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Review

Pubertal hormones organize the adolescent brain and behavior

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Abstract

Maturation of the reproductive system during puberty results in elevated levels of gonadal steroid hormones. These hormones sculpt neural circuits during adolescence, a time of dramatic rewiring of the nervous system. Here, we review the evidence that steroid-dependent organization of the adolescent brain programs a variety of adult behaviors in animals and humans. Converging lines of evidence indicate that adolescence may be a sensitive period for steroid-dependent brain organization and that variation in the timing of interactions between the hormones of puberty and the adolescent brain leads to individual differences in adult behavior and risk of sex-biased psychopathologies.

Keywords: Puberty; Adolescence; Steroid hormones; Neural development; Neural plasticity; Behavioral maturation

1. Puberty and adolescence

Puberty and adolescence are often used synonymously to refer to the developmental transition from childhood to adulthood. Strictly speaking, however, they are not one and the same. Puberty is the period during which an individual becomes capable of sexually reproducing. Adolescence is the period between childhood and adulthood, encompassing not only reproductive maturation, but also cognitive, emotional, and social maturation. A biological hallmark of puberty is the elevated secretion of gonadal steroid hormones, which produce the overt signs of reproductive maturation such as breast development or the appearance of facial hair. A biological hallmark of adolescence is the remarkable remodeling of cortical and limbic circuits, which leads to the acquisition of adult cognition, decision making strategies, and social behaviors.

Puberty and adolescence are intricately linked because the brain is a target organ for steroid hormones. The functional coupling of puberty and adolescence in humans is complicated by the fact that adolescent brain development is dynamic and protracted, occurring over the course of a decade or more. Thus, the adolescent brain is a moving target for steroid hormones, creating the potential for time-sensitive, graded responses to hormones. That is, individual variation in the age of puberty onset creates individual variation in the point at which the brain is influenced by hormones, consequently creating individual variation in developmental trajectory and behavioral maturation.

The purpose of this paper is twofold. The first is to synthesize the growing body of scientific evidence that steroid-dependent organization of neural circuits is a fundamental feature of adolescent brain development, broadening the influence of pubertal hormones beyond a purely activational role to agents of neural rearrangement. The second is to develop the case that the timing of interactions between gonadal steroid hormones and the adolescent brain contributes to individual differences in adult behavior and risk for sex-biased psychopathologies.

2. Organizational and activational effects of gonadal steroid hormones on the nervous system and behavior

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 behavior in specific social contexts. Activational effects are transient;

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they come and go with the presence and absence of hormone and are typically associated with steroid action in adulthood. In contrast, organizational effects refer to the ability of steroids to sculpt nervous system structure during development. Structural organization is permanent, persists beyond the period of developmental exposure to hormone, and programs activational responses to steroids in adulthood.

Conceptualization of the relationship between organizational and activational effects of steroid hormones has evolved over the past 50 years. To explain sex differences in behavioral responses to steroids, Phoenix et al. [87] first proposed that sex-typical adult behavioral (activational) responses to steroid hormones are programmed (organized) by steroid hormones acting on the nervous system during a sensitive period of early development (i.e., not in adulthood). Subsequently, scores of experiments led to the identification of a maximally sensitive period for hormone-dependent sexual differentiation of the brain during prenatal and early neonatal development in non-human primates and rodents (reviewed in [10,130–132]). In the 1970s, Scott et al. [105] laid the theoretical groundwork for the existence of multiple sensitive periods for the progressive organization of the nervous system and noted that sensitive periods for behavioral development are most likely to occur during periods of rapid developmental change. Arnold and Breedlove [8] later pointed out that steroid-dependent organization of the brain can occur outside of sensitive periods of development.

It is now recognized that in addition to the well-known perinatal period of steroid-dependent organization of neural circuits and behavior, adolescence is another period of development during which gonadal hormones organize the nervous system. We have proposed a two-stage model of behavioral development in which the second wave of adolescent organization builds on the perinatal period of sexual differentiation [113]. During the adolescent phase of organization, steroid-dependent refinement of steroid neural circuits results in long-lasting structural changes that determine adult behavioral responses to hormones and sensory stimuli. The two-stage model postulates that pubertal hormones further organize the adolescent brain, but it does not assume that adolescence is necessarily a sensitive or critical period for steroid-dependent organization. In this review, we first describe the hormonal and neural hallmarks of puberty and adolescence, and then review how hormones shape the adolescent brain to influence behavioral maturation in animals and humans. We end with a critique of how well the existing data support the hypothesis that adolescence is a sensitive period for hormone-dependent brain organization in animals and humans.

3. Hormonal events of puberty

Pubertal maturation of the hypothalamic–pituitary–gonadal (HPG) axis begins with activation of neurons that secrete gonadotropin releasing hormone (GnRH). During the prepubertal period, GnRH mRNA and protein are expressed within GnRH neurons, but secretory activity is low and insufficient to support gonadal growth. The onset of puberty is characterized by a gradual increase in the frequency and amplitude of intermittent episodes of GnRH secretion [35,48,82,89,112]. GnRH directs the synthesis and secretion of the pituitary gonadotropins, luteinizing hormone, and follicle stimulating hormone, which act in concert to stimulate the production of gonadal steroid hormones and to complete the process of sperm and egg development. The elevated levels of androgen and estrogen result in the appearance of secondary sex characteristics in peripheral tissues, for example facial hair in boys and breast development in girls.

Puberty is proximally timed by internal and external stimuli that serve as permissive signals for reproductive maturation [18,28,36,111,133]. These permissive signals vary with species and sex, and provide information on the availability of resources necessary for successful reproduction. For example, internal metabolic cues such as insulin, glucose, and leptin indicate that somatic growth and metabolic fuel availability are sufficient to support pregnancy and lactation. Sensory and social cues provide information on the availability of a suitable mate. External cues such as photoperiod and food availability signal whether environmental conditions are optimal to support pregnancy and survival of offspring. The nervous system senses, evaluates, and integrates these multiple permissive stimuli to determine when pubertal activation of the GnRH system will proceed.

The proximal mechanisms underlying the pubertal awakening of the HPG axis have been the subject of much scientific inquiry and several recent extensive reviews [45,79–82,90–92,111,125]. Briefly, pubertal activation of GnRH neurons is the result of a decrease in inhibitory input, an increase in excitatory input, or a combination of the two, depending on species and sex [17,82,92,125]. In addition to the excitatory and inhibitory amino acid neurotransmitters, a number of neuropeptides play supporting roles in the pubertal activation of GnRH secretion. Most recently, kisspeptin and its cognate receptor GPR54 have been recognized as important players in the onset of puberty [54,75,107]. Glial–neuronal interactions at the level of GnRH terminals in the median eminence are also involved in the onset of puberty through glial-derived growth factor facilitation of GnRH release [80].

It is important to recognize the onset of puberty not as a gonadal event, but rather as a brain event. Gonadal maturation is initiated by a nervous system that is informed by permissive internal and external signals. This perspective is underscored by the observations that neonatally gonadectomized monkeys and humans with gonadal dysgenesis associated with Turner's syndrome show a rise in gonadotropin levels at the expected time of puberty, even in the absence of gonadal signaling [46,89,134].

4. Neural events of adolescence

Remodeling of the adolescent brain is accomplished through many of the same mechanisms that are used to form functional neural circuits during early brain development. These mechanisms include neurogenesis [88,97], apoptosis [77], growth of axonal projections and axon sprouting [11,22,68], myelination [12,76,135], dendritic elaboration and retraction [43,72], synaptogenesis [14,15], and synapse elimination [6,38,52,72], often resulting in modifications of the gross morphology of the brain, such as gray matter, white matter, and ventricular volumes [39,40,42,64,118,119]. Not surprisingly, structural changes in the adolescent brain are sex- and brain-region specific, and may or may not be influenced by gonadal steroid hormones, as reviewed below.

4.1. Adolescent remodeling of neural circuits in rodents

Some sexual dimorphisms in gray matter volume emerge during adolescence. Three such examples will be discussed to illustrate the diversity of mechanisms that underlie remodeling of the adolescent brain in rats. First is the sexual dimorphism in the volume of the locus coeruleus, which is larger in females than in males. This sex difference arises over the course of adolescent development through a gradual increase in cell number that is greater and more sustained in females than in males [88]. The addition of larger numbers of cells in females may reflect a sex difference in peripubertal neurogenesis and/or migration of cells into the locus coeruleus. The rat anteroventral periventricular nucleus (AVPV) is another example of a female-biased sexual dimorphism that develops gradually over adolescent development. The enlargement of the female AVPV coincides with functional changes in preovulatory LH surge capacity during puberty [24]. It is not known whether the sex difference in AVPV volume is due to differences in cell number, cell size, dendritic fields, or some other structural feature of AVPV neurons. But whatever mechanism is responsible for the larger AVPV in females, it is not driven by pubertal gonadal hormones, since prepubertal ovariectomy does not prevent the sex difference from emerging during adolescence [24]. The third example is the volume of primary visual cortex, which is male-biased. This sex difference comes about as the result of enhanced cell death in female visual cortex during adolescent development [77]. Unlike the AVPV, the sex difference in visual cortex volume is driven by pubertal hormones, because prepubertal ovariectomy prevents the normally occurring cell death and eliminates the sex difference in adult cell number and volume [78]. These three examples show that brain sexual dimorphisms can arise during adolescent development via sex differences in the addition of neurons or cell death, and that adolescent alterations in cell number and brain region volume may either be driven by pubertal hormones or not. One commonality of the sexual dimorphisms in locus coeruleus, AVPV, and visual cortex is that all are programmed perinatally by gonadal hormones [24,47,76], but their expression in adulthood depends on additional brain organization during adolescence.

In addition to changes in gross morphological features such as gray matter volume and cell number, adolescent remodeling of cortical and subcortical regions also involves changes in synaptic organization at both pre- and postsynaptic levels. Again, we draw on studies in rodents to provide examples of different ways in which synapses are remodeled during adolescence. Andersen and co-workers [4,6,124] have documented sex- and brain region-specific changes in D1 and D2 dopaminergic receptors during adolescent development of the rat brain. In striatum and prefrontal cortex, dopamine receptors are initially overexpressed during early adolescence and then pruned later in adolescence [6,124]. In contrast, dopamine receptors in nucleus accumbens increase around the onset of puberty, but they are not pruned and remain elevated throughout adolescent development into adulthood [124]. The overexpression and subsequent pruning of striatal dopamine receptors are more pronounced in adolescent males than in females [4], but neither process is dependent on pubertal gonadal hormones, as prepubertal gonadectomy does not alter the dynamic pattern of dopamine receptor expression [5]. Concurrent with adolescent changes in dopamine receptors in rat medial prefrontal cortex is a progressive increase in density of afferent input from the basolateral amygdala to prefrontal cortex, which may reflect both axonal sprouting of existing projection neurons and newly arising projections [22,129].

Analyses of Golgi and dye impregnated neurons have revealed adolescent remodeling of dendritic arborizations in telencephalic, diencephalic, and spinal cell groups. In the hippocampus of male mice, dendritic spine density increases at puberty onset and then decreases during late puberty, a developmental pattern that is prevented by gonadectomy prior to puberty [72]. In the posterodorsal medial amygdala of male Syrian hamsters, substantial pruning of dendrites and terminal spine densities occurs during adolescence, but it is not known whether these alterations are hormonally driven [136]. A somewhat different pattern of adolescent remodeling occurs in the female rat preoptic area, in which spine density increases, but dendritic branching decreases, around the time of vaginal opening [7,38]. Finally, in the spinal cord, dendrites of the spinal nucleus of the bulbocavernosus are elaborated during the first month of postnatal life and then retract during adolescence. Dendritic retraction is a steroid-independent event, since it proceeds in rats gonadectomized at the beginning of pubertal development [43].

In summary, as with adolescent changes in the gross morphology of the brain, synaptic remodeling during adolescence may involve both trophic and atrophic events and may or may not be driven by pubertal hormones. The fact that some features of adolescent brain development occur independently of the hormonal changes of puberty underscores that puberty and adolescence are dissociable, and

raises the important developmental question of whether puberty and adolescence are separately timed, or whether the same permissive signals that time the onset of puberty also time the onset of adolescent brain development.

4.2. Adolescent remodeling of neural circuits in humans

There are many parallels in the remodeling of the adolescent brain in animals and in humans. First, human adolescent development involves dramatic and widespread changes in the gross morphology of the brain [42,117–119]. White matter volume increases linearly through adolescence as the result of increased myelination of cortical and subcortical fiber tracts [12,85,86]. Adolescent changes in gray matter volume take an inverted U-shaped course, first increasing and then decreasing. Peak volume occurs at different ages in different lobes. The parietal and occipital lobes generally mature earlier than the frontal and temporal lobes, where gray matter volume does not reach adult steady state until the early to mid 20s [40,42]. The temporal sequence of cortical lobe maturation parallels behavioral development in that primary sensory function matures relatively early, while executive function and sensory association mature relatively late. The age of peak gray matter thickness is also sexually dimorphic, typically occurring one year earlier in girls than in boys and correlating with the earlier average age at puberty onset in girls [39]. Likewise, hippocampal and amygdalar volumes increase during human adolescence in a sex-dependent manner, with hippocampal enlargement occurring only in females and amygdala enlargement only in males [41]. Finally, the bed nucleus of the stria terminalis in humans is sexually dimorphic, with overall volume and number of neurons being greater in males than in females. Interestingly, sex differences in bed nucleus volume do not exist in childhood, but emerge during adolescence [21].

The structural bases of adolescent changes in gross morphology of gray matter in humans have not yet been elucidated, although most investigators interpret the adolescent reduction in gray matter volume as evidence for synaptic pruning. This interpretation is supported by electron microscopic investigations of cortical synapse density in humans and non-human primates, which found that synapse density increases during early postnatal life, and decreases during adolescence to reach an adult plateau [14,15,52,74]. Developmental studies of the monkey prefrontal cortex show adolescent changes in the intrinsic circuitry [68,135] and ingrowth of dopaminergic fibers [11] during adolescence, supporting the conclusion that cortical connectivity is remodeled in primate adolescence.

In summary, the remodeling of the adolescent brain is accomplished through a variety of mechanisms, including both progressive events, such as increases in cell number, dendritic elaboration, and axonal sprouting, and regressive events, such as cell death and synaptic pruning. Virtually all of these basic mechanisms are known to be influenced by steroid hormones in some type of developmental context. An imperative challenge for developmental neurobiology and developmental psychobiology is to identify which aspects of adolescent brain development are driven by pubertal hormones and which are not, and to understand the behavioral consequences of steroid-dependent organization of the adolescent brain.

5. Gonadal hormones organize behavior during adolescence: rodent models

The changes in behavior that take place with adolescent development are profound and far-reaching. The scientific literature on adolescent behavior in animals and humans has been reviewed from a number of different perspectives, and the reader is referred to these papers for comprehensive treatment and analysis of this topic [1,3,19,23,26,67,96,99,111,120,121]. Here we restrict analysis to the maturation of reproductive behavior, agonistic behavior, and anxiety-related behaviors in rodents, and we specifically review the empirical evidence that these behaviors and their underlying neural circuits are organized by gonadal hormones during adolescence. We define organization as the programming of behavioral responses that are long-lasting and persist beyond the period of hormone deprivation or exposure. The literature reviewed in this section provides evidence that organizational effects of pubertal hormones traverse a diversity of species and social behaviors, and that interactions between gonadal hormones and the adolescent brain influence neural responses to social stimuli and the expression of behavior in adulthood.

5.1. Adolescent organization of reproductive behavior

In male rodents, reproductive behavior typically emerges 1–2 weeks after the onset of the pubertal rise in testosterone secretion. In female rats, display of behavioral estrus cycles lags behind vaginal opening by a similar amount of time [115]. The relationship between pubertal hormones and reproductive behavior has traditionally been thought of as purely activational. Converging lines of evidence have led to the more recent conclusion that steroid hormones also have an organizational role during puberty in the maturation of reproductive behavior.

An initial hint that organization of reproductive behavior occurs during puberty came from observations in several species that behavioral responses to gonadal steroid hormones are different in prepubertal and adult animals [9,44,66,70,84,110,115,116]. For example, treatment of prepubertal male Syrian hamsters with subcutaneous pellets containing either testosterone, dihydrotestosterone, or estradiol benzoate fails to activate male reproductive behavior, even though the same hormonal treatments fully activate reproductive behavior in adult castrates [70,98,101]. Similarly, mounts and intromissions can be activated in prepubertal rats and ferrets only by very high doses of hormone [9,44,66,110]. Prepubertal female rats and guinea pigs are also relatively unresponsive to the activat-

ing effects of ovarian steroids on receptive behavior [84,115]. Thus, the prepubertal deficiencies in hormonal responses suggest that the prepubertal brain is not prepared for steroid activation of reproductive behavior, and provide indirect evidence that some type of maturation of steroid-sensitive behavioral circuits occurs during adolescence.

Given the organizational role of gonadal steroids during the perinatal period of sexual differentiation, it is logical to hypothesize that they are also agents of behavioral organization during adolescent neural development. In fact, more than 30 years ago, some authors speculated that pubertal organization of the nervous system may account for observed pubertal increases in behavioral responsiveness to steroid hormones [44,66,116]. More recently, we directly tested the hypothesis that steroid-dependent organization of reproductive behavior circuits occurs during puberty [102]. Behavior was assayed in adult male Syrian hamsters that had experienced adolescent brain development in either the presence or the absence of gonadal hormones. In these studies, hamsters were gonadectomized either before (*Adolescence without Hormones*) or after puberty (*Adolescence with Hormones*). Six weeks later, testosterone was replaced and the males were tested with receptive females. Males in the *Adolescence without Hormones* group consistently displayed significantly fewer mounts, intromissions, and ejaculations than males in the *Adolescence with Hormones* group, even after up to 17 days of testosterone treatment and three exposures to a receptive female (Fig. 1). Thus, the absence of gonadal hormones during adolescent brain development results in a long-lasting impairment of testosterone-induced reproductive behavior. Conversely, the presence of gonadal hormones during adolescent brain development enhances testosterone-induced male reproductive behavior in adulthood, or in other words, masculinizes behavioral responses. We have also found that pubertal gonadal hormones alter the adult male's behavioral responses to ovarian hormones [102]. Adult male Syrian hamsters normally show lordosis behavior if treated with estrogen and progesterone and tested with a stud male [20,65,126]. However, lordosis latency is significantly shortened in males that experience adolescence without hormones, and is similar to lordosis latencies of hormone-primed female hamsters. Thus, testicular hormones during puberty appear to both masculinize and defeminize behavioral responses in adulthood.

In addition to organizing sexual performance, adolescent exposure to gonadal hormones may also organize sexual preference. One group [128] found that gonadectomy of male rats at postnatal day 10 abolished the preference for female partners that is normally observed in sexually naïve adults. These experimental males experienced the perinatal, but not the pubertal, elevation in testosterone. A second group [16] reported no effect of castration at 21 days of age on partner preference when testosterone is replaced in adulthood. At first glance these two reports may seem at odds in their support of a role for pubertal hormones in establishing male-typical partner preferences. However, it may be that postnatal steroid-dependent organization of partner preference in the rat occurs very early, perhaps in the second or third week of postnatal life.

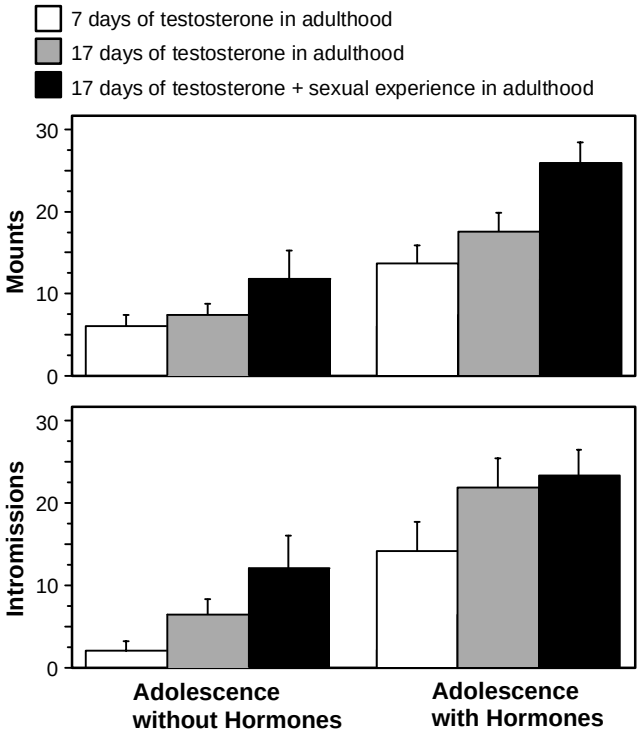

Fig. 1. Gonadectomy before puberty reduces testosterone-facilitated adult sexual behavior in male hamsters. Males gonadectomized prepubertally (*Adolescence without Hormones*) mounted and intromitted less frequently than males gonadectomized postpubertally (*Adolescence with Hormones*) after either 7 or 17 days of testosterone treatment begun in adulthood, 6 weeks post-gonadectomy. When given 17 days of testosterone and repeated sexual experience with a receptive female, the *Adolescence without Hormones* group still showed reduced levels of sexual behavior compared to the *Adolescence with Hormones* group. For both mounts and intromissions, there were significant interactions between age at gonadectomy (*Adolescence without Hormones* or *Adolescence with Hormones*) and treatment (7 days of testosterone in adulthood, 17 days of testosterone in adulthood, or 17 days of testosterone in adulthood plus sexual experience). Data are redrawn from [102].

Recent experiments in our laboratory indicate that pubertal ovarian hormones organize circuits mediating female reproductive behavior [103]. Female hamsters that undergo adolescent brain development in the absence of ovarian hormones show shorter lordosis latencies compared with females that undergo adolescence in the presence of the ovaries, suggesting that pubertal ovarian hormones defeminize behavioral responses in female hamsters, as do testicular hormones in males. However, these same females do not display increased mounting behavior after two weeks of adult testosterone treatment, suggesting that ovarian hormones do not masculinize neural circuits during puberty. Similarly, exposure of female rats to testosterone during early puberty (PND15-30) defeminizes the expression of proceptive behavior, but does not masculinize the expression of mounting behavior [13]. In contrast, when ovarian hormones or estradiol are present for the entire

duration of puberty, female rats display increased mounting behavior [25]. Thus, the influence of gonadal steroids during puberty on reproductive behavior may depend on both the timing of exposure during adolescence as well as the particular species.

5.2. Adolescent organization of agonistic behaviors

Scent marking is commonly used by mammals to communicate information to conspecifics about territory, fertility, and social status. Syrian hamsters rub flank glands against objects in their environment to convey dominance status during male–male encounters [27,33,53]. Flank marking in adult hamsters is modulated by testosterone. We have shown that testosterone does not activate flank marking in either prepubertal hamsters or in hamsters castrated prior to puberty and treated in adulthood [71,104]. These results demonstrate that gonadal hormones during puberty organize neural circuits underlying flank marking behavior and program the steroid-dependent activation of this behavior in adulthood, as we found with maturation of male hamster reproductive behavior. Similarly, territorial scent marking in tree shrews is organized by the pubertal rise in testosterone, since castration prior to puberty prevents activation of this behavior by testosterone in adulthood [31]. Interestingly, prepubertal castration of tree shrews did not affect familiarization marking (in the absence of conspecific scents) or sexual marking (in the presence of female scents), indicating that testicular hormones during adolescence organize scent marking that is specific to male–male social encounters in this species.

Aggressive behavior is also organized by steroid hormones during adolescence. While the adult display of aggression does not rely on the presence of testosterone in Syrian hamsters, aggressive behaviors decline during adolescent development [100], suggesting a role for pubertal gonadal secretions in the developmental decrease of this behavior. However, prepubertal gonadectomy does not cause males to remain in the highly aggressive prepubertal state. Instead, males deprived of hormones during adolescence display extremely low levels of aggressive behavior, significantly lower than control males gonadectomized after puberty [104]. Organizational effects of adolescent hormones have also been reported in mice and gerbils, two species that exhibit testosterone-dependent adult aggression. Male DBA/1Bg mice are normally very aggressive, but the absence of gonadal hormones during adolescence prevents activation of aggressive behavior by testosterone in adulthood [109]. Similarly, adult testosterone treatment only partially restores aggressive behavior in prepubertally castrated male gerbils [69].

We also have found evidence for hormone-dependent pubertal organization of submissive behaviors in male hamsters [104]. Males gonadectomized before puberty and tested in a resident-intruder paradigm in adulthood displayed significantly more escape dashes when compared with males gonadectomized after puberty in similar testing conditions. In addition, "tail up walking," a submissive behavior commonly observed during male–male hamster encounters, is inhibited by the presence of testosterone in adulthood, but only in males that have undergone adolescent development in the presence of gonadal hormones. Thus, similar to our results with flank marking, androgenic regulation of tail up walking behavior in adulthood is dependent on the presence of gonadal hormones during adolescent development.

Agonistic behaviors in female rodents may also be organized during adolescence. If female mice are ovariectomized at the onset of puberty (30 days of age), treated with testosterone for 3 weeks during adolescent development, and then tested 6 weeks after discontinuation of testosterone treatment, levels of aggressive behavior toward another female in a neutral arena are much higher than in females treated with vehicle [29]. Thus, adolescent exposure to androgen has long-term effects on aggression in female mice. In addition, the development of sex differences in the topography of dodging behavior, a stereotypical movement shown by rats when protecting food against an intruder, requires the presence of ovarian hormones both neonatally and during puberty [34].

5.3. Adolescent organization of anxiety-related behaviors

The amount of locomotor activity in an open field is often used as an index of anxiety, xenophobia, or depression in rodents. Adult male rats ambulate less than female rats when tested in an open field arena, indicating that this environment is more anxiogenic to males than to females. Testicular hormones do not play an activational role in male ambulation, as castration in adulthood does not increase open field ambulation [114]. However, testicular hormones appear to organize the sex difference in open field ambulation, because castration either at the onset of puberty or in mid puberty leads to increased ambulation in adulthood [16]. Similar to open field ambulation, male–male social interactions are reduced in a novel environment in comparison to interactions in a familiar environment, but female–female social interactions are not different in novel and familiar environments. The response to novel environment is not present in prepubertal males, but emerges during puberty and is dependent on the presence of gonadal hormones [94]. For example, either prepubertal castration or treatment with an aromatase inhibitor during puberty prevents the development of the novel environment effect in male rats [58,93]. Testosterone replacement from 30-60 days of age in prepubertally castrated males reinstates the effect of novel environment on social interactions in adulthood. Castration in adulthood does not affect social interactions in a novel environment [93]. Thus, the sex difference in social interactions in a novel environment is organized by gonadal steroid hormones during puberty, even though testicular hormones in adulthood do not play an activational role in this behavior. Gonadal hormones appear to organize this anxiety-related behavior by altering

the benzodiazepine–GABA receptor complex responses to environmental challenge [95].

Anxiety and stress modulate learning and memory differently in males and females [108]. In adulthood, female rats acquire classically conditioned eyeblink responses more quickly than males under unstressed conditions. However, after exposure to a stressor, this type of associative learning is impaired in females, whereas in males it is enhanced. This interaction between sex and stress on learning emerges during puberty, as stress does not alter trace conditioning in either sex prior to puberty [51]. It is not known whether pubertal gonadal hormones play an organizational role in the development of this sex by stress interaction on hippocampus-dependent associative learning. However, pubertal testosterone does exert organizational effects on the hippocampus in male rats via an androgen receptor-dependent mechanism. Specifically, activation of androgen receptor during puberty leads to long-term depression in CA1 in response to a tetanizing stimulus in adulthood, whereas when androgen receptor activation is blocked during puberty, long-term potentiation occurs in response to a tetanizing stimulus [49]. This result demonstrates that synaptic plasticity in the hippocampus is organized by pubertal androgens and provides a potential mechanism by which pubertal hormones could organize certain types of learning and memory.

6. Do gonadal hormones organize behavior during adolescence in humans?

In humans, experimental manipulation of exposure of the adolescent brain to gonadal steroids is not possible. However, cases of precocious or delayed puberty in humans are experiments of nature that provide insight into the effects of steroids on the human adolescent brain. Some people experience early or late puberty as a result of disorders of the HPG axis (reviewed in [46]). Central precocious puberty (CPP) is a disorder in which HPG axis activity begins well before the normal age of puberty onset. Idiopathic hypogonadotropic hypogonadism (IHH) is a disorder in which the HPG axis is not activated at the normal age of puberty onset, resulting in low or undetectable levels of circulating gonadal steroids during adolescent development. People with these disorders are typically treated with a variety of compounds that act on the HPG axis to normalize neuroendocrine activity.

Only a few studies in these patients address whether the presence or absence of gonadal hormones during adolescent development influences adult behavior. In one study, spatial cognition was compared in males with IHH beginning before puberty and in males with acquired hypogonadotropic hypogonadism in adulthood [50]. Spatial cognition was impaired in males not exposed to pubertal steroids, both in comparison to healthy control subjects and males with acquired IHH in adulthood [50]. Women with CPP also show differences from control subjects in spatial functioning [30], suggesting that early exposure of the brain to pubertal hormones also affects this cognitive system in females. With respect to psychosocial development, clinical hormone treatment of patients with absent or delayed puberty that is begun during the normal age range for puberty results in normal development, but hormonal treatments started after the age of 20 are ineffective (reviewed in [73]). Thus, although clinical treatment typically precludes the study of gonadal steroid and brain interactions in humans, the information that is available provides evidence for an organizational effect of gonadal hormones during adolescence on spatial cognition and psychological function.

7. Is adolescence a sensitive period for steroid-dependent remodeling of the brain?

The foregoing review establishes unequivocally that gonadal hormones organize numerous neural circuits and behaviors during adolescence. A still unanswered but central question is whether adolescence is a particularly sensitive period of development for steroid-dependent organization, similar to the perinatal critical period for sexual differentiation of the brain and behavior. If it is, then the effects of gonadal hormones on the adolescent brain should be quantitatively and/or qualitatively different from effects on the prepubertal or adult brain. In addition, adolescence would be a second vital juncture during which carefully timed exposure of the brain to gonadal hormones permanently alters developmental trajectory to influence adult behavior. Alternatively, it may be that the adolescent brain is no more sensitive to the organizational effects of gonadal hormones than is the prepubertal or adult brain, and steroid-dependent organization occurs during adolescence simply because puberty also occurs during that time. A third possibility is that the neural changes that take place during adolescence open a window of sensitivity to hormonal organization that remains open indefinitely until such hormone-dependent organization results in the crystallization or gelling of neural circuits and a diminishment of neural plasticity from that point forward.

Although we know of no empirical tests of the hypothesis that adolescence is a particularly sensitive period for steroid-dependent organization, some of the data reviewed in this paper provide indirect support for the hypothesis. Research in our laboratory demonstrates that up to two weeks of steroid treatment of prepubertal hamsters fails to activate male reproductive behavior. If during normal pubertal development, gonadal hormones first organize neural circuits and then activate reproductive behavior, then both effects can apparently be accomplished within two weeks, since the expression of male reproductive behavior lags behind the initial rise in testosterone secretion by approximately 10 days. This suggests that prepubertal males should express reproductive behavior after two weeks of hormone treatment if the neural circuits are capable of being organized before adolescent brain development. Since this is not the case, the neural circuits

mediating reproductive behavior appear to be differentially responsive to gonadal steroids before and during adolescence. We have also found that up to 17 days of testosterone treatment in adulthood fails to reduce the behavioral disparity between males that experience adolescent brain development in the presence or absence of gonadal hormones (Fig. 1) indicating that a window of opportunity for organization is closed, or at least partially shut, by the end of the period of adolescent brain development, even if gonadal hormones have not been encountered during adolescence. The data on hormone replacement therapy in human males with IHH support a similar conclusion, since hormone replacement in adulthood does not reverse the effects of low levels of hormone during adolescence on spatial ability and psychosocial development [50,73]. A short-coming of these studies in humans and our studies in hamsters is that cumulative lifetime exposure to testosterone was not controlled for, therefore definitive conclusions cannot be made.

8. The timing of interactions between pubertal hormones and the human adolescent brain affects risk for psychopathology

If adolescence is a particularly sensitive period for hormone-dependent organization in humans, then variation in the onset of puberty should lead to individual differences in behavior. In fact, early puberty in humans has been identified as a risk factor for a variety of psychopathologies, including eating disorders and depression. The underlying causes for this increased risk are debated. Physiological and hormonal changes during puberty may alter neural circuits directly. Alternatively, the physiological changes associated with early puberty may alter an adolescent's social experiences during puberty, causing an increased risk for psychopathology.

Eating disorders are sex-biased psychopathologies that emerge during puberty. They are rare in males and uncommon in prepubertal girls [106]. Both of these factors suggest a possible role for pubertal hormones in the etiology of eating disordered behaviors. This hypothesis is supported by twin studies showing: (1) that non-shared environmental factors account for all of the variance in disordered eating symptoms in prepubertal twins, but genetic factors account for the majority of variance in postpubertal twins [62], and (2) that higher levels of circulating estradiol are correlated with higher probability of disordered eating [61]. Among early adolescent girls, measures of both eating disordered behavior and dissatisfaction with body image are higher among those girls who have gone through menarche and the early stages of puberty [57,63]. Early maturing females are also more likely to have bulimia nervosa and bulimic behaviors than on-time and late maturing females [56]. Twelve year old girls symptomatic for eating disorders have greater breast and pubic hair development than controls [59,60], suggesting either an earlier onset of puberty or a faster tempo of development in this sub-clinical population. In a clinical population, adults with bulimia nervosa retrospectively report an earlier age at menarche [32]. Attention to disordered eating in males is increasing, but empirical studies lag behind those in females. Using first ejaculation as a marker of pubertal development, boys who matured on time were less likely to develop bulimia nervosa relative to boys who matured very early or very late [56]. Although a definitive causal link has not been demonstrated, a variety of evidence has associated early puberty onset with increased risk for eating disordered behavior.

Like eating disordered behavior, depression is more common in women than men and typically has a pubertal onset of diagnosis. Females who experience menarche early are at higher risk for depression and depressive symptoms [37,55,123]. During early adolescence, early maturing boys have significantly greater depressive tendencies than on-time and later maturing boys, but in late adolescence, late maturing boys show the greatest number of depressive symptoms [2]. In contrast, early maturing females display higher levels of depressive symptoms throughout adolescence [37]. Circulating estrogens and androgens correlate with negative feelings and mood (reviewed in [122]), suggesting that pubertal increases in neuroendocrine activity may be related to pubertal onset of depression. Although circulating steroids likely contribute to depressive symptoms, they do not explain the persistence of higher depressive symptoms in early maturing females past puberty onset.

Taken together, these data suggest a possible link between individual differences in puberty onset and individual differences in behavior and risk for psychopathology. In humans, the direct effects of hormones on the brain, socialization by other individuals, and internal perceptions of pubertal body changes cannot be experimentally separated. However, the number of studies showing a lasting effect of early puberty on individual differences suggests that gonadal hormones may organize neural circuits. Future experiments on pubertal timing in animal models of eating disorders, depression, or other types of psychopathology are needed to link the observed correlations in the human literature to a causal effect of the timing of the onset of puberty.

9. Summary and conclusions

Imaging of the human adolescent brain has sparked scientific interest in studying adolescence from a neurobiological perspective, and it has captured the public's fascination with the profound neuronal rewiring that takes place during this period of development. This review highlights the organizational role of gonadal steroid hormones, which become elevated during puberty, in sculpting the adolescent brain. The organizational influences of gonadal hormones during adolescence occur in both females and males, occur across a wide range of species including humans, and impact many behaviors.

The recognition that the actions of pubertal hormones during adolescence have long-lasting consequences on brain structure and function raises fundamental questions that demand experimental study for a better understanding of the variables and interactions that influence behavioral maturation. One broad category of questions has to do with interactions between hormones and experience in shaping the adolescent brain. If hormones organize behavior during adolescence, do they do so via direct modification of neural circuits, or do they do so indirectly via modification of peripheral tissues or sensory systems that change the way individuals view themselves or are treated by others, i.e., modification of experience? Do certain types of experience mitigate situations in which the brain is intercepted by hormones at unusual times in development, such as precocious or delayed puberty? A second category of questions relates to the timing of interactions between gonadal hormones and the adolescent brain. Adolescence is clearly pivotal for behavioral development [1,3,23,120], and the adolescent brain is clearly more plastic than the adult brain in response to insult [83,127]. Thus, it is essential to determine whether adolescence is a sensitive or critical period for steroid-dependent organization of the brain because of the potential for hormones to permanently affect the brain's capacity for change. Answers to these questions will not only reveal fundamental principles of developmental neurobiology and psychobiology, but they will also yield new insights into the etiology and therapeutic interventions for sex-biased psychopathologies that emerge during adolescence.

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