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How Do Pubertal Hormones Impact Brain Dynamics and Maturation?

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Abstract

Adolescence is characterized by maturation of reproductive and other social behaviors and social cognition. Although gonadal steroid hormones are well-known mediators of these behaviors in adulthood, the role these hormones play in shaping the adolescent brain and behavioral development has only come to light in recent years. This chapter reviews the organizational effects of pubertal hormones on sex-specific behaviors that mature during adolescence and the neurobiological mechanisms of structural organization of the adolescent brain by pubertal hormones. Important questions are identified to direct further study of the relationship between pubertal hormones, the adolescent brain, and experience.

Introduction

The adolescent transition from childhood to adulthood requires a metamorphosis of brain and behavior as individuals acquire the ability to function independently in adulthood. This gain of function involves the reorganization of neural circuits, especially those regulating sex-typical reproductive function and social behaviors. Recent work in both animals and humans reveals that reorganization of the adolescent brain involves many of the same developmental processes used during initial construction of the nervous system, including neurogenesis, programmed cell death, elaboration and pruning of dendritic arborizations and synapses, and sexual differentiation (reviewed in Juraska et al. 2013; Schulz and Sisk 2016; Herting and Sowell 2017). Given the extent of neural plasticity during this time, the adolescent brain is particularly sensitive to experience and nervous system insult, which likely contributes to the

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adolescent emergence of a number of psychiatric illnesses that disproportionately affect either females or males (Merikangas et al. 2010).

The onset of puberty marks the beginning of adolescence, and a growing body of evidence supports the view that gonadal steroid hormones, which become elevated during puberty, play a major role in shaping the adolescent brain and behavior. Indeed, gonadal steroid hormones influence virtually all of the early developmental processes noted above, yet research on how hormones influence these processes during adolescence, and the consequences for behavioral maturation, is just beginning to shed light on how pubertal hormones influence brain dynamics during adolescence. Not all structural and behavioral changes that occur during adolescence are driven or modulated by hormones. This review focuses on those that are.

Organizational and Activational Effects of Gonadal Hormones

Gonadal steroid hormone action in the nervous system can be dichotomized as activational or organizational. Activational effects refer to the ability of steroids to modify the activity of target cells in ways that facilitate expression of particular behaviors in specific contexts. Activational effects are transient; they come and go with the presence and absence of hormones and are typically associated with steroid action in the adult brain. In contrast, organizational effects refer to the ability of steroids to sculpt nervous system structure and function during development. Organizational effects are long-lasting, persist beyond the period of developmental exposure to hormones, and program activational responses to hormones in adulthood.

Conceptualization of the relationship between organizational and activational effects of steroid hormones has evolved over the past fifty years. To explain sex differences in behavioral responses to hormones in adulthood, Phoenix and colleagues first proposed that sex-typical adult behavioral (activational) responses to steroid hormones are programmed (organized) by steroid hormones acting on the nervous system during early development (Phoenix et al. 1959). Subsequently, scores of experiments led to the identification of a sensitive period for hormone-dependent sexual differentiation (organization) of the brain during prenatal and early neonatal development in nonhuman primates and rodents (reviewed in Baum 1979; Wallen 2005). Research over the past twenty years has revealed that in addition to the perinatal period of hormone-dependent organization of behavioral neural circuits, adolescence is another period of development during which gonadal hormones organize the nervous system (reviewed in Schulz and Sisk 2016).

The current conceptual framework of organizational and activational effects of gonadal steroid hormones is a two-stage model of development in which the perinatal period of hormone-dependent organization is followed by a second wave of organization during puberty and adolescence (Figure 8.1). During this

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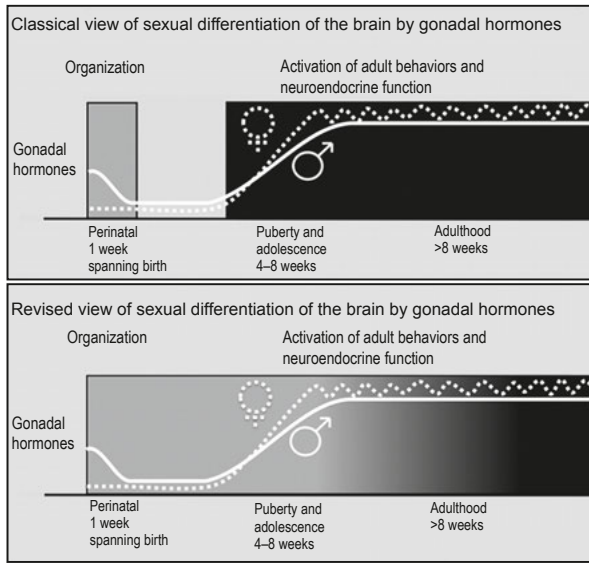

Figure 8.1 Schematic representation of the classical and revised views of sexual differentiation of the rodent brain and behavior. In the classical view, brain architecture is permanently masculinized by exposure of the male brain to testicular hormones during a brief perinatal period. In the absence of testicular hormones during this period, the default developmental trajectory is a feminine brain. When gonadal hormones become elevated at the onset of puberty, they activate sex-specific behaviors. In the revised view, the period of organization/structural differentiation is extended, continuing well through puberty and adolescence, during which both testicular and ovarian hormones organize the male and female brain, respectively. There is some evidence to support the idea that the perinatal and peripubertal periods comprise an extended postnatal window of decreasing sensitivity to organizational effects of gonadal hormones, and that this window of sensitivity closes by the end of adolescence. The two periods of brain organization and sexual differentiation are driven by the two naturally occurring times of elevation in gonadal hormone levels. From Juraska et al. (2013).

second wave, pubertal hormones organize neural circuits in the developing adolescent brain by inducing long-lasting structural changes in the nervous system that program adult activational responses to hormones and socially relevant sensory stimuli. In this model, hormone-driven adolescent organization reinforces and refines the sexual differentiation that occurred during perinatal neural development (i.e., what occurs during perinatal brain organization determines the substrate upon which pubertal hormones act during adolescent organization). One important distinction between the perinatal and pubertal periods of organization is the contribution of ovarian hormones. Perinatal organization is accomplished primarily through the masculinizing and defeminizing effects of testicular hormones; ovarian hormones, which are not elevated perinatally, do not play a major role, and the developing brain is not actively feminized.

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In contrast, both testicular and ovarian hormones are actively involved in the pubertal organization of brain and behavior.

Hormone-Dependent Organization of Behavior during Adolescence

The general experimental strategy used to determine whether behavioral circuits are organized during adolescence is to manipulate circulating levels of gonadal hormones during that time and then assess behavior in adulthood. Typically, animals are gonadectomized prior to the onset of puberty to allow adolescent development in the absence of endogenous gonadal hormones, and then the hormone is replaced in adulthood prior to behavioral tests. The behavior of animals treated in this way is compared with that of those similarly treated, except that gonadectomy, washout period, and hormone replacement all occur in adulthood. With this experimental design, the observed deficits in adult behavior of animals that did not experience gonadal hormones during adolescence can be attributed to the absence of organizational effects if hormone replacement in adulthood does not reverse these deficits. Studies employing this general paradigm in a number of different species provide a growing body of evidence that gonadal hormones organize a variety of social and nonsocial behaviors in both males and females.

Males

When testosterone is absent during adolescence, a wide range of male-typical adult social behaviors is compromised. For example, 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 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 in sociosexual behaviors. Conversely, the presence of testicular hormones during adolescence masculinizes neural circuits underlying sociosexual behaviors and enhances activational responses to testosterone in adulthood.

Which features of sociosexual behaviors are organized by pubertal testosterone? It does not seem to be the performance or motor execution of the 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. Instead, research suggests that pubertal

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testosterone organizes social proficiency: the ability to make behavioral adaptations as a function of social experience (De Lorme et al. 2013; De Lorme and Sisk 2013, 2016). For example, 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 pattern of behavior 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 is instead reestablished via aggression in subsequent encounters (De Lorme and Sisk 2013). Thus, during adolescence, pubertal testosterone organizes neural circuits that govern social cognition, the mental processes by which an individual encodes, interprets, and responds to sensory information from a conspecific. To identify neurobiological correlates of behavioral organization, future research should thus focus on brain regions that evaluate social stimuli and govern behavioral flexibility, such as the amygdala and components of the mesocorticolimbic reward circuit.

On average, men outperform women in tests of spatial cognition, and this sex difference in humans may be organized by pubertal hormones. Evidence for this comes from a study of men with either prepubertal- or adult-onset idiopathic hypogonadotropic hypogonadism (IHH), a condition in which a deficiency in gonadotropin-releasing hormone (GnRH) levels or pituitary insensitivity to GnRH results in reduced levels of gonadotropins, gonadal steroid hormones, and fertility (Hier and Crowley 1982). Men with prepubertal-onset IHH had low or undetectable levels of circulating gonadal steroids during the normal time of puberty and adolescence, whereas men with adult-onset IHH experienced normal levels of pubertal gonadal hormones during adolescence. Spatial cognition is impaired in men with prepubertal-onset IHH, both in comparison to healthy control subjects as well as to men with adult-onset IHH, suggesting that the presence of testicular hormones during puberty organizes circuits underlying spatial cognition. In a separate study, women with a variation of congenital adrenal hyperplasia, which leads to slightly but chronically elevated levels of adrenal androgens during childhood and early puberty, performed better in a virtual Morris water maze (a test of spatial memory) compared with healthy subjects. These data suggest that exposure to adrenal androgens during adolescence organizes (masculinizes) spatial ability in females (Mueller et al. 2008). Rodent work demonstrates that spatial memory is hippocampus-dependent, and synaptic plasticity in the hippocampus appears to be organized by pubertal androgens. Specifically, activation of androgen receptor during puberty results in long-term depression in CA1 in response to a tetanizing stimulus in adulthood, whereas if androgen receptor activation is blocked during puberty, long-term potentiation occurs in response to

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a tetanizing stimulus in adulthood (Hebbard et al. 2003). These findings in rodents provide a potential mechanism by which pubertal testosterone could organize hippocampus-dependent learning and memory in humans, including spatial cognition.

Females

Behavioral receptivity to males is feminized during adolescence by ovarian hormones, specifically estradiol, as shown in studies using an aromatase knockout mouse model in which estrogen is not synthesized, but estrogen receptors are fully functional. Female knockout mice display significantly less lordosis behavior compared to wildtype or heterozygous mice following adult ovariectomy and hormone treatment, suggesting that endogenous estrogen normally feminizes reproductive responses to estradiol and progesterone in adulthood (Bakker et al. 2002). In another study, estradiol was systematically administered during development either prior to the onset of normative ovarian secretions of gonadal steroid hormones (postnatal days 5–15), or the earliest time frame for ovarian secretions of gonadal steroid hormones (P15–P25). Whereas administration of estradiol between P5–P15 had no effect on lordosis behavior in wildtype or knockout animals, administration between P15–P25 significantly increased lordosis behavior in the aromatase knockout animals (Brock et al. 2011). These data provide compelling evidence for the feminization of female reproductive behavior by estradiol during early adolescent development in female mice. Other social behaviors that are organized by ovarian hormones during puberty include the female pattern of rough and tumble play as well as maternal behavior (reviewed in Schulz and Sisk 2016).

For females, reproductive success depends on being fertile and finding a mate as well as on being physiologically prepared to sustain a pregnancy and provide nutrition for her young. It appears that elevated levels of ovarian hormones during puberty organize behaviors related to fertility, which is contingent on metabolic signals that predict sufficient energy availability to sustain pregnancy, lactation, and maternal care. In rats, defense of food is a sexually dimorphic behavior, with males and females displaying different postural strategies for guarding their food source. Prepubertal ovariectomy alters the defense strategy to be more phenotypically male, whereas adult ovariectomy has no effect on this behavior; this indicates that ovarian hormones during adolescence actively feminize postural strategies for food defense (Field et al. 2004). Pubertal estradiol also feminizes ingestive responses to metabolic signals in rats. Treatment with mercaptoacetate, a drug that interferes with fatty acid oxidation, increases food intake in male but not female rats. Prepubertally ovariectomized (OVX) females display a male-like response to mercaptoacetate and increase their food intake in adulthood, whereas adult OVX females do not increase food intake in response to mercaptoacetate. Furthermore, the effect of prepubertal ovariectomy is prevented by estradiol replacement during

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puberty, indicating a role for estradiol in organizing (feminizing) the response to metabolic challenge (Swithers et al. 2008).

Neurobiological Mechanisms Underlying Hormone-Dependent Organization of the Adolescent Brain

It is presumed that adolescent organization of brain structure has something to do with adolescent organization of behavior. Currently, however, we can only point to correlational relationships between hormone-dependent organization of structure and behavior during adolescence. Hormone-dependent organization of brain structure during adolescence involves many of the same developmental processes that are in play during the perinatal organizational period: cell proliferation and differentiation, cell death and survival, synapse proliferation and selective elimination, and myelination. In this section I review what is known so far about how gonadal hormones influence these developmental processes during puberty and adolescence, with a focus on brain regions known to be involved in behaviors that are organized during this same time.

Anteroventral Periventricular Nucleus and Posterodorsal Medial Amygdala

Hormonal regulation of adolescent development of the anteroventral periventricular nucleus (AVPV) and posterodorsal medial amygdala (MePD) has been the focus of research because both cell groups are sexually dimorphic, undergo structural (organizational) change during puberty, are rich in steroid hormone receptors, and are involved in reproductive function and social behaviors that mature during puberty and adolescence. Gonadal hormones contribute to the adolescent organization of the AVPV and MePD by influencing cell proliferation and survival as well as synaptic and glial cell complexity.

The rat AVPV is one of the few examples of a female-biased sexual dimorphism: it is larger and more cell-dense in females than in males. The AVPV integrates a hormonal signal from the ovaries (elevated estradiol levels) with a circadian signal from the suprachiasmatic nucleus to provide the neural trigger for generation of the preovulatory surge of luteinizing hormone (LH) that results in ovulation (reviewed in Simerly 2002). The AVPV has also recently been linked to aggressive behavior in males and maternal behavior in females (Scott et al. 2015). The sex difference in AVPV volume emerges during pubertal development (Davis et al. 1996), along with the capacity for females to generate an LH surge. The neuroendocrine positive feedback trigger for ovulation is sexually differentiated: male rats are incapable of generating an LH surge at any age.

The male rat MePD is larger and contains more neurons and glial cells than the female MePD; it evaluates chemosensory information from conspecifics

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and integrates these external cues with internal hormonal signals to regulate a variety of social behaviors that mature during adolescence. Although the MePD is sexually dimorphic prior to puberty, the dimorphism becomes significantly greater across adolescent development due, at least in part, to increases in astrocyte number as well as astrocyte branching in males. Furthermore, males carrying the testicular feminization mutation (tfm) of the androgen receptor and females do not display MePD increases in astrocyte number and branching during adolescence. In contrast, wildtype males display normative increases in MePD astrocyte number and branching, indicating that normative androgen receptor function is necessary for the adolescent development of this sexual dimorphism (Johnson et al. 2013).

The increase in volume of the female AVPV and the male MePD during puberty prompted us to ask whether addition of new cells may be another mechanism of structural change in these brain regions. In an initial study, a daily injection of the cell birthdate marker BrdU (200 mg/kg, intraperitoneal injection) was given to male and female rats on P30–P32, which is right around the onset of puberty (the initial rise in gonadal hormone secretion) in rats (Ahmed et al. 2008). Brains were collected 21 days later and immunohistochemistry was performed to visualize BrdU-immunoreactive (BrdU-ir) cells that were born on P30–P32. We found sex differences in the number of pubertally born cells, with more cells added to the female AVPV than to the male and more cells added to the male MePD than to the female. Gonadal hormones drive these sex differences in the number of pubertally born AVPV and MePD cells. In females, prepubertal ovariectomy reduces the number of pubertally born AVPV cells to a number indistinguishable from that of males but does not affect the number of pubertally born MePD cells. Conversely, in males, prepubertal castration reduces the number of pubertally born MePD cells but does not affect the number of pubertally born AVPV cells (Figure 8.2). Cell addition during puberty may be an active mechanism either for *preserving* structural and functional sexual dimorphisms in the face of remodeling of the adolescent brain or for *creating* new sex differences that emerge during adolescence.

Phenotyping studies using double-label immunohistochemistry for colocalization of BrdU and cellular markers for mature neurons, astrocytes, or microglia show that ~50% of pubertally born AVPV cells differentiate into one of these cell types within a month of proliferation (see Figure 8.3; Mohr et al. 2016). In the female AVPV, ~10% of pubertally born cells express estrogen receptor alpha. We do not know whether an even larger proportion of the cells would be activated or steroid receptor-expressing if these newly born cells were asked to be functionally active during differentiation and maturation.

Some pubertally born MePD and AVPV cells appear to be functionally integrated within the cell group. In male hamsters, some pubertally born MePD cells are activated (express fos) after a sexual encounter with a receptive female (Mohr and Sisk 2013). In female rats, some pubertally born AVPV cells express fos after estrogen and progesterone priming to induce an LH surge (see

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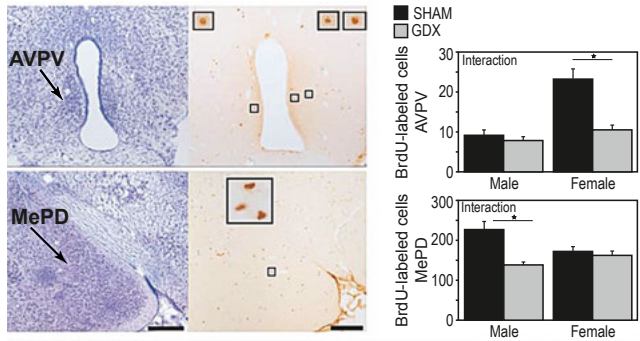

Figure 8.2 New cells are added to the anteroventral periventricular nucleus (AVPV) and posterodorsal medial amygdala (MePD) during puberty in rats. The cell birthdate marker bromodeoxyuridine (BrdU) was given to male and female rats at the onset of puberty (postnatal days 30–32, 200 mg/kg/day, intraperitoneal injection) and brain tissue was collected 21 days later. More cells are added to the female AVPV than to the male AVPV, and more cells are added to the male MeDP than to the female MeDP. Prepubertal gonadectomy abolishes these sex differences. *significant effect of prepubertal gonadectomy, $p < 0.05$; GDX, gonadectomized rats; SHAM, control rats. From Ahmed et al. (2008).

Figure 8.4; Mohr et al. 2017). We used a mitotic inhibitor, cytosine arabinoside (AraC), to block cell proliferation during puberty to ask whether this blockade affects the ability to generate a LH surge following hormone priming. Female rats received intracerebroventricular infusions of AraC or vehicle (which also contained BrdU) for 28 days during puberty, then were ovariectomized and

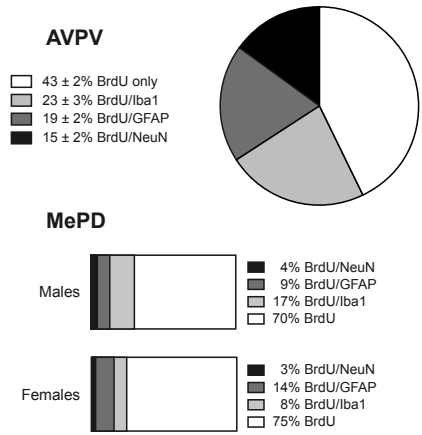

Figure 8.3 Proportion of pubertally born cells that co-localize markers for mature neurons (NeuN), astrocytes (GFAP), or microglia (Iba1). Over half of pubertally born AVPV cells in the female rat differentiate into neurons, astrocytes, or microglia within 21 days of proliferation. Longer survival times may allow additional cells to mature. From Mohr et al. (2016).

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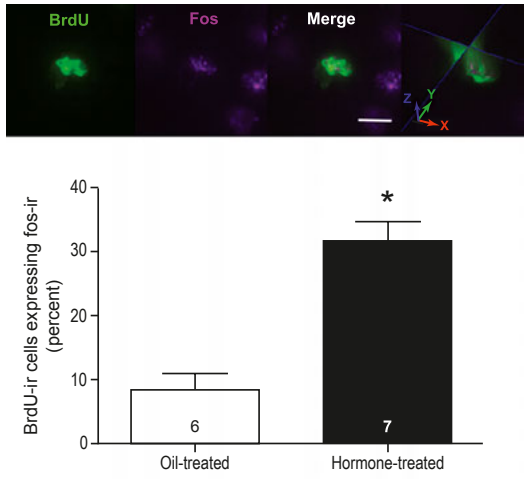

Figure 8.4 Pubertally born AVPV cells are activated by estradiol and progesterone. Hormone induction of the luteinizing hormone surge caused a significant increase in the proportion of immunoreactive bromodeoxyuridine (BrdU-ir) cells that express fos-ir (*$p < 0.001$); x, y, and z indicate planes of section in the 3-dimensional orthogonal view (right-most image). Adapted after Mohr et al. (2017).

hormone-primed to generate an LH surge. AraC significantly reduced the number of cells added to the AVPV during puberty by 50–60%. This inhibition of cell proliferation during puberty blunted and delayed the hormone-induced LH surge (Figure 8.5; Mohr et al. 2017). These findings support the idea that pubertally born cells become functionally incorporated into the circuitry of the AVPV.

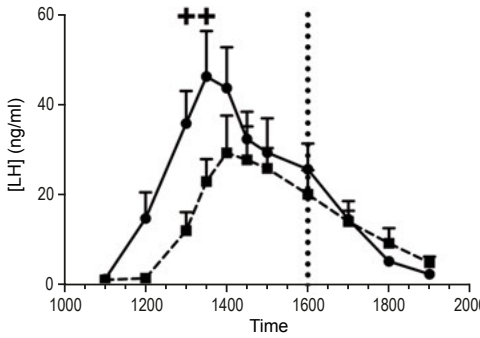

Figure 8.5 Knock-down of cell addition with the mitotic inhibitor cytosine arabinoside (AraC) during puberty dampens and delays the hormone-induced luteinizing hormone (LH) surge. Rats were on a 14:10 light:dark cycle; dotted vertical line denotes lights off. Female rats received intracerebroventricular infusions of AraC or vehicle (which also contained bromodeoxyuridine, BrdU) for 28 days during puberty; they then were ovariectomized and hormone-primed to generate an LH surge. AraC reduced the number of cells added to the AVPV during puberty by 50–60%. + significant difference between control and AraC-treated rats, $p < 0.01$. Adapted after Mohr et al. (2017).

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Cerebral Cortex

Neuroimaging studies demonstrate that gray matter volume decreases during human adolescence (reviewed in Herting and Sowell 2017). Earlier studies reported a curvilinear pattern of development, in which volumes peak at approximately 11 years of age in girls and 12.5 years of age in boys, followed by a significant decline in volume that tapers off in the 20s in both sexes (Giedd et al. 1999). More recent studies indicate that this curvilinear pattern is not present in all cortical areas, with some showing a more linear decrease in volume across development (Ducharme et al. 2016). The timing of adolescent-related decreases in volume is not uniform across cortices. The dorsal parietal regions decrease the earliest whereas the dorsolateral prefrontal cortex is one of the latest areas to show gray matter decline (Gogtay et al. 2004). The temporal cortex reaches peak volume at approximately 16.5 years of age in both girls and boys, followed by less volume decline than one sees in the frontal and parietal regions (Giedd et al. 1999). Some of these volumetric changes in cortical structures can be predicted by the Tanner stage, and recent studies indicate that estradiol and testosterone predict volume and rate of change in cortical volume (Peper et al. 2011; Herting and Sowell 2017).

Rodent studies provide insight into the mechanisms by which prefrontal cortical gray matter volume changes occur during adolescence. Sex-specific cortical volume decreases also occur across adolescence in rats, with the adult volume of the medial prefrontal cortex (mPFC) being greater in males than in females. While no sex difference is present in the number of ventral mPFC neurons early in adolescence at 35 days of age, males display significantly more neurons by 90 days of age (Markham et al. 2007). Furthermore, prepubertal gonadectomy (GDX) prevents the decline in neuron number in females but not in males, suggesting that ovarian hormones drive the emergent sexual dimorphism during adolescence (Koss et al. 2015). In addition to decreases in neuron number observed in females, dendritic spines significantly decrease in both sexes between days 35 and 90, but only females show a loss of mPFC basilar dendrites (Koss et al. 2014). Since the majority of excitatory synapses are found on dendritic spines, these changes suggest a sexually dimorphic adolescent remodeling of synapses and, in particular, excitatory synapses.

White Matter

While gray matter volume decreases during adolescence, white matter increases linearly across adolescence, with similar growth curves and trajectories in frontal, parietal, and temporal cortices (Giedd et al. 1999; Paus et al. 1999). Boys, however, show a steeper age-dependent slope of increase in white matter volume than girls, resulting in larger white matter volumes in boys (Lenroot and Giedd 2006). Just as gonadal hormones shape adolescent gray matter changes, gonadal hormones have likewise been implicated in pubertal-related

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increases in white matter volumes (reviewed in Herting and Sowell 2017). For example, pubertal maturation is associated with increases in white matter density in frontal, parietal, and occipital lobes in boys (Perrin et al. 2009). The extent of the increase in white matter volume in adolescent boys is positively correlated with androgen receptor (AR) activity, as assessed by the number of CAG repeats in the AR gene (Perrin et al. 2008). Furthermore, pubertal levels of testosterone and estradiol are associated with cortical microstructural development in boys and girls, respectively. Pubertal testosterone predicts white matter increases in boys, whereas pubertal estradiol is associated with white matter decreases. Thus, these relationships between estradiol and testosterone and cortical white matter may partly explain the emergent sexual dimorphism during adolescence.

Rodent studies provide further insight into the mechanisms by which pubertal hormones may influence cortical white matter development. Like humans, white matter volume increases across adolescent development in rodents, resulting in a male-biased sexual dimorphism (Willing and Juraska 2015). Testosterone may drive increases in white matter in males by increasing axon diameter via an androgen-receptor mediated mechanism (Pesaresi et al. 2015). Estradiol in females may also contribute to the sexual dimorphism in white matter. Prepubertal ovariectomy in females significantly increases white matter volume in females, whereas prepubertal castration does not impact white matter volume in males (Koss et al. 2015). Thus, under normative developmental conditions, the pubertal onset of ovarian secretions may slow the development of white matter volume in females resulting in the male-biased dimorphism in adulthood.

Remaining Questions

What Is the Role of Social Experience in Survival, Differentiation, and Functional Incorporation of Pubertally Born Cells?

Physical exercise promotes neurogenesis, whereas social isolation and stress impair neurogenesis. We found that an enriched environment (running wheel in the home cage) increased the number of pubertally born MePD cells and the proportion that are activated by social interaction (Mohr and Sisk 2013). This indicates that experience can promote the functional incorporation of new cells into existing neural circuits. An important question for further research is whether and how specific types of social experience influence not only cell proliferation and survival during adolescence, but also cell fate and function. Our research shows that about half of pubertally born AVPV and MePD cells have not differentiated into mature neurons or glia when examined within one month after they were born. However, in our experiments, rats were singly housed and thus not given opportunities for social interaction. Would social

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experience facilitate the differentiation and integration of pubertally born cells into neural circuits that govern social behaviors, perhaps in sex-dependent and brain region-specific ways? What are the cellular and molecular mechanisms by which experience determines pubertally born cell fate? Answers to these questions will advance understanding of brain dynamic coordination and plasticity during adolescence.

Is Adolescence a Sensitive Period Distinct from the Perinatal Period, or Is It Part of an Extended Period of Postnatal Sensitivity for Hormone-Dependent Organization?

From a developmental perspective, it is of interest to know whether the perinatal and pubertal periods are distinct windows of sensitivity to organizational effects of gonadal hormones, or whether the two periods of hormone-dependent organization are driven by naturally occurring elevations in gonadal hormones. We tested the hypothesis that adolescence marks the opening of a second sensitive period for the organizing actions of testosterone on adult male reproductive behavior (Schulz et al. 2009b). This hypothesis predicts that exposure to testosterone during adolescence, but not before or after adolescence, will result in full activational responses to testosterone in adulthood. Male hamsters were gonadectomized at 10 days of age (after the perinatal period of sexual differentiation), and then treated with testosterone for 19 days either before (10–29 days of age), during (29–48 days of age), or after (64–83 days of age) the normal time of puberty. In adulthood, males were again treated with testosterone for one week prior to a behavioral test with a sexually receptive female. Testosterone treatment before and during puberty, but not after puberty, activated male sexual behavior in adulthood, demonstrating that (a) adolescence is not a discrete sensitive period for the organizing actions of testosterone on adult reproductive behavior and (b) the window of sensitivity to organizational effects closes at the end of adolescence. Furthermore, prepubertal testosterone treatment had the greatest impact on adult reproductive function, suggesting that the potential for testosterone to organize reproductive behavior decreases across postnatal development.

I propose that the classical view of organizational and activational mechanisms of steroid action be revised to incorporate an extended window of decreasing postnatal sensitivity to the organization of adult behavior by gonadal hormones. This proposed framework is based on our study of male reproductive behavior, and it will be important for future research to determine whether the proposed window of decreasing sensitivity to hormone-dependent organization generalizes to females and other behaviors. If it does prove to generalize, then it has implications for how the timing of puberty affects hormone-dependent organization of brain and behavior. For example, would precocious puberty result in a greater degree of organization or limit capacity for experience-dependent plasticity later in development?

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A recent study in humans lends support to the possibility of an extended postnatal window of decreasing sensitivity to gonadal steroid hormones. Beltz and Berenbaum (2013) hypothesized that if sensitivity to organizational effects of gonadal steroid hormones decreases across adolescence, then the age at which adolescents undergo puberty should be inversely associated with the effectiveness of gonadal steroid hormones in organizing spatial (men) or verbal (women) ability. Participants reported whether they experienced specific pubertal events much earlier, somewhat earlier, the same, somewhat later, or much later than their peers to determine a pubertal timing score; their verbal and spatial abilities were also assessed. Among men, an effect of pubertal timing on three-dimensional mental rotation test scores was found, with early maturers outperforming late maturers. In contrast, no effects of pubertal timing on verbal or spatial ability were detected in women. Beltz and Berenbaum conclude that their findings are consistent with the hypothesis of declining sensitivity to the organizing actions of testosterone throughout adolescent development.

Is Adolescent Brain Development Experience Expectant or Experience Dependent?

The distinction of experience-expectant and experience-dependent development is based on two categories of environmental information or experience that influence nervous system development (Greenough et al. 1987; see also Kolb, this volume). The first category is experience that is ubiquitous for all individuals of a given species throughout most of its evolution. Experience-expectant development of neural circuits involves a critical period during which this experience *must* occur, otherwise the underlying function is severely compromised. Two examples of experience-expectant development in humans are (a) the requirement for visual sensory experience for normal wiring of visual cortex and binocular vision and (b) exposure to spoken words for normal acquisition of oral language. The second category is experience that is unique to a particular individual and sculpts neural circuits in a more refined way. Examples of experience-dependent development include exposure to one's native language, and growing up in an enriched or impoverished environment. Experience-dependent development does not involve a well-defined critical period, although there may well be certain times during development that a particular experience exerts more profound influences than at others; such times are more accurately described as sensitive periods.

Can we neatly categorize adolescent brain development as being either experience expectant or experience dependent? At first glance, it might seem obvious that adolescence is experience dependent, because it is hard to name an experience that *must* occur during that time to create a functional adult brain; conversely, it is easy to cite experiences that shape the trajectory of adolescent brain development. However, there is one adolescent experience that has been

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ubiquitous for all humans throughout our evolution: the appearance of gonadal hormones during puberty. By that definition, adolescence would be an experience-expectant developmental period during which the absence of gonadal hormonal influences would result in seriously compromised maturation of neural circuits underlying social behaviors. Nevertheless, existing data suggest that adolescence is *not* an experience-expectant critical period of development during which the absence of exposure to gonadal hormones would totally incapacitate an individual; instead it is an experience-dependent sensitive period for influences of gonadal hormones on brain and behavioral development.

As reviewed above, when male rodents are gonadectomized prior to the onset of puberty they are capable of expressing social behaviors, such as sex and aggression in adulthood, but show impairments in interpreting social cues received from conspecifics. Thus in rodents, it appears that gonadal hormones program aspects of social cognition and behavioral flexibility, and not social behavior per se. Experiments of nature in humans point to the same idea. For example, men with congenital hypogonadotropic hypogonadism do not undergo a natural puberty and typically do not begin testosterone replacement therapy until 17 years of age or older, effectively resulting in much of their adolescent development occurring in the absence of testicular hormones. Once on testosterone replacement therapy, these men are able to have sexual relationships but report long-lasting psychosexual problems, such as difficulty with intimate relationships and body image concerns (Dwyer et al. 2015). Thus, the trajectory of adolescent maturation of social cognition depends on (is influenced by) gonadal hormones, but the adolescent social brain does not expect (does not require) gonadal hormones for adult social behaviors to be expressed.

A related concept is metaplasticity: the plasticity of plasticity. At the cellular level, metaplasticity entails a change in the physiological or biochemical state of neurons or synapses that alters their ability to generate synaptic plasticity at a later time. As applied to adolescent development, metaplasticity means that the history of activity of neural circuits during adolescence (i.e., the experiences that are encountered) can make these same circuits either more or less plastic in adulthood. Metaplasticity during adolescence results in some paradoxical outcomes which, at first glance, can be hard to digest. Take, for example, the organizational effects of pubertal testosterone on male social cognition. When a neural circuit is organized by testosterone, by definition the circuit becomes less plastic than it was before the organizing action. Yet one of the long-lasting organizational effects of testosterone on behavior is to render the male rodent more flexible during social encounters, better able to adapt his behavior as a result of social experience. How does testosterone jell a circuit during adolescence yet, in doing so, make that circuit seemingly more plastic in social situations later in adulthood? Answering this question is a major challenge for future research.

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