developing in human children, we could compare the amount of response in frontoparietal networks during a working memory task in adults and children. Such comparisons are complicated, however, by the fact that the overall amount of neural activity in a given system reflects not only the stable properties of that system but the degree of their engagement during a particular cognitive task. Thus greater activity in children during a working memory task might reflect the immaturity of the working memory system. Alternatively, it could reflect the relative difficulty of the working memory task for children and therefore the increased processing required within this cognitive system.

One alternative to measuring the overall amount of neural activity during a task is to measure information selectivity; that is, the degree to which a given brain area responds selectively to one type of information over another (Saxe et al. 2009). Although information selectivity measures are not immune to difficulty, they are arguably less prone to reflecting merely the degree of difficulty of the current task for the age group in question. One example of such work comes from the field of social cognition. There is evidence that cortical areas that support social cognition increase their information selectivity into late childhood/early adolescence. In adults, a subset of socially relevant cortical regions are specifically involved in reasoning about the internal mental states (e.g., their beliefs, desires, and goals) of social agents (Saxe and Kanwisher 2003). For example, the right temporoparietal junction (RTPJ) is highly active when participants comprehend stories or view images that require representing an agent's mental state (e.g., Rachel thought it was going to rain) but not stories about agents that do not require "mentalizing" (e.g., Rachel went to the store to buy milk) or stories about physical events (e.g., the bridge is going to fall down). Studies with children show that this preference for mentalizing emerges slowly over the course of development and is not adult-like until late childhood/early adolescence. In

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children, unlike in adults, the RTPJ responds similarly to all stories about social agents. Furthermore, across children, the degree of specialization in the RTPJ correlates with performance on mentalizing tasks outside the scanner, even when age is factored out (Gweon et al. 2012). Whether this change emerges as a result of social/linguistic experience, intrinsic maturation, or both is currently under investigation. It is worth noting that delays in theory of mind performance have been observed in deaf children who grow up without access to sign language. By contrast, deaf children who grow up with early access to sign language perform similarly to hearing controls (Schick et al. 2007). This suggests that theory of mind development is influenced by linguistic experience during childhood and early adolescence.

A further aspect of human brain function that continues to develop well into adolescence is spontaneous as well as task-driven synchronized rhythmic neural activity, so-called neural oscillations (see Vakorin and Doesburg 2016). In humans such oscillations can be measured using electrophysiological recordings such as EEG and MEG. Changes in spontaneous neural oscillations begin in infancy and continue throughout childhood and adolescence. They include not only a restructuring of neurophysiological synchronization among brain areas but also (a) reduction in overall power in oscillation, (b) acceleration of the peak frequency of alpha oscillation, and (c) reduction in lower-frequency oscillations (< ~10 Hz) and increase in higher-frequency oscillations (> ~10 Hz) (Miskovic et al. 2015; Vakorin et al. 2017). Development of such coordinated neurophysiological activity is atypical in neurodevelopmental disorders such as autism, and is associated with symptomatology (Vakorin et al. 2017).

Task-related oscillations also develop throughout childhood and adolescence. For example, increased activity and interelectrode synchronization have been reported in beta- and gamma- (>30 Hz) frequency ranges during Gestalt visual perception (Rodriguez et al. 1999). This percept-dependent network synchronization has also been shown to change throughout child and adolescent development, with qualitative maturational shifts suggesting late restructuring of neurophysiological networks during adolescence (Uhlhaas et al. 2009b). Such developmental changes in task-dependent neurophysiological synchronization may contribute to cognitive and behavioral maturation, as age-dependent increases in interregional synchronization during performance of a language task have been shown to correlate with individual differences in language abilities (Doesburg et al. 2016). Neural oscillations could play an important role in experience-dependent plasticity, since the synchrony of neural firing profoundly affects the nature of the resulting plastic changes (Uhlhaas et al. 2009b).

Although substantial evidence suggests that cortical oscillations change during development in humans and in animals, there are important challenges in determining the neurobiological and cognitive significance of measured oscillations. For example, not all oscillatory activity measured by MEG and

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EEG reflects oscillatory neural activity; alternatively, it is not clear whether non-oscillatory neural activity is measured as oscillation by MEG and EEG. This limitation is particularly severe when measuring high-frequency oscillations (e.g., in the gamma band). Non-oscillatory, nonsynchronized activity (spikes, EPSPs, IPSPs) gives rise to signals in the high-frequency band and mimics, when band pass filtered, gamma oscillations. Because it is high-frequency activity, it is often characterized as gamma activity but does not necessarily reflect true oscillatory process. Special analysis procedures are required to distinguish true oscillatory signals from other causes of EEG and MEG oscillations. A key goal in outstanding research is to link measurements of brain development in humans (e.g., changes in oscillations observed in EEG) to neurophysiological processes measured in studies with animal models.

Adolescent development is also associated with changes in the synchronization of spontaneous activity across regions and networks, as measured by correlating the spontaneous fluctuations in hemodynamic activity in fMRI (Biswal et al. 1995). This is sometimes referred to as "resting-state connectivity" or "functional connectivity." In adults, functionally related areas express coordinated fluctuations in activity, even in the absence of a task. For example, activity is correlated among areas within a network, such as the dorsal attention network, the salience network, and default mode network, and is less correlated between networks. These are examples of intrinsic connectivity networks (ICNs) that have been identified using functional connectivity measures with fMRI.

The correlation structure of ICNs changes over the course of development, including during adolescence. Specifically, there is a shift toward progressively stronger interactions among functionally related areas and progressively weaker interactions with anatomically proximal but functionally unrelated areas (Fair et al. 2008, 2009). This can be conceptualized as a strengthening of "within network connectivity" and a weakening of "between network connectivity" (Dosenbach et al. 2010). This refinement of the correlation structure of hemodynamic activity during adolescence is a continuation of a process that begins in the perinatal period (Smyser et al. 2010).

Developmental changes in spontaneous neurophysiological network, as measured by fMRI (ICNs), may be related to some of the spontaneous oscillatory activity measured by MEG and EEG. The anatomical structure of correlations in cross-frequency coupling and the envelope of alpha (8–12 Hz) and beta (15–30 Hz) activity recapitulate ICN topographies in MEG (Brookes et al. 2011; Florin and Baillet 2015). Age-related increases of neurophysiological amplitude correlations in ICNs during childhood and adolescence are also strongest in the alpha- and beta-frequency ranges (Schäfer et al. 2014), suggesting that spontaneous MEG and fMRI correlations may capture overlapping aspects of organization in coordination of large-scale activity.

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Linking Markers of Human Brain Development to Changes in Experience

The developmental changes in neural activity described above have not been directly linked to experience as opposed to maturation. Doing so based on studies with typically developing children is challenging. However, comparisons across populations with different developmental experiences makes it possible to tease apart these variables in human development. One example of such research comes from studies of blindness. These studies suggest that both the informational selectivity within a cortical area and functional coordination of activity across regions are influenced by developmental experience.

Studies of visual cortex function in individuals who are congenitally blind demonstrate that the basic functional properties of cortical networks can change dramatically as a result of developmental experience. In individuals who are blind from birth, so-called "visual" cortices respond to auditory and tactile stimuli (Sadato et al. 1996; Gougoux et al. 2005). Remarkably, visual areas appear to take on higher cognitive functions, including language and mathematical reasoning (Röder et al. 2002; Amedi et al. 2003; Bedny et al. 2011; Kanjlia et al. 2016). For example, a subset of visual areas responds more to spoken sentences than noise, more to sentences than lists of words, and more to grammatically complex than grammatically simple sentences (Röder et al. 2002; Lane et al. 2015). By contrast, dorsal regions within visual cortex of blind individuals participate in numerical tasks: they are active when participants solve spoken math equations and activity scales with equation difficulty (Kanjlia et al. 2016). The information selectivity of visual cortices, therefore, changes dramatically as a result of blindness (Bedny 2017).

The functional coordination of visual cortex activity with other regions also changes in blindness. In particular, activity in "visual" areas becomes more correlated with frontoparietal networks (Deen et al. 2015). Furthermore, different subregions of visual cortices become functionally coupled at rest with distinct higher cognitive frontoparietal networks, and resting-state specialization in functional connectivity is related to specialization in task-based responses. Number-responsive visual areas (e.g., middle occipital gyrus and foveal V1) become coupled with a frontoparietal network that is involved in numerical processing. By contrast, language-responsive visual areas (e.g., lateral occipital and posterior fusiform regions, peripheral V1) become coupled with inferior-frontal regions involved in linguistic processing (Figure 11.2) (Bedny et al. 2011; Lane et al. 2015; Kanjlia et al. 2016). Together, this evidence demonstrates that both information selectivity within a cortical area and the functional coordination of cortical networks are profoundly influenced by developmental experience.

Studies with individuals who became blind as adults further suggest that the capacity of cortex to respond to changes in experience is qualitatively different in childhood and adulthood. Although visual cortices show responses to

From "Emergent Brain Dynamics: Prebirth to Adolescence,"
April A. Benasich and Urs Ribary, eds. 2018. Strüngmann Forum Reports, vol. 25, series ed. Julia R. Lupp.
Cambridge, MA: MIT Press. ISBN 9780262038638.

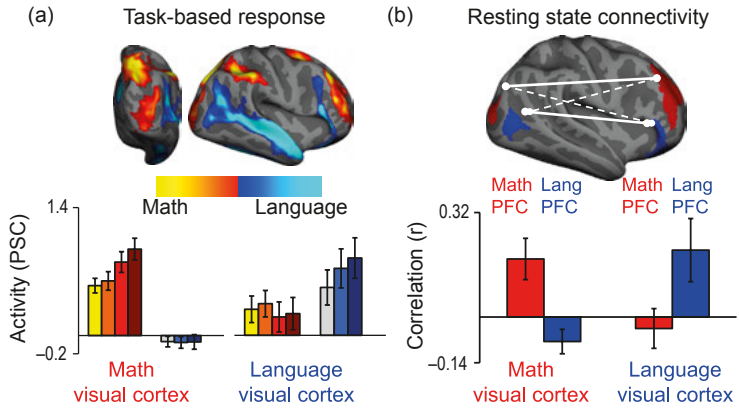

Figure 11.2 (a) BOLD activity during sentence comprehension task (blue) and math equation task (red) in congenitally blind participants. Contrast depicts math task > sentence task ($P < .05$, corrected). White circles highlight visual cortex responses that are absent in those who are sighted. Bottom graphs show percent signal change (PSC) in two visual cortex areas with different functional profiles in blind individuals: a math-responsive visual cortex region and language-responsive visual cortex region. Red bars show responses to equations of varying difficulty; darker reds indicate the hardest equations. Blue colors show sentences of differing grammatical complexity; darker blues indicate more complex sentences. Gray bars show responses to nonword lists. (b) Resting-state connectivity patterns in blind individuals show that while the math-responsive visual cortex region is more correlated with math-responsive prefrontal cortex (PFC), the language-responsive visual cortex region is more correlated with language-responsive inferior PFC areas.

nonvisual stimuli, even in those who become blind as adults, there is evidence that such changes are less functionally specific and less behaviorally relevant (Cohen et al. 1997; Bedny et al. 2012; Collignon et al. 2013). Studies of sensory loss thus suggest that developmental experience plays a unique role in determining the functional architecture of the human brain.

Conclusions

Childhood and adolescence are periods of particular sensitivity to the influences of experience on the human brain. Studies with animal models have uncovered local circuit neurophysiological mechanisms that govern these periods of enhanced sensitivity. In humans, many functional properties of the brain continue to change throughout childhood, adolescence and beyond, including regional cortical information selectivity, neural network correlations, and oscillatory activity. Evidence from studies of plasticity in sensory loss suggests that such functional properties of cortical networks can be fundamentally altered by experience and that sensory experience during development has especially potent effects on cortical function. Two key challenges for future research are (a) to

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link neurophysiological mechanisms of critical period plasticity identified in animals to developmental changes in human behavioral and brain function and (b) to understand how complex experience (such as play) influences the function of higher cognitive systems in both animals and humans.

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