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Brain Plasticity in the Adolescent Brain

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Abstract

Adolescence is a time of enhanced neural plasticity, including both experience-expectant plasticity and experience-dependent plasticity. Experience-expectant changes are likely related to socioaffective behaviors, including play, sex, and social interactions, all of which come to dominate the life of adolescents. The most likely candidates driving plasticity in adolescence include the generation of new neurons and/or glia, the formation of connections either by axon extension or synapse formation, pruning or growth of dendrites and thus synapses, thinning of the cortex, epigenetic changes, and changes in the excitatory–inhibitory balance. A range of factors influence plasticity in the adolescent brain (e.g., play, drugs, sensorimotor experiences, stress, diet, cerebral injury, and the immune system). The onset of the sensitive period is around the onset of pubertal gonadal hormone production, but may or may not be triggered by the hormone release. The offset of the sensitive period may be related to myelination, which reduces plasticity, and the timing of the offset likely varies in different cortical regions.

Introduction

The general term "sensitive period" refers to times when the brain is unusually responsive to experiences during development. The term "critical period" is a special type of sensitive period in which specific experiences result in irreversible changes in brain organization or function (Knudsen 2004). In this chapter, I will use the concept of sensitive period, in part because although much is known about irreversible experience-dependent changes in the infant brain, far less is known about such changes in adolescence.

As Knudsen (2004) pointed out, the effect of experiences during sensitive periods can be seen in behavior, but behavioral changes are really a property of changes in neural circuits. Although behavioral changes can be obvious and even dramatic, they can also be subtle. Measurement is dependent upon

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behavioral tests, which often underestimate long-term behavioral changes. As a result, a clear definition of the adolescent sensitive period requires other measures of brain/behavioral correlates, ranging from noninvasive imaging (structural, connectional, and functional MRI, electrophysiological measures) to measurements of structural changes of neural networks, and eventually to molecular measures including changes in the expression of genes (epigenetics) and their products.

What is, however, adolescence? This is hardly a simple question. Some psychologists have argued that adolescence is a social construct that functions to allow adults to control adolescents (for further details, see Steinberg 2016). Given that nonhuman animals clearly show behavioral and brain changes during adolescence, it is hard to argue that it is cultural or social in nature. The real challenge is to identify when this period of development begins and ends. One common onset marker is the onset of puberty, which in humans is around 12 years of age and in rats around 28–30 days (Spear 2000). The more difficult question is: When does it end? The end of obvious behavioral changes often has been used, but when we consider changes in the brain, this becomes less certain. There are multiple potential markers—e.g., reduced neural pruning, myelination, gliogenesis (aside from oligodendrocytes), mature connectivity—but all of these changes take place according to different timetables and manifest differently in different parts of the brain. I am persuaded by the general argument that adolescence is a period of heightened neural plasticity relative to the juvenile and adult brain (e.g., Knudsen 2004; Fuhrmann et al. 2015; Steinberg 2016). The onset of enhanced plasticity likely coincides with the release of gonadal hormones, but the timing of the reduction in plasticity at the end of adolescence has not been well studied. I will argue, however, that at least for some cortical regions, it is likely later than it is often considered to be.

A sensitive period in adolescence is characterized by greatly increased plasticity; it is thus likely adaptive as there is considerable learning about the environment, and especially the social environment (Blakemore 2008). But enhanced plasticity is a double-edged sword: it renders the brain vulnerable to a wide range of experiences, such as stress, psychoactive drugs, brain trauma (e.g., concussion), and variations in the patterns of play that influence brain organization and function differently than in adults. It is no accident that many forms of mental illness become apparent in adolescence (e.g., Tottenham and Galván 2016).

In this chapter, I explore the nature of sensitive period plasticity, especially in adolescence. After a discussion of the factors likely to influence plastic changes in adolescence, I examine the role of preadolescent experiences on trajectories in adolescence. Specific examples of brain plasticity during adolescence are then examined, and I conclude with a set of questions intended to prompt future enquiry.

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The Nature of Plasticity in the Adolescent Brain

To understand that nature of plasticity, we must confront two distinctly different issues: the types of plasticity and the mechanisms by which plasticity plays out in the adolescent brain.

Types of Plasticity

Three types of plasticity can be distinguished in the early developing brain: experience-independent, experience-expectant, and experience-dependent.

Experience-independent plasticity results from the fact that it is impractical for the genome to specify all connections in the brain; instead, it generates a rough approximation of connectivity that is modified by both internal and external events, both prenatally and in the early postnatal period. For example, projections of the retinal ganglion cells to the lateral geniculate nucleus arrive from both eyes and eventually segregate into layers having projections from just one eye. However, the initial projections overlap: to separate the layers, the retinal ganglion cells are spontaneously active, allowing them to correlate their activity with nearby cells but independent of the other eye, which has a different pattern of spontaneous activity. Neurons that are active together increase their connections whereas those that are not coincidentally active weaken their connections.

Experience-expectant plasticity occurs mostly during early postnatal development. A good example is found in the development of sensory processing, when the brain "expects" to be stimulated by a range of sounds, visual and tactile inputs, etc., that will vary depending upon the environment. The brain becomes expert in discriminating inputs that it receives and loses the ability to make fine discriminations when an input is not experienced. For instance, a human infant may be born into a family that speaks one of hundreds of languages, each of which has a distinct phonetic structure. A child raised hearing Korean will thus be exposed to different speech sounds than a child raised in an English-speaking environment. Early in life, infants are able to discriminate the speech sounds of all languages, but over the first year of life, the auditory system begins to change such that the infant becomes expert in discriminating sounds in the language of its environment but loses the ability to discriminate sounds not experienced.

Experience-dependent plasticity, a process whereby the connections of ensembles of neurons are modified by experience, begins in early postnatal life and continues over the entire course of life. One common example is seen in the effects of so-called "enriched experiences." When laboratory animals are housed in highly stimulating environments, the patterns of neural connections are modified, resulting in animals that have enhanced cognitive and motor functions. Although such changes are often thought to reflect the generation of new synapses, there is also a loss of synapses as the networks

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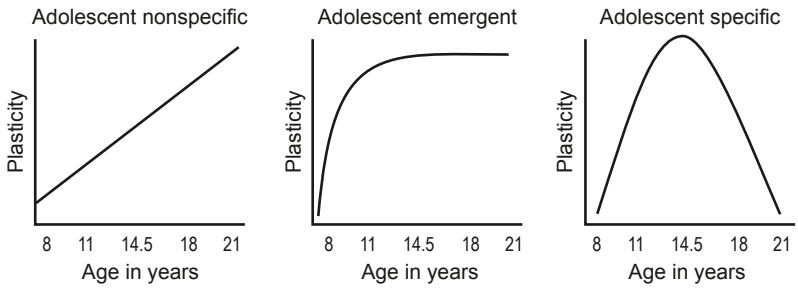

Figure 9.1 Patterns of plasticity in the developing brain. Adapted after Casey (2013).

are remodeled. This is especially evident when animals are given psychoactive drugs, which results in regionally specific increases and decreases in synaptic density.

What is the nature of plasticity in the sensitive adolescent period? It seems likely that experience-dependent plasticity plays a major role. However, in principle there could be some form of experience-expectant plasticity, likely related to the production of gonadal hormones in puberty and changes in social behavior. Casey (2013) has suggested that there are three distinct forms of adolescent developmental changes (Figure 9.1). Changes in brain and behavior may be *adolescent nonspecific*, which reflect a continuation of processes already in progress; *adolescent emergent*, which increase rapidly up to adolescence and then are relatively constant for some period of time; or *adolescent specific*, which emerge for the adolescent period and then decline. The latter type would best reflect the contention that adolescence is a period of enhanced plasticity.

An alternate version of the Casey model was proposed by Fuhrmann et al. (2015). Like Casey, they imagine an adolescent specific and nonspecific period, but also suggest that plasticity may decline continuously from childhood through adolescence and into adulthood. The problem, of course, is that different scenarios can only be discriminated if we know how the plastic changes appeared before and after adolescence. This is a significant area of ignorance.

Mechanisms of Plasticity

In the search for understanding plasticity in the adolescent brain, several potential mechanisms deserve consideration:

- neurogenesis,
- gliogenesis,
- changing neural networks (e.g., fcMRI),
- cortical thinning,
- changes in neuronal or glial morphology,

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- changes in synaptic structure and number,
- epigenetic changes, and
- changes in the excitatory–inhibitory balance.

Although none of these have been found to be specific to adolescence, they are driven by factors that may be relevant to adolescence. The most likely candidates, considered in turn below, include the generation of new neurons and/or glia; the formation of connections, either by axon extension or synapse formation, pruning, or growth of dendrites and thus synapses; epigenetic changes; as well as changes in the excitatory–inhibitory balance.

Although neurogenesis in the cortex is complete by birth in placental mammals, it can be stimulated postnatally under special circumstances. We have shown that it can occur spontaneously in rats or mice after injury to the olfactory bulb or midline cortex in the second, but not the first, week of life (e.g., Kolb et al. 1998). It can also be stimulated by growth factors, such as FGF-2, after injury in the second week of life (e.g., Monfils et al. 2006). In both cases, the new neurons form functional connections that support at least partial behavioral restitution. There is no evidence from our studies that spontaneous neurogenesis occurs after injury in adolescence, and I am unaware of any studies administering growth factors (e.g., EGF, FGF-2) after cortical injury in adolescence. It seems likely that neurogenesis could occur, however, because administration of growth factors in adult rats following cortical stroke does stimulate the production of neural precursors, which can be driven to differentiate with erythropoietin. Although the neurons do not mature normally or form functional connections with the adjacent brain, they do enhance behavioral recovery (Kolb et al. 2007).

Not only can neurons potentially be generated, glia can as well. Glial cells constitute about 50% of the cells in the human brain, with astrocytes constituting the largest population. Although astrocytes arise from radial glial cells in the subventricular zone in early development, the major source of astrocytes in postnatal rodents is the proliferation of undifferentiated astrocytes already located in the white matter and cortical layers V–VI. This proliferation derives from symmetric division in which the progeny integrate into the existing glial network (Ge et al. 2012). It is known that postnatal experiences, such as enriched housing, can increase the production of astrocytes, but little is known about any special factors that might influence astrocytosis in the adolescent brain. This important gap in knowledge, however, needs to be addressed, given the critical role that astrocytes play in synaptic connectivity.

In addition to astrocyte proliferation in adolescence, myelin formation increases, partly to increase conduction speed along axons. Functional MRI studies have shown that increasing myelin formation in adolescents increases the efficiency of communication across brain regions compared to younger children. Myelin formation in adolescence, however, may serve other functions. First, there are changes in myelin related to learning. For example,

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Sampaio-Baptista et al. (2013) showed that rats trained to reach through a slot to grasp food exhibit changes in white matter tracts in somatosensory cortex. Similar changes can be seen in humans as well. In a study where subjects were trained for two hours on a car-racing video game, diffusion tensor MRI revealed changes in white matter in hippocampus and parahippocampal gyrus (Hofstetter et al. 2013). More recently, the micro changes were found in white matter during a language task (Hofstetter et al. 2017). In the latter study, Hofstetter et al. introduced lexical items (flower names) that were new to participants for about an hour and found rapid changes in white matter tracts underlying the cortex. The extent of change correlated with behavioral measures of the lexical learning rate.

Second, as myelin continues to form, it may act to close the adolescent sensitive period by inhibiting axon sprouting and the creation of new synapses (Fields 2008).

MRI studies have also used structural MRIs to calculate changes in cortical volume, cortical thickness, and surface area. Although there are inconsistencies in the literature, a recent study of four independent longitudinal data sets have demonstrated decreasing cortical thickness and cortical volume that increases with age during late childhood (as of 7 years of age) and across adolescence before leveling off at around 20 years (Tamnes et al. 2017). In addition, there is a small decrease in cortical area during adolescence. Thus, the major change in the cortex during adolescence is cortical thinning.

Considerable evidence indicates that adolescence is an active time of changes in connectivity. One powerful way to examine connectivity changes is by using resting-state functional interactions and networks with rs-fcMRI. This technique allows us to analyze how cerebral activity changes over age within regions, as well as how the interactions between ages also change with age. Vogel et al. (2010) reviewed such studies and identified two general properties: (a) regional interactions, primarily local in children, change during development to become interactions that span longer cortical distances; (b) these developmental changes segregate local regions and integrate them into disparate subnetworks (see also Khundrakpam et al. 2013). However, it is not just neocortical networks that change during adolescence. Cortical connections with the amygdala, striatum, and hippocampus are also changing (see Figure 9.2). For example, Casey et al. (2015) provided an oversimplified illustration of the types of changes in prefrontal-subcortical circuitry: the interconnections and their relative strength change with development, providing insight into the emotional, social, and other nonemotional behaviors of adolescents. An important principle is that changes in connectivity must be precise enough for an altered circuit to process information differently and carry out the altered (or new) function.

Connectivity can also be inferred from measurements of synaptic changes. The most accurate, and labor intensive, method is to use electron micrographs to count synapse numbers throughout columns across different cortical regions.

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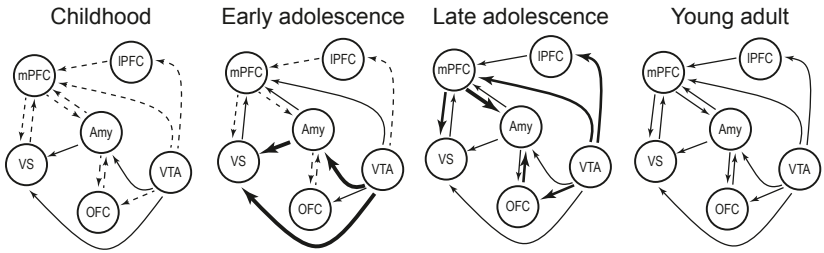

Figure 9.2 Simplistic illustration of hierarchical changes in connectivity from subcortico-subcortical to cortico-subcortical circuits with age. mPFC: medial prefrontal cortex; lPFC: lateral prefrontal cortex; OFC: orbitofrontal cortex; VS: ventral striatum; Amy: amygdala; VTA: ventral tegmental area. Modified after Casey et al. (2015).

Rakic et al. (1994) summarize such heroic studies in five different cortical regions in the rhesus monkey from the E50 through 20 years of postnatal age. Across all areas a rapid increase in synapses occurred postnatally, followed by a stable period for several years with a sharp decline beginning about age 3, which is roughly the onset of puberty, depending upon the area studied. The end of the rapid pruning varies widely, ending at about 4 years in visual cortex but continuing for many more years in prefrontal cortex (PFC). Once again, the end of the sensitive plastic period appears regionally specific, likely reflecting an extended plastic period in association regions.

A simpler method for estimating synapse number is to use a Golgi impregnation stain, which allows the analysis of dendritic complexity as well as length and spine density. The plasticity of dendritic morphology is high early in development but becomes stable by adolescence. Dendritic spines (the location of most excitatory synapses) remain, however, highly labile across adolescence (e.g., Koleske 2013). The relative stability of dendrites coupled with the synaptic plasticity allows the brain to fine-tune spine-based synaptic connections. Although there have been many studies of spine density at specific ages in development, I am unaware of a study parallel to the Rakic et al. electron microscopy (EM) studies in any laboratory species. In our own studies with rats, we have compared spine density in early adolescence (P30) to late adolescence (P55) to adulthood (P120), finding little change in parietal and occipital cortex from P30 to P55 but a sharp drop into adulthood. This result would seem to be at odds with the EM studies, yet there is one fundamental difference: the Golgi studies focused on the distal tips of the dendrites of pyramidal neurons, which are usually the most sensitive region to experiences, whereas the EM studies did not have this bias. The advantage of the Golgi studies is that a much larger range of cortical areas can be sampled fairly quickly.

If the brain is perturbed at P10 or P35, large changes occur during adolescence in dendritic complexity and spine density relative to controls not

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seen after similar perturbations after P90. This suggests that there is more plasticity than is apparent in the "normal" brain. Finally, one unexpected finding is that changes in two prefrontal regions are starkly different: there is little change in spine density in medial PFC from P60–P90, but a significant increase in spine density in orbital PFC over the same time period. In view of the importance of social behavior in adolescence, it is likely that the longer plasticity in the orbitofrontal cortex (OFC), which is central to social interaction and especially social context, should continue longer than other prefrontal regions.

Epigenetics can be viewed as a second genetic code, the first one being the genome, which is an organism's complete set of DNA (see also Moore and Kobor, this volume). Epigenetics refers to the changes in gene expression that do not involve alteration of the DNA sequence but rather the processes by which enzymes read the genes within the cells. Thus, epigenetics describes how a single genome can code for many phenotypes, depending on the internal and external environments. Epigenetic mechanisms influence the brain throughout the lifespan and are integrated with environmental changes characteristic of developmental milestones (e.g., Kanherkar et al. 2014).

Although genome-wide association studies have identified many genes associated with the regulation of the time at puberty, these genetic variants account for only a small fraction of the variation in the timing of puberty in humans. Epigenetic differences thus appear to play a significant role in the timing of puberty and adolescence as well as in the integration of hormonal, social, environmental, and genetic information. This complex interaction includes exposure to adverse experiences such as chronic stress and drug exposure (alcohol, cannabis) that significantly alter gene expression, often in a sexually dimorphic manner (e.g., Morrison et al. 2014). One fundamental difference between childhood and adolescence is that environments tend to be less structured for adolescents, at least in some cultures, leading to greater individual differences in experiences and thus in gene expression.

Considerable work has shown that the critical period in infancy results from an appropriate balance of excitatory and inhibitory (E–I) inputs (see Figure 9.3). The maturation of inhibitory GABA circuits underlies the timing of onset of the critical periods, which vary across brain regions. Premature onset of the critical period is prevented by various factors; for example, polysialic acid acts on neural cell adhesion molecules, which act on parvalbumin (PV) in GABA interneurons. When other factors promote PV cell maturation, the critical period begins. The critical period closes as molecular brakes emerge to dampen plasticity, and thus limit adult plasticity (for a review, see Takesian and Hensch 2013). A key point is that it is possible to reopen the critical period by manipulating the E–I balance chemically, such as by using valproate. It is thus possible that the critical period could be reopened in adolescence by some type of endogenous process, possibly gonadal hormones. As a general rule

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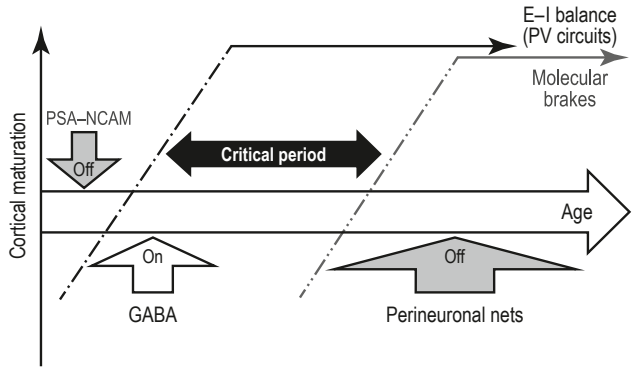

Figure 9.3 Proposed mechanism for turning on and off critical periods. Plasticity is blocked initially by factors such as polysialic acid (PSA) on neural cell adhesion molecule (NCAM), thus limiting the parvalbumin system (PV). Critical period onset is triggered as various factors enhance the GABA PV system. The critical period closes as molecular brakes (e.g., perineuronal nets) emerge to dampen plasticity. Adapted after Takesian and Hensch (2013).

of thumb, when there are changes in gonadal hormones, there are changes in neural plasticity.

The question here is whether the onset of adolescence acts to release the brakes in place in early development, or if there is a *de novo* set of molecular experiences that might be in play. One other possibility is that experience-expectant plasticity renders the brain more sensitive to certain kinds of experiences (e.g., social), which in turn drives circuits to self-organize. This could account for the opening of an adolescent sensitive period but provides no clear mechanism for closing it.

Perinatal Programming and Plasticity in the Adolescent Brain

There is considerable evidence that adult disease may have developmental origins (e.g., Barker 2004). Expanding on this idea, it can be argued that there is a sensitive period during which early experiences alter epigenetic programming that initially result in no obvious behavioral effects in infancy, but later surface in life to alter the brain and behavior. For instance, pre- or postnatal stress, nutrition, or drug exposure can alter the epigenome and induce later changes in adolescent brain and behavior (see review by Mychasiuk and Metz 2016). Exposure to high doses of alcohol on P4–9 triggers the production of astrocytes in adolescent rats (Helfer et al. 2009). In humans, the effects of early-life chronic stress is often first observed when periadolescent children (11–12 years of age) start to diverge in their developmental trajectories (Andersen and Teicher 2008). Thus, depressive symptoms are rarely observed in children when they are initially exposed to early stress; they are delayed about 9 years

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after the abuse (for further examples, see Andersen 2016). Early experiences may not only lead to behavioral pathology but may result in reduced plasticity in adolescence. For example, gestational exposure to nicotine blocked the effects of enriched housing in adolescence (Mychasiuk et al. 2014).

The effects of early-life experience may not be apparent and remain hidden until the adolescent brain is exposed to special experiences (e.g., alcohol, nicotine, enriched housing). Similarly, experiences in adolescence may change the manner in which the adult brain changes to experience in adulthood. Exposure to psychoactive drugs alters the neuronal structure in the adult PFC (for a review, see Robinson and Kolb 2004). Similar effects on the immature PFC have been proposed to interfere with the development of prefrontal circuits and increase risk for psychiatric problems in adulthood, including substance abuse (e.g., Jordan and Andersen 2017).

Special Examples of Plasticity in the Adolescent Brain

Before special examples in the adolescent brain are addressed, it is worthwhile considering what types of factors influence the brain in early development (for a more extensive review, see Kolb et al. 2013).

Factors Influencing Plasticity in the Early Developing Brain

Since the 1950s there has been considerable interest in the effects of early experiences on brain development. Although it was initially assumed that large changes in experience (e.g., being raised in darkness) would be required to influence brain development, it has become clear that an unexpectedly large range of experiences can alter brain development:

- age,
- sensory and motor experience,
- pre- and postnatal stress,
- psychoactive drugs,
- parent-child relationships,
- peer relationships,
- diet,
- gut bacteria, and
- immune system.

In addition, even fairly innocuous-appearing experiences can profoundly affect brain development. Furthermore, the magnitude of the changes is much larger than expected. A brief discussion of these factors follows, with an emphasis on studies of laboratory animals. Although other factors most certainly

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alter early development, our focus here is on those that are also likely to influence the adolescent brain.

Age

Precise embryological age is a critical factor in understanding plasticity in early development. Although there is a tendency to think of early postnatal development as a time of enhanced neural plasticity, this is not always the case. For example, if the cerebral cortex of rats is damaged during the first few days of life, the functional outcome is poor and the brain does not show successful neural compensation. However, similar damage during the last few days of gestation or in the second week of life stimulates remarkable plasticity, and behavioral outcomes are surprisingly good (e.g., Kolb 1995). A difference of just a few days in early development makes an enormous difference to brain plasticity.

Sensory and Motor Experiences

Sensory and motor experiences can easily be manipulated through extreme deprivation (e.g., rearing animals in total darkness) or by placing animals in quasi-enriched environments. Raising animals in severely deprived conditions interferes with development and often leads to permanent loss of function, often associated with reduced dendritic branching in the neocortex. By contrast, rearing animals in enriched environments stimulates synaptic changes in most cerebral regions, with increases in the number and density of blood vessels, neuron soma size, dendritic elements, synapses, gene expression, and glia. Animals do not actually need to be housed in these environments because if either of their parents lived in them prior to conception, the offspring's brains will be similar to the animals who actually lived there.

Fairly minor modifications of sensory inputs can also modify both brain and behavior. For example, when we tactilely stimulated newborn rats with a light brushing for 15 min three times daily until weaning, there was a significant increase in brain weight, dendritic length in cortical pyramidal neurons, and skilled motor behavior (e.g., Kolb and Gibb 2010). We have also shown that the tactile stimulation increases the production of FGF-2 in the skin, and FGF-2 crosses the developing blood–brain barrier to stimulate receptors in the cortex.

Pre- and Postnatal Stress

The general findings of studies of gestational stress is that behaviorally, offspring exhibit increased anxiety, altered play behavior, impaired skilled reaching, and slower spatial learning (reviewed by Kolb et al. 2017). Postmortem analyses revealed decreases in overall brain (but not body) weight and

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decreased spine density in OFC, but increased spine density in mPFC and changes in gene expression in these regions.

There is a large literature on the effects of maternal separation in rodents with consistent evidence that the duration is critical. Short duration (3–15 min daily) is beneficial to the offspring as it alters the hypothalamic-pituitary-adrenal axis, making it more efficient allowing better recovery from stress. In contrast, longer periods of maternal separation (e.g., 3 hr per day) is associated with increased anxiety in adult male offspring, disrupted play behavior in both sexes, decreased brain weight in males (but not females), increased dendritic complexity, and spine density in both mPFC and OFC.

Psychoactive Drugs

All psychoactive drugs, including prescription drugs, appear to change the structure of neurons, especially in PFC and nucleus accumbens (e.g., Robinson and Kolb 2004). Less is known about the effects of drug exposure during development, although it has long been known that early exposure to alcohol is deleterious for brain development. There is growing evidence that prenatal exposure to a wide range of drugs—including nicotine, amphetamine, fluoxetine, valproic acid, morphine, and marijuana—alter behavior, neuronal structure, and epigenetics in the adult offspring (e.g., Vassoler et al. 2014). Less is known about exposure to such drugs in early development, although antipsychotics administered to mice prior to weaning lead to markedly simpler dendritic structure and reduced spine density in pyramidal neurons across the cerebral cortex.

Diet

Although there is a considerable literature on the effects of early-life nutrition on normal and abnormal behavioral development, relatively little is known about the role of early nutrition and brain plasticity. Most studies have focused on the effects of deficiencies in specific nutrients, such as iron and choline. An intriguing question is whether early brain development might be enhanced by mineral or vitamin supplements. There is evidence that feeding dams diets with enhanced choline or combinations of nutrients increases cognitive function, nerve growth factor in the hippocampus and neocortex, as well as increased dendritic branching and length in cortical neurons in adulthood.

Gut Bacteria

Over the past decade, the idea has emerged that gut bacteria, the microbiome, interacts with the brain and can alter brain plasticity. Manipulation of the microbiome in newborn mice can influence motor and anxiety-related behaviors,

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and although the authors did not specifically examine brain plasticity, they did describe changes in the turnover of noradrenaline, dopamine, and serotonin in the striatum as well as changes in the production of synaptic-related proteins in cortex and striatum (Diaz Heijtz et al. 2011).

Factors Influencing Plasticity in the Adolescent Brain

There is a much smaller literature examining the factors that alter the adolescent brain, but interest has been growing over the past decade (see Spear 2016). Here I review a range of factors that have been shown to have special effects in adolescents and consider the possibility of others.

Play

Play may be an example of an experience-expectant behavior for the adolescent sensitive period. Although rats engage in play throughout their lifespan, play begins around weaning. Around P25–30, the full complement of play behaviors has emerged, with play reaching a peak about P30–40, followed by a decline beginning about P60. The PFC plays a central role in play behavior, and its development is strongly influenced by play. Bell et al. (2010) manipulated the amount of play that rats could engage in and found a negative correlation between dendritic complexity/spine density in mPFC and the amount of play. In contrast, complexity of neurons in OFC was positively correlated with the number of conspecifics (playmates or adults) present. Burleson et al. (2016) replicated this effect in hamsters and, in addition, found that play deprivation in adolescent hamsters increased the vulnerability to social stress in adulthood. In another study, Himmler et al. (2013) found that play experience changes the effect of nicotine on the same prefrontal neurons affected by play and stress. Taken together, these results suggest that a special adolescent behavior (play) can have a significant impact on the function and organization of the adult PFC.

Sensory and Motor Enrichment

Enriched housing is one of the most powerful experiences that can affect cerebral networks. Although it is generally expected that enrichment would have similar effects in young and older brains, and likely bigger effects in younger brains, this is not the case. We have compared the effects of two months of complex housing in young (P25), young adult (P90), and senescent (P300) rats (Kolb et al. 2003). As expected, the older groups showed increased dendritic complexity and spine density in parietal and visual pyramidal neurons; the young group, however, had a significant decrease in spine density, but an increase in dendritic length. One effect of this arrangement is that it would be easier to add synapses in response to other experiences in the young group.

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Given that the young animals were complex housed for the entire adolescent period, this could be another adolescent experience-expectant example in the adolescent brain.

As noted for the infant brain, tactile stimulation is a powerful experience. Given that the adult brain is also affected by tactile stimulation, it would be interesting to determine how the adolescent brain responds to this type of experience.

Drugs

Adolescence is a common time for the initiation of psychoactive drug use (for an extensive review, see Spear 2016). A recent review of MRI studies on adolescent users of alcohol and other drugs (marijuana, nicotine, other stimulants, and a variety of illicit drugs) concludes that the frontal lobe is the most common region showing alterations (Silveri et al. 2016). Overall, the brain alterations appear larger than those observed in adults and, as noted earlier, it has been proposed that the interference with the development of prefrontal circuits increases the risk for cognitive and psychiatric problems, including substance abuse, in adulthood (e.g., Jordan and Andersen 2017). This is likely due, in part, to effects on brain plasticity in adulthood.

There is an extensive literature on the effects of adolescent drug exposure in laboratory animals showing a wide range of neural effects, as summarized in Table 9.1 (Spear 2016). Overall, drug effects are larger in adolescents than in adults. Although these neural effects are correlated with extensive cognitive/behavioral and affective/social behavior changes, it is not well understood how these effects vary with exposure age, what the underlying mechanisms might be, and how they might influence brain plasticity later in life.

Stress

Although much is known about the effects of stress during adulthood and the perinatal period, surprisingly little is known about the effects of stress on brain plasticity in adolescence. Perinatal and adult stress both alter the structure of neurons in the PFC, hippocampus, and amygdala, although in differing ways at the two time points. Given that the adolescent sensitive period is one of increased plasticity, the adolescent brain may be more vulnerable to stress-related behavioral changes such as anxiety, depression, psychotic episodes, and so on. This is especially so given that the brain regions most sensitive to stress, including the PFC, hippocampus, and amygdala, all continue to mature during adolescence.

Eiland et al. (2012) exposed rats to daily restraint stress from P20 to P41 before looking at behavioral and neuronal changes. In short, they found behavioral changes that differed from similar stress in adulthood but found dendritic retraction in both hippocampus and mPFC and increased dendritic material in

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Table 9.1 Effects of repeated adolescent exposure to ethanol (EtOH), nicotine (NIC), cannabinoids (CBs), cocaine (COC), and methamphetamine stimulants (STIM) on neural behavior: impaired/attenuated (↓); enhanced (↑); alterations, often complex, were reported (Y); effect is greater in adolescence than in adults (Adol>Adult); effect is less in adolescence than in adults (Adol<Adult) (after Spear 2016).

	EtOH Adol>Adult	NIC Adol>Adult	CB Adol>Adult	COC ?	STIM Adol<Adult
Neurogenesis	↓				
Cell death	↑	↑			↑
Spines/dendritic branching	↑ (immature spines)	↑			
Electrophysiological alterations	Y			Y	
Neuroimmune activation	Y				
Histone acetylation, epigenetic regulation	Y			Y	
Alterations in:					
Acetylcholine	Y	Y			Y
Glutamate/GABA	Y	Y	Y	Y	Y
Dopamine	Y	Y	Y	Y	Y
Serotonin		Y	Y		Y
CB			Y		
Affected regions:					
Prefrontal cortex	Y	Y	Y	Y	Y
Hippocampus	Y	Y	Y	Y	Y
Nucleus accumbens	Y	Y	Y	Y	
Amygdala	Y	Y	Y	Y	Y

the basolateral amygdala. The dendritic changes in females differ from what is observed in adults, as adult females show dendritic expansion in mPFC neurons that are projecting the amygdala and do not exhibit hippocampal dendritic retraction. Because the animals' brains were examined in adolescence (~P45) it is not known if the dendritic changes persist or change by adulthood.

Finally, although not specifically directed toward the effects of adolescence stress on neural plasticity, there is a growing literature on the association between stress exposure and the altered development of the amygdala, PFC, and ventral striatal dopaminergic systems in human adolescence (for a review, see Tottenham and Galván 2016). The general consensus is that these systems are vulnerable to stress in adolescence, leading to the emergence of a range of abnormalities in affective processing.

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Diet

Just as in infant brain development, diet is likely to have an important contribution to changes in the brain during adolescence but few studies have directly studied how brain or behavior might be altered, especially by additives. It seems unlikely that specific nutrients will have large effects but preliminary studies using a combination of vitamin and mineral supplements are suggestive. For example, EmpowerPlus™ is a blend of 36 vitamins, minerals, and antioxidants and includes a proprietary blend of herbal supplements such as gingko biloba and the amino acid precursors for neurotransmitters (choline, phenylalanine, glutamine, and methionine). EmpowerPlus™ has been studied extensively for its effects on a wide range of behavioral problems (e.g., Simpson et al. 2011). In one open label trial, Kaplan et al. (2004) gave children (aged 8–15 yr) with mood and behavioral problems EmpowerPlus™ for several months and found improvement on a variety of outcome measures. In addition, several studies have shown benefits with EmpowerPlus™ and similar concoctions in adults with mood disorders (Rucklidge and Kaplan 2013). Rats fed this diet during development, including adolescence, show significant increases in dendritic length in cortical pyramidal neurons, although no behavioral measures were made.

Cerebral Injury

Although there is an extensive literature on the effects of brain injury in the perinatal brain in rats, cats, and monkeys (for a review, see Kolb et al. 2013), injury in adolescence has largely been neglected in laboratory animal studies. Nemati and Kolb (2011) showed that if the mPFC is damaged at P35 versus P55, there is a dramatic difference in outcomes. Animals with bilateral P35 lesions show remarkably better outcomes than similar lesions at P55 or adulthood, and this is associated with increased dendritic complexity and spine density in pyramidal neurons in adjacent cortical regions. Curiously, in a similar experiment in animals with unilateral motor cortex lesions, the effect was reversed: animals with P35 lesions were as impaired on motor tasks as adults, whereas those with P55 lesions showed good recovery, which was again correlated with dendritic changes in adjacent parietal cortex (Nemati and Kolb 2010). It is not clear if this difference relates to the location of the lesion or to a unilateral versus bilateral difference.

One additional aspect to studies of cerebral injury involves the timing of compensatory changes in adolescence after perinatal injuries. Using rats, we have shown that there are severe behavioral deficits in adults with cortical injuries in the first week of life but very good recovery after similar lesions in the second week. The recovery is correlated with dendritic hypertrophy and/or increased spine density in cortical pyramidal neurons, whereas the absence of recovery is correlated with atrophy of these neurons (for a review,

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see Kolb et al. 2013). The question is: When do neuronal compensations occur? To this end, we made mPFC lesions on either P1 or P10 (Kolb and Gibb 1991). One set of animals were given behavioral tests on P22–25 and their brains harvested on P28. A second group were given the same tests on P55–58 and their brains harvested on P60. Both the P1- and P10-lesioned rats were severely impaired on the early behavioral tests, but the P10-lesioned rats showed substantial recovery on later tests, which was correlated with dendritic hypertrophy present only in the older brains. It appears that during adolescence the enhanced plasticity in the P10-lesioned animals led to the enhanced behavioral and neuronal compensations. The question remaining, however, is why this occurred. What is different in the P1- and P10-lesioned brains in adolescence? This may be due to some type of epigenetic difference, but this remains to be shown.

One inference that we can draw from the above study is that adolescence may be an especially important time for implementing treatments to remediate early-life negative perturbations on the brain and behavior, such as stress or gestational drug exposure.

Immune System

The immune system intricately interacts with the nervous system throughout life. Various aspects of brain plasticity, including neurite outgrowth and synaptic pruning, are regulated in part by the immune system. Although much is known about the maturation of the immune system in embryonic and perinatal development, very little is known about its maturation during adolescence. Recent studies have shown changes in cytokine expression in rats across adolescence and that earlier exposure to stress can influence this expression (for a review, see Brenhouse and Schwarz 2016). Microglia, the primary immune cells of the brain, become active in response to a variety of perturbations. Their role in adolescence has not yet been studied thoroughly, but they are likely to play a role in the sensitive period and may act in some way to mediate onset/offset as well as neural plasticity.

Conclusions and Unanswered Questions

Adolescence can be seen as a sensitive period in which there is a sharp increase in neural plasticity. Although most plastic changes are likely to be "experience-dependent," there may be "experience-expectant" plastic changes in adolescence, perhaps related to gonadal hormones or the increase in socioaffective behaviors. The onset of the sensitive period is around the onset of pubertal gonadal hormone production, but may or may not be triggered by the hormone release. The offset of the sensitive period may be related to the completion of

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myelination, which can reduce plasticity. The offset of the sensitive period is likely different in different cortical regions, with the OFC being among the last regions to mature, likely reflecting the continuing impact of adolescent socioaffective experiences. Among the many questions that remain, I highlight the following:

- What is the role of glia in controlling the onset and offset of the sensitive period?
- Are the brakes on the early sensitive periods turned off during adolescence and, if so, how?
- How do experiences in adolescence vary with exposure age, what are the underlying mechanisms of their effects, and how might they influence brain plasticity later in life?
- What are the sex differences in the timing of the sensitive period and the role of experiences in altering brain plasticity during this period?
- Are there experience-expectant plastic changes in adolescence? If so, what are they?
- How do changes in gene expression in adolescence influence the duration of the sensitive period?
- What is the role of the immune system in controlling the onset/offset of the sensitive period and synaptic plasticity during this period?

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