The neural basis of puberty and adolescence

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The pubertal transition to adulthood involves both gonadal and behavioral maturation. A developmental clock, along with permissive signals that provide information on somatic growth, energy balance and season, time the awakening of gonadotropin releasing hormone (GnRH) neurons at the onset of puberty. High-frequency GnRH release results from disinhibition and activation of GnRH neurons at puberty onset, leading to gametogenesis and an increase in gonadal steroid hormone secretion. Steroid hormones, in turn, both remodel and activate neural circuits during adolescent brain development, leading to the development of sexual salience of sensory stimuli, sexual motivation, and expression of copulatory behaviors in specific social contexts. These influences of hormones on reproductive behavior depend in part on changes in the adolescent brain that occur independently of gonadal maturation. Reproductive maturity is therefore the product of developmentally timed, brain-driven and recurrent interactions between steroid hormones and the adolescent nervous system.

Puberty and adolescence mark the metamorphosis of the child into the adult. Biologists have typically viewed puberty from an endocrine perspective because the overt signs of reproductive maturation are driven by hormonal changes occurring during this period of development. Over the past four decades, an appreciation for the neural control of hormone secretion and a gradual awareness of extensive brain remodeling during adolescence have shifted the emphasis to a neural basis for reproductive maturation. Neuroscientists wish to answer two main questions about puberty: how is it timed and what are the underlying neural mechanisms? This review summarizes the neurobiology of puberty and describes the complexity of the maturational processes that underlie the transition into adulthood.

The terms puberty and adolescence are often used interchangeably. To specialists, however, puberty refers to the activation of the hypothalamic-pituitary-gonadal axis that culminates in gonadal maturation. Adolescence refers to the maturation of adult social and cognitive behaviors. These nuances of terminology capture the two essential elements of adulthood: production of gametes and a behavioral means for bringing male and female gametes together. The central position of this review is that gonadal maturation and behavioral maturation are two distinct brain-driven processes with separate timing and neurobiological mechanisms, but they are intimately coupled through iterative interactions between the nervous system and gonadal steroid hormones. The collective endpoint of these two processes is the reproductively mature adult.

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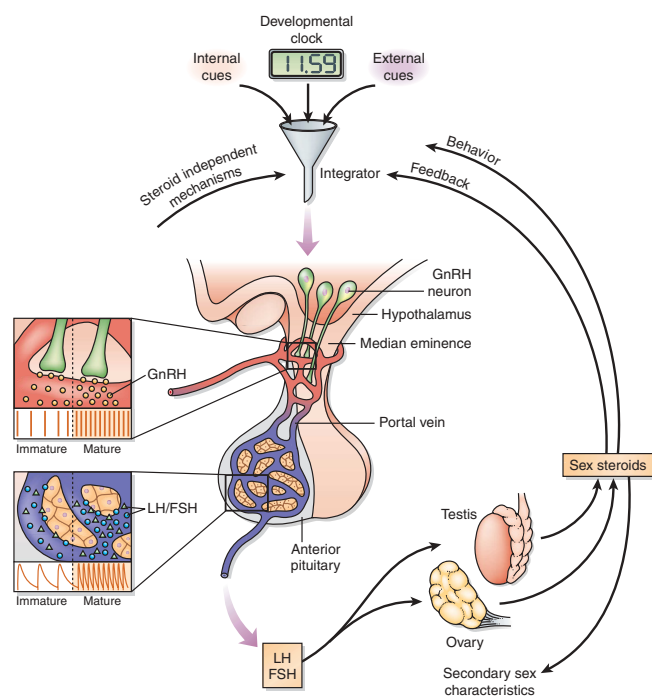
GnRH neurons are central to gonadal and behavioral maturation

The control of GnRH secretion is fundamental to reproductive maturation. GnRH is a decapeptide produced by specialized neurons that intermittently secrete pulses of hormone from nerve terminals positioned in the median eminence of the basal hypothalamus (**Fig. 1**). GnRH enters the pituitary portal vasculature and travels to the pituitary to signal the synthesis and secretion of the pituitary gonadotropins: luteinizing hormone (LH) and follicle stimulating hormone (FSH). Blood-borne LH and FSH act on target cells in the testes and ovaries to direct the production of sperm and eggs, as well as the secretion of steroid hormones. Gonadal steroids are vital to both gonadal function and reproductive behavior. Within the gonads, steroid hormones participate in spermatogenesis and follicle maturation. Within the brain, steroids influence GnRH secretion via neuroendocrine feedback loops and facilitate sexual behavior. Modulation of GnRH pulse frequency is the primary mechanism by which the body alters its reproductive status during development, and a relatively short interpulse interval is required to produce a pattern of gonadotropin and steroid hormone secretion that supports gonadal function and reproductive behavior.

Determining the neural mechanisms that underlie episodic GnRH secretion has proved to be a major conceptual and technical challenge due to the neuroanatomy of the GnRH system (for review, see refs. 1,2). First, despite their enormous responsibility, GnRH neurons are surprisingly few in number, with only 1,000–3,000 cells consistently found across mammalian species. Second, GnRH neurons arise from the nasal placode region during early embryologic development, migrate into the brain and spread diffusely throughout the diagonal band of Broca, septum, organum vasculosum of the lamina terminalis, preoptic area and hypothalamus. The widespread distribution of GnRH cell bodies has hampered efforts to describe the sources and phenotypes of direct afferent inputs to these neurons. Finally, most GnRH neurons have a

Figure 1 GnRH neurons projecting to the median eminence direct pituitary gonadotropin and gonadal steroid hormone secretion. Sex steroids promote secondary sex characteristics in peripheral tissues, regulate GnRH neurons via a neuroendocrine feedback loop and facilitate social behaviors by acting on central neural circuits. The pubertal increase in GnRH neuronal activity and episodic gonadotropin secretion is grossly timed by a developmental clock and fine-tuned by the neural integration of multiple permissive internal and external signals. At the onset of puberty, steroid feedback and steroid-independent neural mechanisms are engaged to disinhibit and excite GnRH neurons.

simple bipolar or unipolar morphology, and innervation of GnRH cell bodies is sparse compared to neighboring neurons. Yet GnRH neurons somehow fire synchronously to produce the intermittent episodes of hormone release in the median eminence. Recent successes with *in vivo* electrophysiological monitoring of GnRH activity are beginning to shed light on how amino acid neurotransmitters and steroid hormones alter GnRH excitability and synchrony[3–8], but the neurobiological basis of the GnRH pulse generator remains elusive.

In most mammals, transient activation of the hypothalamic-pituitary-gonadal axis during late prenatal or early postnatal life results in an increase in circulating gonadal steroids, which participate in sexual differentiation and other programming of the nervous system. GnRH secretion declines soon thereafter, and hormone pulse frequency slows to about one discharge every few hours throughout the prepubertal period, which may last several years in long-lived species. After this period of quiescence, puberty begins when GnRH secretion once again gradually increases and remains high to stimulate gonadotropin and steroid hormone secretion, this time resulting in complete gonadal maturation and the capacity to express reproductive behavior. But what times the resumption of frequent GnRH secretion to drive the pubertal transition?

Multiple permissive signals time onset of puberty
A perpetual goal for researchers is to find the 'trigger' that induces the re-emergence of GnRH secretion at puberty. Findings reported in the

scientific and popular press have implicated various candidates, including melatonin, body fat, leptin and most recently a single gene! Hope is now fading for finding a single trigger for puberty because of the number and complexity of the variables that determine reproductive success[9–11]. Rather, we are finding that multiple signals are involved. Thus far, scientists have identified signals that permit puberty to occur or progress, but do not cause puberty. We call these 'permissive' signals.

Researchers have made much progress toward identifying the permissive signals and locating their respective sensors. Not surprisingly, the permissive signals vary with species and sex, and most relate to energy balance. The consequences of puberty, such as the defense of territory or mate, pregnancy and care of young, are energetically expensive. For this reason, the timing of puberty is critical: the individual must perceive whether it has grown sufficiently (through metabolic cues), what its relationship is to other individuals (through social cues) and whether conditions are optimal to begin the reproductive process (through environmental cues). For example, metabolic fuel availability, insulin, glucose and leptin in females serve as important signals for the attainment of somatic growth sufficient to support pregnancy. Sensors in the hypothalamus and hindbrain monitor these signals and permit high-frequency GnRH release when the signals reach appropriate levels[12–18]. Except in the extreme, energy imbalance affects reproductive maturation and fertility relatively less in males, perhaps because males do not face the risk of pregnancy and lactation. For many seasonal breeders, the photoperiod signals the optimal time of year for puberty onset[19,20]. The circadian clock in the suprachiasmatic nucleus measures day length by controlling melatonin production in the pineal gland. The duration of the nocturnal elevation in melatonin encodes day length, and melatonin receptors in the thalamus and hypothalamus transduce this signal to GnRH neurons (for review, see ref. 21). In other species, sensory cues from conspecifics permit the onset of GnRH secretion at puberty[22,23].

Multiple permissive signals determine the precise timing of puberty onset and are integrated in a species-specific manner to allow or not allow the pubertal increase in GnRH to proceed, depending on the interplay, balance and hierarchy among the signals (**Fig. 1**). The integrating mechanism is still unknown. A matter of debate is whether integration is intrinsic to the GnRH neuronal system, with subpopulations of GnRH neurons receiving different types of synaptic input corresponding to the various signals, or whether there is an independent master integrator providing a 'go/no-go' signal to GnRH neurons.

A developmental clock ultimately times puberty onset
Combinations of permissive signals cannot fully explain the timing of puberty, as the use of such signals is not unique to this period of life. Many are used later on to time other transitions from low- to high-frequency GnRH secretion, such as the resumption of fertility after birth and lactation, seasonal anestrus, restricted diet or high energy expenditure. One could argue that puberty is unique because it represents the first alignment of several permissive signals that result in a maturation that is never again replicated. However, this line of reasoning is unsatisfying because the starting point for an infertile juvenile is not the same as for an infertile adult. We are left with the simple recognition that there is a maturational component in the juvenile that makes puberty unique. Such a view leads to the concept of an innate developmental clock that times the unfolding of primary genetic programs and produces the internally derived signals that in turn determine the responses to both internal and external permissive signals. According

to this broad reasoning, permissive signals would not influence the ticks of the developmental clock, but their combination would determine precisely when the puberty alarm would sound.

If the maturational component of puberty is a clock mechanism, then there must be key regulatory genes that are an integral part of the developmental process. Among the candidates, genes encoding members of the POU homeodomain family of transcription factors were first proposed as master regulators for the onset of puberty because of their temporal and spatial expression patterns in the hypothalamus and their ability to transactivate genes encoding GnRH or proximal regulators of GnRH synthesis and secretion[24–27]. More recent reports have nominated *GPR54* as the 'puberty gene.' *GPR54* encodes a G protein–coupled receptor, and mutations in the gene lead to the absence of increased GnRH secretion at puberty[28,29]. Despite these identified genetic mechanisms, we are extremely cautious about designating any of these genes to be a master regulator of puberty. Rather than being part of a developmental clock, they may simply act as downstream mechanisms governing GnRH synthesis and release. Identification of master regulatory genes directing the unique maturational component of the first and most important transition to fertility remains an unsolved part of the puberty mystery.

Sex differences in the timing of puberty

Males and females often initiate and end puberty at different times, and the magnitude and tempo of these differences are species dependent. The order is as well. For example, girls show outward signs of puberty before boys, but male lambs begin puberty before female lambs. We know little about the mechanisms for these timing differences, but whatever they are, they must originate within the brain, given its essential role in regulating GnRH secretion. Most likely, these mechanisms are both genetic and programmed, but a pure genetic basis is difficult to evaluate because neurons are bathed in a variety of substances during development. We are beginning to appreciate how the timing of puberty can be prenatally programmed by sex steroids. For example, studies in sheep reveal that prenatal administration of testosterone to the developing female will advance the time of the pubertal GnRH rise by several months[30,31] such that it resembles the earlier timing seen in males. Moreover, the timing of the pubertal GnRH rise depends on when the female is first exposed to the sex steroid, as well as the amount and duration of exposure. Although it is attractive to suppose that the timing of puberty and certain dysfunctions in adult reproduction may have fetal origins, the neuroanatomical basis of such effects is not clear. Prenatal steroid organization of postnatal GnRH secretion does not involve changes in the number, distribution or morphology of GnRH neurons in the rat, monkey or sheep[32–34], as they are the same in both sexes. This reinforces the notion that whereas the basal activity of these 'pacemaker' neurons could be endogenous, the GnRH neurosecretory system requires external input to modulate physiologically meaningful changes in activity. Thus, sexual differentiation of presynaptic input to the GnRH system is important for its differential function in the developing male and female. Indeed, this hypothesis is supported by electron microscopy in the sheep, where there are more synaptic contacts on GnRH neurons of adult females than males, and prenatal exposure of females to testosterone decreases the number of synapses in females[35].

Steroid-independent vs. steroid-dependent mechanisms

The developmental clock and permissive signals that time the onset of puberty engage two broad types of neural mechanisms that impose prepubertal quiescence of GnRH neurons and their subsequent activation at the onset of puberty. As a theoretical framework, these mecha-

nisms can be categorized as those that act without hormonal information from the gonads (steroid independent) and those that act in the presence of gonadal steroids (steroid dependent).

In some altricial species, those that are not well developed at birth, steroid-independent mechanisms are primarily responsible for the postnatal changes in the pattern of GnRH secretion. Researchers have studied this most in the rhesus monkey and rat[27,36–38]. For example, after elimination of gonadal steroids by neonatal castration of male monkeys, gonadotropin levels remain very low during the two-to-three-year prepubertal period, but then gradually rise to high levels at the expected age of puberty, a pattern of hormone secretion that is the same as that observed in gonad-intact males[36,38]. Similarly, peripubertal LH secretion increases in both gonad-intact and ovariectomized female rats[39] and in humans with no circulating gonadal steroids due to gonadal dysgenesis[40,41]. These same steroid-independent mechanisms also operate prenatally in precocious species such as the guinea pig and sheep, which are well developed at birth[42].

Steroid-dependent mechanisms that regulate GnRH release involve changes in sensitivity to gonadal steroid negative-feedback regulation of GnRH neurons[43]. During the prepubertal period, GnRH neurons are highly sensitive to negative feedback, which permits only a slow frequency of GnRH release so that the gonads remain immature. At the onset of puberty, sensitivity to negative feedback decreases, which permits expression of high-frequency GnRH pulses that subsequently drives the pubertal increase in gonadotropin secretion and leads to gonadal maturation. This remarkable change in the 'gonadostat' clearly underlies the pubertal increase in GnRH secretion in some species, most notably in sheep, hamsters and ferrets[44–46]. In these species, early postnatal gonadectomy results in an immediate increase in gonadotropin secretion, and levels remain elevated during the prepubertal period in the absence of steroid hormones. Replacing steroid hormones causes gonadotropins to return to the typically low levels during the prepubertal period of high sensitivity to negative feedback. During the pubertal transition, the 'escape' from negative feedback is manifest by an increase in gonadotropin levels at the time of puberty in face of constant levels of steroid hormone.

As a theoretical construct, the dichotomy of steroid-independent and steroid-dependent mechanisms has increased our appreciation of the different ways that the body controls GnRH secretion. However, in most species, both types of mechanisms come into play at different points during puberty to boost GnRH secretion. For example, after a steroid-independent increase in GnRH secretion at the onset of puberty in female monkeys, a decrease in sensitivity to steroid negative feedback drives a late puberty increase in GnRH pulse frequency[47]. Perhaps the steroid-independent system provides coarse control and the steroid-dependent system provides fine control. In this sense, in nonhuman primates and children, the steroid-independent control of GnRH secretion would determine the year when first ovulation is possible, whereas the steroid-dependent control mechanism would determine the week when first ovulation occurs. This may not be the case in all species, for a decrease in sensitivity to negative feedback in male hamsters leads to the initial pubertal increase in gonadotropin secretion, which is enhanced during late puberty by steroid-independent mechanisms[45].

GnRH neurons are excited at puberty

Both steroid-independent and -dependent mechanisms, driven by the brain, suppress GnRH secretion during the prepubertal period and enhance GnRH secretion during puberty, but what are the downstream mechanisms that regulate GnRH neurons? Although these mechanisms do not control the timing of puberty, they form a critical

part of the terminal pathway that conveys temporal information from the upstream steroid-independent and -dependent integrator systems and regulates the GnRH neurosecretory network. In the search for neural mechanisms that directly modulate GnRH secretion, most research has focused on whether pubertal activation of GnRH neurons results from a decrease in inhibitory input or an increase in excitatory input to the GnRH system, as well as which neurochemicals provide the inhibitory and excitatory tone (for review, see refs. 27,37,38,48). The answers are species- and sex-dependent. In female monkeys, the pubertal rise in GnRH secretion seems to result from a decrease in GABAergic inhibition and a concomitant increase in glutamatergic excitation of GnRH neurons, along with potentiation of glutamate excitation by norepinephrine and neuropeptide Y[38]. In male monkeys, a similar disinhibition/excitation of GnRH neurons operates at the onset of puberty, except that neuropeptide Y is the prime candidate for prepubertal inhibition of GnRH release[38]. In rats, the evidence for strong tonic prepubertal inhibition of GnRH is not clear; however, glutamatergic NMDA receptor activation accelerates, and NMDA receptor blockade delays, the onset of puberty[27,49], indicating an increased excitatory drive of GnRH neurons at puberty. Researchers have also proposed that glial-neuronal interactions at the level of GnRH terminals are involved in the onset of puberty through facilitation of GnRH release by glial-derived growth factors in the epidermal and transforming growth factor families[50].

In no species do we definitively know whether pubertal disinhibition and excitation of GnRH secretion involves changes in direct or indirect synaptic input to GnRH neurons. Some GnRH neurons express receptors for GABA and glutamate[51–53], and the proportion of GnRH neurons that express the NMDA-R1 subunit increases with pubertal development in female rats[52]. In addition, the number of synaptic contacts onto GnRH perikarya increases with pubertal development in rats and monkeys[54,55]. The unraveling of how GnRH neurons are inhibited before puberty and activated at the onset of puberty will no doubt keep neuroscientists occupied for some time to come, and the final picture will surely be complicated. As a case in point, recent reports of a switch from GABA depolarization of GnRH neurons before puberty to GABA hyperpolarization of GnRH neurons at the time of puberty[56] must be reconciled with the finding that blockade of GABA action increases GnRH secretion[38].

A pubertal decrease in sensitivity to steroid negative feedback does not seem to be related to changes in nuclear steroid hormone receptor expression within GnRH or other types of neurons, although this conclusion remains tentative because the direct sites and mechanisms of action for steroid regulation of GnRH secretion are unknown. In addition to nuclear receptor-mediated alterations in gene transcription within neurons, steroid hormones influence GnRH cell excitability by modulating ion conductance across potassium, chloride and calcium channels[3,8]. One interesting but unexplored possibility is that pubertal changes in the gonadostat are mediated by developmental changes in ion channel subunit expression in GnRH neurons or their upstream neuronal regulators, which could also be involved in the dynamic interplay between GABAergic and glutamatergic control of GnRH secretion described above. Finally, it must be noted that these immediate controls of GnRH secretion, including those described for neurotransmitters and even steroid-dependent and -independent regulation, may not be unique to the pubertal transition because numerous reversals to infertility may occur during the lifespan. The re-emergence of high-level GnRH secretion after these periods of adult infertility may use these same immediate, general mechanisms.

Behavioral maturation during adolescence

Up to this point, we have considered that the timing of gonadal activation lies in an elusive developmental clock whose signals integrate with permissive cues to modulate a passive GnRH neurosecretory system and drive the maturational changes in sex steroids. How does this scheme relate to the parallel changes occurring in behavior during maturation? In one sense, the timing of adolescent behavioral maturation depends on the timing of gonadal maturation because steroid hormones are required for the overt expression of reproductive behavior. However, it is clear that some important aspects of behavioral maturation are not driven solely by the appearance of steroid hormones at the time of puberty, because hormone treatment fails to fully activate copulatory behavior in prepubertal animals, indicating a need for further maturation of central and peripheral tissues before behavior can be expressed[57–62]. Thus, as with puberty, there appears to be a developmental clock that times behavioral maturation during adolescence and that limits the age at which fully mature adult reproductive behavior can be expressed. A critical question is whether the developmental clock timing behavioral maturation is the same as that timing gonadal maturation.

Gonadal steroids are well-known regulators of reproductive behavior, influencing the structure and function of behavioral circuits during both early development and in adulthood. In males, testosterone and its metabolites facilitate sexual motivation and copulatory behaviors[63,64]. In females, estradiol and progesterone facilitate proceptive and receptive behaviors that signal a readiness to mate[65,66]. Traditional thinking holds that gonadal steroids, acting during a sensitive period spanning late embryonic and early neonatal development, sexually differentiate neural circuits that are destined to mediate adult male and female reproductive behavior (see accompanying review[67] in this issue). In adulthood, steroid hormones facilitate reproductive behavior in specific social contexts by eliciting cellular responses within the previously sexually differentiated neural circuits. The irreversible changes in nervous system structure and the programming of adult behavioral responses to hormones caused by exposure to steroids during early neural development are called 'organizational effects'; the facilitation of reproductive behavior by steroids in adulthood, which is reversible if hormone is removed, is called an 'activational effect'.

As originally conceived, the organizational-activational framework for steroid control of reproductive behavior presumed a strictly activational role for gonadal steroids during adolescence. A recent modernization of this thinking incorporates dual roles for steroid hormones, which not only activate, but also organize neural circuits during adolescence[68]. For example, castration of male hamsters after the neonatal period of sexual differentiation, but before puberty, reduces testosterone-induced activation of behavior in adulthood compared to castration of males after puberty[69]. Furthermore, neither prolonged hormone replacement nor sexual experience in adulthood reverses these behavioral deficits, demonstrating irreversible and adverse consequences for behavior if gonadal hormones are absent during adolescence[69]. Two other examples of behaviors that are organized during adolescence are territorial scent marking in tree shrews[70] and social interactions in a novel environment in rats[71,72]. In both cases, the absence of gonadal hormones or pharmacological blockade of their action during adolescence prohibits adult-typical expression of the behavior, even if hormones are replaced in adulthood. Moreover, the inability of hormone treatment in adulthood to reverse the consequences of hormone absence during adolescence in all of these cases suggests that adolescence may be a sensitive period for further steroid-dependent organization of neural circuits mediating reproductively relevant social behaviors.
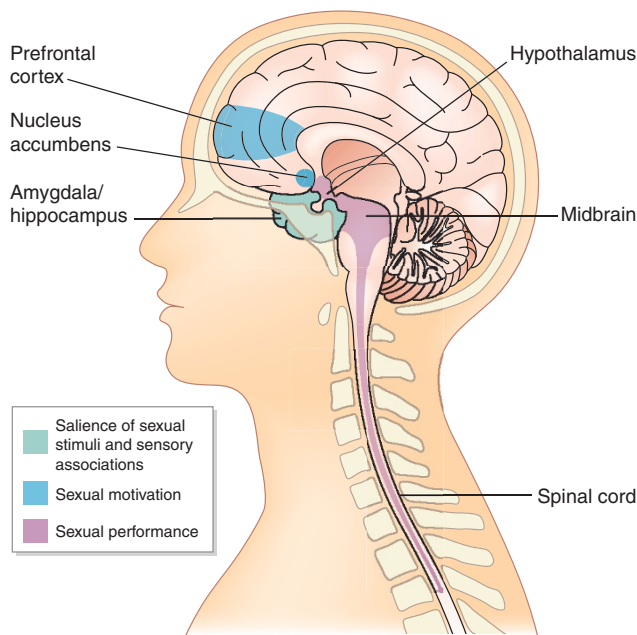
Figure 2 Adolescent maturation of reproductive behavior requires remodeling and activation of neural circuits involved in salience of sexual stimuli and sensory associations, sexual motivation and sexual performance. Structural remodeling of the brain during adolescence occurs through both steroid-dependent and steroid-independent mechanisms.

The sequence of events during steroid-dependent adolescent maturation of reproductive behavior may be an initial reorganization of circuits that further sensitizes them to hormone activation, followed by activation of behavior in an appropriate social context. This could explain why exogenous steroid treatments that reliably activate reproductive behavior in adults are less effective at doing so in prepubertal animals[57–62]. Steroid treatments may be more efficacious in adults either because adult brains have already been organized and primed for more rapid activational responses, or because the prepubertal brain is less sensitive to organization and activation by steroid hormones.

The neural circuits mediating reproductive behavior include areas involved in sensory associations and motivation (amygdala), male mounting and female receptive behaviors (preoptic area, ventromedial nucleus of the hypothalamus) and motor control of behavior (central gray, ventral tegmentum, spinal nucleus of the bulbocavernosus, dorsal horn). Cells in many of these regions express nuclear receptors specific for androgens, estrogens and progestins. Receptor activation by hormone elicits a variety of cellular responses through receptor-mediated transcriptional activity and alterations in cell excitability. Reproductive behavior is complex and its manifestation relies on receipt of sensory stimuli from a partner, motivation to mate and motor output (**Fig. 2**). Not surprisingly, virtually all of the classical amino acid and gaseous neurotransmitter systems are involved, as well as numerous neuropeptides and scores of receptor subtypes. A summary is beyond the scope of this review, but neural mechanisms of male and female reproductive behavior have been extensively reviewed by others[63–68,73–76].

Compared with activation of neural circuits by steroid hormones, we know relatively little about steroid-dependent organization during adolescence. Presumably, there are many similarities to the processes involved in steroid-dependent sexual differentiation during early

neural development, such as regulation of cell death and survival, and synaptic density and connectivity (see accompanying review[67] in this issue). Some structural sexual dimorphisms are established during puberty and adolescence, such as size of the rat hypothalamic anteroventral periventricular nucleus[77], cell number in the rat visual cortex[78], size of the rat locus coeruleus[79], dendritic arborizations of spinal motor neurons[80] and size of the human bed nucleus of the stria terminalis[81]. The enduring structural and functional changes resulting from adolescent reorganization of the brain impart uniqueness to behavioral maturation that is never exactly repeated, even, for example, during annual reactivation of reproductive behavior in seasonally breeding species. A challenge for future research will be to clarify which changes in behavioral circuits during adolescence result from activational effects and which result from organizational effects of steroid hormones.

Steroid-independent behavioral maturation
Although we have recognized for decades the contribution of both steroid-dependent and steroid-independent mechanisms to the pubertal rise in GnRH secretion, the idea that both types of mechanisms contribute to behavioral maturation is even newer than the understanding that steroid hormones both organize and activate reproductive behavior during adolescence. An experimental protocol similar to that used to show steroid-independent influences on pubertal activation of GnRH secretion reveals that the propensity for male reproductive behavior increases during adolescence, even if the organizational and activational effects of steroids during adolescent development are eliminated by prepubertal castration. Specifically, copulatory behaviors in adult male hamsters can still be activated by an activational dose of testosterone, even though the hamsters were castrated before puberty. However, the levels of behavior are not as high as those seen in males in which gonadal hormones were present during adolescence[69]. In contrast, copulatory behavior cannot be activated in prepubertal males[61]. That behavior cannot be activated before puberty, but can be activated in adulthood even when gonadal hormones are absent during adolescence, demonstrates that steroid-independent maturational changes occurring during adolescence contribute to the ability to express adult reproductive behavior, and underscores the separation of gonadal maturation and behavioral maturation.

The neurobiological underpinnings of steroid-independent maturational changes in circuits mediating reproductive behavior are unknown. However, steroid-independent structural changes during adolescence have been described for other neural systems. For example, high expression of dopamine receptors in the striatum characterizes early adolescence in the rat and is followed by a pruning of these receptors in later adolescence. This pattern is more pronounced in males than in females, but in both sexes it proceeds even when gonadal hormones are removed before puberty[82,83]. Disturbances in this developmental programming have been linked to schizophrenia[84] and attention-deficit hyperactivity disorder[85]. Identifying the structural correlates of behavioral maturation, and distinguishing between those that are driven by steroid hormones and those that are not, is an area ripe for discovery.

Sexual salience of sensory stimuli and sexual motivation
Steroid activation of reproductive behavior does not occur in a vacuum. It also requires perception of sexually salient sensory stimuli, which are encountered in social interactions and modulate activity within steroid-sensitive behavioral circuits. Maturation of adult reproductive behavior also requires the acquisition of sexual salience of sensory stimuli (**Fig. 2**). For example, the odor of an adult female is

BOX 1 THE TEEN BRAIN: IT'S ABOUT TIME

The course of brain development is particularly susceptible to perturbation during periods of rapid change. As brain-hormone interactions during the adolescent brain 'growth spurt' are integral to behavioral maturation, temporal dissociations between gonadal maturation and adolescent brain development that occur in humans are likely to have consequences for adult behavior. For example, eating disorders or extreme exercise significantly delay gonadal maturation; thus, the brain may encounter steroid hormones after adolescent brain development has progressed. Will steroid hormones have the same influences on the nervous system in these individuals? Animal models predict they would not. At the other extreme, precocious puberty results in exposure of the brain to steroid hormones in early childhood. Will premature organizing effects of steroids alter the developmental trajectory of the brain? Animal models predict they would. At the very least, variations in the temporal sequence of gonadal maturation and adolescent brain development would be expected to contribute to individual differences in adult behavior and risk for sex-biased psychopathologies. These implications for human behavior and mental health mandate more research on behavioral outcomes of hormone-brain interactions during puberty and adolescence.

likely to mean one thing to a weanling male (mom) and yet another thing to an adult male (potential mate).

Odor preferences, neural and behavioral responses to sensory stimuli, and social affiliations all change with adolescent development. For example, in species in which chemosensory stimuli are important, preference for opposite-sex odors emerges with adolescent development[86], and neuroendocrine and neurochemical responses to odors that are typical in adults do not occur in juveniles[87,88]. In rhesus monkeys, juvenile males indiscriminately mount males and females, whereas adult males almost exclusively mount females in sexual contexts, indicative of maturation of sensory and behavioral cues that motivate the behavior[89].

In adulthood, steroid hormones alter both the quality of sensory stimuli produced by a potential mate and the responses elicited by those stimuli[90–92]. In addition to these activational effects, steroids may organize circuits during adolescence in a way that programs sensory responses and associations. Gonadal steroids organize both primary sensory cortex[78] and sensory association areas such as the amygdala and hippocampus[93,94] during perinatal and/or adolescent development. For example, ovarian hormones during adolescence promote programmed cell death in rat visual cortex, leading to an adult sex difference in cell number and cortical volume[78]. Via an androgen receptor–mediated process, testicular hormones during adolescence program a shift from long-term potentiation to long-term depression in hippocampal CA1 synaptic plasticity[94]. These organizing effects are likely to influence responses to sensory stimuli in adulthood.

Closely linked to acquisition of sensory associations and sexual salience is the development of sexual motivation (Fig. 2). Behavioral indicators of sexual motivation are generally not present in juvenile animals, and it has been argued for both males and females that acquisition of sexual motivation is a key component of reproductive maturation[63,95]. Researchers further postulate that steroid hormones stimulate sexual motivation, and that some process occurring during adolescence links sexual behavior to a hormonally modulated motivational system[95]. Research has also proposed that pubertal activation of the adrenal gland (adrenarche) is related to adolescent development of sexual attraction[96].

A better understanding of the neural mechanisms that underlie adolescent development of sexual motivation is likely to come from our increasing awareness of adolescent remodeling of cortical, limbic and reward areas of the brain. This remodeling includes processes such as increased myelination and decreased gray matter volume in cortical areas[97–103], synaptic elaboration and subsequent pruning in striatum and prefrontal cortex[82,104–106], cell death in primary visual cortex[78,107,108] and changes in connectivity in the amygdala and prefrontal cortex[109,110]. There are also sex differences in the timing and magnitude of these structural changes[81,102]. Brain areas involved in sensory associations and motivation mature much later than primary sensory and motor areas, and adolescent brain maturation in humans continues through the early twenties[98]. Collectively, these brain rearrangements are postulated to be linked to adolescent changes in decision making, risk taking, planning, drug sensitivity and reward incentive[111–113].

Summary

We have attempted to make the case that attainment of adult reproductive status involves both gonadal and behavioral maturation, and that both processes come about through a series of brain-driven, developmentally timed events that are modulated by internal and external sensory cues. Gonadal and behavioral maturation are intimately linked through multiple and complex interactions between the nervous system and gonadal steroid hormones. The brain initiates activation of the GnRH system at puberty onset, leading to an increase in steroid hormone production. Steroid hormones in turn modulate GnRH secretion in the brain, and organize and activate neural circuits mediating reproductive behavior during adolescence. These effects of hormones on behavior depend in part on pubertal changes in the nervous system that occur independently of gonadal maturation. Thus, while gonadal maturation and behavioral maturation are separate and interacting processes, the two are normally temporally coordinated, presumably maximizing reproductive success. Research in animal models unambiguously shows that disruptions in this temporal coordination influence neural responses and behavior in adulthood. This, together with evidence that adolescent development is a time of experience-dependent brain reorganization[111,112], suggests that individual differences in adult behavior could arise in part from normal variation in temporal coordination between gonadal and behavioral maturational processes (Box 1).

Neuroscientists have made enormous strides in calling attention to the role of the brain in reproductive maturation, in identifying the proximal signals and neural mechanisms that drive the activation of GnRH neurons at the onset of puberty, in characterizing the neural circuits that mediate reproductive behavior and in recognizing adolescence as a time of profound remodeling of the brain. Three fundamental questions remain. What are the workings of the developmental clock(s) that provides gross timing of reproductive maturation? What is the neural basis for the integration of permissive signals that fine-tune the timing of reproductive maturation? What are the consequences of adolescent remodeling of the brain for adult behavior? Future work on these questions will deepen our understanding of the process of puberty and adolescence.

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