Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex?

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Abstract

Postnatal brain development is studded with sensitive periods during which experience dependent plasticity is enhanced. This enables rapid learning from environmental inputs and reorganization of cortical circuits that matches behavior with environmental contingencies. Significant headway has been achieved in characterizing and understanding sensitive period biology in primary sensory cortices, but relatively little is known about sensitive period biology in associative neocortex. One possible mediator is the onset of puberty, which marks the transition to adolescence, when animals shift their behavior toward gaining independence and exploring their social world. Puberty onset correlates with reduced behavioral plasticity in some domains and enhanced plasticity in others, and therefore may drive the transition from juvenile to adolescent brain function. Pubertal onset is also occurring earlier in developed nations, particularly in unserved populations, and earlier puberty is associated with vulnerability for substance use, depression and anxiety. In the present article we review the evidence that supports a causal role for puberty in developmental changes in the function and neurobiology of the associative neocortex. We also propose a model for how pubertal hormones may regulate sensitive period plasticity in associative neocortex. We conclude that the evidence suggests puberty onset may play a causal role in some aspects of associative neocortical development, but that further research that manipulates puberty and measures gonadal hormones is required. We argue that further work of this kind is urgently needed to determine how earlier puberty may negatively impact human health and learning potential.

Keywords

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1. Introduction

An organism's experience interacts with its genetics to significantly impact brain development. For parents, educators, and mental health professionals, it is critical to understand how and when experience maximally impacts childhood brain development in order to improve outcomes from educational and therapeutic interventions by timing them to coincide with periods during which they will have the greatest efficacy.

One particularly important period of development is childhood, which is unusually long in humans. Some hypothesize that this extended period of development evolved to allow children to learn complex foraging skills and adapt to complex social and cultural practices prior to reaching sexual maturity (Bock and Sellen, 2002; Kaplan et al., 2000; Konner, 2010). In modern times, childhood is when most humans learn to speak, read and write, perform arithmetic, and perform numerous other cognitive skills. These high-level skills are thought to rely on the associative neocortex, which, during childhood, may be exceptionally plastic in order to enhance learning capacity and experience dependent sculpting of neural circuits. As childhood ends, we lose the more radical forms of neocortical plasticity and learn in a more conservative manner. We also become more independent while learning new behaviors and skills that aid in the transition to adult life and parental behavior. Here we discuss the evidence that the onset of adolescence may represent a shift in sensitive period for experience dependent plasticity in the neocortex and different forms of associative learning. Given that puberty onset marks the transition from childhood to adolescence, it is a strong candidate in the search for mechanisms regulating developmental transitions in neocortical brain plasticity.

While puberty is a conspicuous biological marker in this transition, it is unclear if gonadal steroids impact neocortical brain plasticity. Correlative evidence ranging from studies of language acquisition to recovery from stroke suggests neocortical neural plasticity and the capacity for some dramatic forms of learning and recovery decrease after the age of puberty onset. However, there is little evidence, either positive or negative, to causally link puberty onset with loss of plasticity. In the present review, we have chosen to focus on studies that examine the associative regions of the neocortex and relate brain or behavioral changes to pubertal status, gonadal steroids, and/or mechanisms that regulate sensitive periods in sensory neocortex. We first review studies of learning, memory, and executive function before covering some of the biological underpinnings that may regulate these effects. Based on the anatomical changes reviewed, we propose a biological model for sensitive period regulation in the associative neocortex inspired by successful models developed for sensory cortices. Overall, we uncover an intriguing array of changes in the neurobiology and function of associative neocortex with inflection points near the ages of pubertal milestones. However, we conclude that more experimental work is needed to fully determine how puberty affects postnatal brain development. Finally, we discuss the urgency of understanding the role of puberty in brain development because the age at puberty onset is advancing in developed nations and early puberty is associated with increased risk for psychopathology and negative behavioral outcomes.

2. Puberty as a life history transition

Life history theory posits that an animal has finite time and resources and thus must selectively allocate these resources toward various evolutionary endpoints, including survival, growth, bodily maintenance, reproduction, and raising offspring (Ellis et al., 2009; Roff, 2002; Stearns, 1992). Evolution has selected for certain species specific life-history patterns that are genetically encoded and hard-wired in the brain, however, many are impacted by experience such that different postnatal experiences may result in alternate life-history strategies. The importance assigned to each behavioral or physiological endpoint varies by age and stage of development (Hochberg and Belsky, 2013). Thus, a successful organism's life history represents a balance between survival at any given stage of development and lifetime inclusive fitness (Konner, 2010). For example, during childhood and adolescence relatively more energy may be allocated toward somatic growth, while in adulthood growth is restricted so that more energy can be allocated toward reproductive ends (Ellis et al., 2009).

Brain development may also reflect the demands of specific life stages (Fig. 1). At different stages of development, animals must emphasize gaining certain knowledge or developing certain cognitive or physical skills. These skills and knowledge structures will be retained, refined, and combined over time for exploitation at later ages (Spear, 2000). Thus, because their basic needs (e.g. nutrition and protection) are provided by their parents, juveniles may allocate their time and energy toward exploring and learning about their natal environment. Numerous lines of evidence suggest that the brain is highly plastic during this period, presumably to first establish basic sensory processing and then build on this base by attaining further information that is most relevant for their life-stage; for example, in humans, natal language is a basic skill acquired in the early environment. Once the basics of the natal environment are established, animals transition toward independence, exploring more broadly to gather new types of information (particularly social and foraging information) that will be important to navigate dispersal, mate selection, and territory establishment (Lynn and Brown, 2009; Spear, 2000). Thus, development is likely studded with a series of sensitive periods in which experience-dependent plasticity in specific circuits, including those in associative regions of neocortex, is timed to coincide with access to important information.

In models of adaptive developmental plasticity, natural selection sculpts sensitivity to cues that predict the future environment and matches behavioral phenotypes to bodily states (Nettle and Bateson, 2015). One of the great challenges for modern neuroscience is to isolate the specific neural circuits and mechanisms that regulate the multiple cognitive and emotional sensitive periods in human development.

The start of puberty, which marks the end of childhood and the onset of adolescence, is a critical life history transition (Ellison et al., 2012). In mammals, independence from parental care and dispersal typically occur during the peripubertal period, but the timing of independence and dispersal varies by species, season, sex, and even individual factors. As such, it is possible that the onset of puberty and/or independence may herald a shift in sensitive periods for experience dependent plasticity. During this period, plasticity attuned to

information from parents or the natal environment may close, while plasticity related to social opportunities and sampling the wider environment may peak (Crone and Dahl, 2012). When adult stability and reproductive status are reached, we may expect brain plasticity to shift to a new mode to fulfill these different needs (Fig. 1). Upon reaching adulthood, the brain may shift again to exploit the skills and knowledge attained across both developmental epochs to successfully survive, compete for mates, reproduce, and raise offspring.

In Figure 1 we present a simplified heuristic model of the duration and timing of different hypothetical sensitive periods matched to life-history stages. Puberty onset is marked as a potential trigger point that causes juvenile plasticity (green line) to decline and enhances plasticity in circuits more appropriate for adolescence (red line). While animals establish mating patterns and are able to care for themselves, adolescent behavioral patterns decline and adult behavioral patterns (blue line) with differential sensitivity and tuning emerge. The causal role of puberty onset as the trigger closing the juvenile period and opening the adolescent period is unknown. Other factors like age, adrenarche, or experience (including feedback from social experience and independent decision making itself), could play a role in this transition. Before we review the evidence, we quickly review the ages of pubertal milestones in humans and experimental rodent models.

3. Comparing pubertal milestones in humans and rodent models

In order to understand if we can meaningfully compare puberty with brain maturation across animals and humans, we must know if pubertal milestones are similar between species and at what ages they are attained. Fortunately, we find comparable milestones that enable us to align development in humans with that of rats and mice (Fig. 2).

Puberty onset in animals, including humans, is initiated by an increase in pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus, which signals the pituitary to release lutenizing hormone and follicle stimulating hormone that mature the gonads and increase production and release of gonadal steroids. The mechanism that determines the age at puberty onset is unknown, but it appears to involve complex changes to regulatory circuits upstream of GnRH neurons, including kisspeptin neurons that stimulate GnRH release (Mayer et al., 2010; Seminara et al., 2003), RFRP-3 neurons that inhibit release (Poling and Kauffman, 2015), and significant roles played by glial regulation of growth factors and GnRH stimulatory molecules (Lomniczi et al., 2013). Once initiated, puberty likely exerts its broad effects on brain and body through the rise in gonadal steroids. In both sexes, circulating gonadal steroids (predominately estradiol and progesterone in girls and testosterone in boys, although both sexes experience rises in all three hormones at puberty) rise across puberty until reaching adult concentrations (Boswell, 2014; Rilling et al., 1996). In girls, the rise in circulating estradiol first manifests externally through the start of breast development (Divall and Radovick, 2008; Marshall and Tanner, 1969), which is followed 1–3 years later by first menses (menarche) (Anderson and Must, 2005; Hansen et al., 1975) and eventual ovulation and regular menstrual cyclicity within another 1–3 years (Boswell, 2014; Divall and Radovick, 2008; Legro et al., 2000). In boys, milestones are more difficult to observe; the first external indicator of puberty onset occurs with testosterone-induced increase in testicular volume along with a change in the color and texture of the scrotal skin

(Marshall and Tanner, 1970; Sørensen et al., 2010). After this, a gradual increase in sexual maturity occurs. Although not tied to the same orderly sequence of binary milestones as in girls, the gradual progression of male pubertal development can still be assessed in a semi-continuous manner, e.g. by Tanner staging (Fig. 2).

The sequence of pubertal milestones is similar in humans and rodents, suggesting that rodents may serve as a valid model for human pubertal development (Fig. 2). In female rodents, the first indicator of the pubertal rise in estradiol is vaginal opening, during which increased circulating estradiol induces apoptosis in cells that form a thin sheath over the vaginal opening (Ito et al., 2014; Rodriguez et al., 1997). This is followed some days later by first estrus and a few days later by onset of regular cyclicity (Nelson et al., 1990). These rodent milestones are regulated by the rise in estradiol, just as the milestones in humans. In males, increased testosterone at puberty induces separation of the prepuce from the glans penis (preputial separation; (Korenbrot et al., 1977) accompanied by increasing testicular volumes and eventual attainment of fertility.

Once gonadal steroids rise in the bloodstream, they can access and act on any cells expressing the cognate receptor. Steroid receptors are distributed widely across the cortex in a number of mammalian species (Almey et al., 2014; Blurton-Jones and Tuszynski, 2002; Finley and Kritzer, 1999; Kritzer, 2004; Kritzer, 2006; López and Wagner, 2009; Zsarnovszky and Belcher, 2001) and can affect cell physiology over the long term by acting as transcription factors to regulate gene expression (Heldring et al., 2007) or rapidly through non-genomic second messenger cascades (Micevych and Dominguez, 2009). The mechanisms by which steroids influence their cortical substrates are numerous, complex, and outside the scope of the present review, but regardless of their mechanism, steroid receptor expression in the cortex provides a clear mechanism by which pubertal steroids may directly influence cortical plasticity at puberty. The ontogeny and distribution of gonadal steroid receptors in the cortex will be discussed in more detail in section 7.

4. Puberty is advancing

Over the last decades, the average age at puberty onset in girls has advanced by multiple years (Aksglaede et al., 2009; Biro et al., 2013; Herman-Giddens, 2006; Rosenfield et al., 2009). The data for boys is less clear but suggest a similar trend of smaller magnitude (Herman-Giddens et al., 2012; Sørensen et al., 2010). In North American boys and girls, earlier maturation is more common in black, Hispanic and low socioeconomic status children (Biro et al., 2010; Biro et al., 2013; Herman-Giddens, 2006; Herman-Giddens et al., 2012). In one study, the mean age of breast budding in black or Hispanic girls occurred at 8.8 and 9.3 years old (respectively) compared to 9.7 in white or Asian girls (Biro et al., 2013). Earlier puberty may be partly caused by increases in food intake and body mass index, but racial differences may also be independent of differences in body mass index (Rosenfield et al., 2009).

It is unknown what is causing this trend of advancing puberty but numerous factors may accelerate puberty in humans and animals including a stressful early environment or absence of a father in the household (Belsky, 2012), early exposure to endocrine disruptors (Meeker,

2012), or childhood obesity (Ahmed et al., 2009). In rodents, injecting leptin (a hormone released by adipose tissue) in juvenile mice advances puberty onset (Chehab et al., 1997), providing a mechanism by which obesity may induce puberty. From a life history theory standpoint, earlier sexual maturation may reflect an adaptive developmental response and distinct life history strategy that maximizes reproductive fitness in a harsh environment (Belsky, 2012).

Regardless of the underlying etiology of advancing puberty, it is clear that puberty onset is associated with enhanced risk for psychopathology and behavior problems, including anxiety and depression, (Deardorff et al., 2007; Deardorff et al., 2013; Ge et al., 1996; Ge et al., 2001; Graber et al., 2004; Graber et al., 2006; Hayward et al., 1997; Silberg et al., 1999), and substance abuse (Graber et al., 1997; Stice et al., 2001). Unfortunately, the relative roles that biology and social factors play in the development of puberty-related psychopathology is difficult to determine from studies in humans (Graber, 2013).

Even if early puberty onset weren't associated with psychopathology, there would be reason for concern. If puberty onset closes sensitive periods in associative neocortex, then advanced puberty onset may truncate the juvenile period of early learning and enhanced plasticity. Further, if this biological limit comes earlier in already disadvantaged groups, then it may enhance disparities in learning and future potential for achievement. For example, it is important to know if reading interventions (or other forms of training) should be timed before puberty onset to ensure that they are effective. We might also consider that other forms of experience or interventions (for example, related to enhancing social development) are best timed to occur after puberty onset to achieve maximal impact.

5. How does the function of associative neocortex change during peripubertal development?

The associative cortices are thought to develop later than sensory cortices (Huttenlocher and Dabholkar, 1997), but it is not well understood if the associative cortices have sensitive periods for plasticity of function equivalent to those found in sensory regions. In this section, we will review evidence that humans and animals experience sensitive periods for skills and behaviors that are likely regulated by associative neocortex. Further, we will review the evidence that puberty affects this plasticity. The following is not an exhaustive review of these many functions but rather a brief overview of evidence suggesting that puberty may be important for regulating these sensitive periods.

5.1 Language learning

In the 1960's, Eric Lenneberg outlined a theory that a sensitive period for language acquisition was closed by the onset of puberty. This argument was based on evidence that children recovered language function after resection of either the cerebral cortex of the right or left hemisphere, but adults undergoing the same procedure experienced aphasia after left but not right hemisphere resection (Lenneberg, 1967). He viewed these data as evidence that puberty crystallized language capacity and prevented interhemispheric transfer of language abilities after left hemisphere damage (Lenneberg, 1967).

A number of studies subsequently measured the age at which acquiring a new language or recovering from trauma to language centers of the brain became impaired. These studies broadly support Lenneberg's hypothesis that peripubertal development is associated with significant decline in language plasticity. Ability to learn a second language begins to decline around the age of normal puberty onset (~9–11 years old), which continues throughout adolescence before leveling off in adulthood (DeKeyser, 2000; Dekeyser et al., 2010; Johnson and Newport, 1989; Newport, 1990); however, some have argued that a second language acquisition, contrary to primary language acquisition, is not subject to sensitive period learning (Hakuta et al., 2003).

There is biological evidence that the location of language centers in the neocortex is highly plastic, but this plasticity is decreased in groups measured at postpubertal ages. In a case study, researchers scanned a child's brain before and after he underwent a left hemispherectomy at 9 years old to control intractable epilepsy. Scans at 7.5 and 10 years old revealed that language function, measured through BOLD signal pattern, had transferred from the left to the right hemisphere, suggesting interhemispheric transference was still possible at the age of 9 (Hertz-Pannier et al., 2002). Another study demonstrated that infants and children exposed to a second language showed overlapping BOLD signal patterns when processing both languages in adulthood, but adults who became fluent in a second language after the first decade of life (mean age 11.2 years old) recruited different neural networks to process their second language (Kim et al., 1997). These data suggest that by the second decade of life, language network plasticity had either declined or entered a different state.

Studies of language-specific learning problems (in which other aspects of intellectual function remain intact) have also identified age 10 as a cutoff point for behavioral plasticity; studies show that complex sensory processing is delayed in subjects diagnosed with dyslexia and other language-specific impairments, but improvements can be observed until age 10. After age 10, improvement stalls and subjects never 'catch up' with typically developing individuals (Wright and Zecker, 2004).

Together, these studies suggest that sometime around 10 years of age, which is around the onset of puberty in boys and girls, we lose juvenile capacity for plasticity in cortical language centers. It is important to recognize that none of these papers measured pubertal milestones or gonadal steroids. Thus, any inferences about puberty's role are based on average age at puberty onset (Fig. 2), which varies substantially between individuals and sexes.

5.2 Birdsong learning

Birdsong learning can be considered an animal model of at least the motor aspects of language learning. Song motor plasticity is reduced after sexual maturation in species that learn one song for life (zebra finches), but in species that learn each season (canaries), plasticity is regulated by seasonal changes in gonadal steroids (Doupe and Kuhl, 1999). In zebra finches, pre-pubertal exposure to testosterone impairs song learning by inducing early song crystallization, consistent with the idea that hormones are sufficient to close a sensitive period of song flexibility (Korsia and Bottjer, 1991). In a parallel finding, gonadectomy combined with androgen receptor blockade during adolescence disrupts the development of

crystallized adult song, suggesting that hormones are necessary for normal song crystallization (Bottjer and Hewer, 1992); however, gonadectomy and androgen receptor blockade in adulthood have no effect on already crystallized song (Bottjer and Hewer, 1992), although androgen receptor blockade enhances and testosterone reduces the capacity for adult song flexibility after nerve injury (Williams et al., 2003). Taken together, data from these songbirds are consistent with the idea that pubertal hormones close sensitive periods for flexible song learning in birds.

5.3 Stroke and recovery

Researchers using rodent models have systematically varied the age at which they induce lesions in the frontal cortex while measuring executive function outcomes in adulthood. Age clearly affects prospects for recovery of executive function after focal injury in rat models; rats recover poorly from lesions made in the first week of life, but lesions made during the second week of life—roughly analogous to the first year of life in humans (Kolb and Cioe, 2000)—often results in full recovery of executive function in adulthood (Kolb, 1987; Kolb and Gibb, 1990; Kolb et al., 1998; Nonneman and Corwin, 1981; Prins and Hovda, 1998). The data are more sparse during the late juvenile to peripubertal period (~P35-P40), but prepubertal rats recover better from lesions than postpubertal rats (Nemati and Kolb, 2010; Nemati and Kolb, 2012). Still, recovery potential from late juvenile lesions is lower than P7–14 rats (Kolb and Nonneman, 1978; Nemati and Kolb, 2012; Prins and Hovda, 1998). These data suggest that recovery capacity peaks during the second week of life before gradually declining across the juvenile period. Recovery potential then becomes adult-like around the onset of puberty. These same series of studies suggest that the heightened recovery from lesions may be conferred from heightened cellular plasticity and regrowth of dendritic arbors and spines (Dallison and Kolb, 2003; Kolb et al., 1996) and that part of the recovery may occur from partial restitution of the damaged brain area rather than solely from transference of function (Dallison and Kolb, 2003).

5.4 Reading, mathematics, and academic performance

Basic reading and mathematics skills are thought to depend on associative neocortex and are typically established in the prepubertal period from age 4–9 (by grade 3) (Blank, 2006; Hernandez, 2011). In the late 90's, The LA Times and Baltimore Sun even supported "Reading by 9" campaigns that chose age 9 as a critical cutoff. It is unclear if age 9 (grade 3) is a cutoff for biological reasons or if there are also important curricular changes at this time, shifting pupils from "learning to read" to "reading to learn"(Wanzek et al., 2010). However, studies of reading interventions for readers behind grade level have found diminishing effects of intervention after age 9 (or grade 3) (Wanzek and Vaughn, 2007; Wanzek and Vaughn, 2013). Prepubertal reading and math skills are also thought to predict later outcomes (Hernandez, 2011; Jordan et al., 2009; Jordan and Levine, 2009). Interestingly, earlier reading interventions are not always better. Interventions for children with special needs showed increases in effect size with increasing age, suggesting a potentially later sensitive period (up to age 12, in a cutoff of a meta-analysis; Kroesbergen and Van Luit, 2003). No study of which we are aware has measured the effects of teaching or interventions before and after puberty to establish if puberty onset regulates sensitivity to teaching or intervention.

Studies have looked at pubertal status and school performance, with an eye toward identifying advantaged and/or vulnerable populations. In 1964, Douglas and Ross at the London School of Economics asked, "is the physical spurt at puberty paralleled by a speeding up of mental development? Do those who come into puberty early do better at school, and if so do they retain their advantage in the secondary schools?" Using data from 5000 subjects from a 1946 cohort of the British National Survey on Health and Development, they found that early maturers of both sexes showed superior performance at age 8, 11 and 15, and this appeared to be independent of social class, which in the post world war II years was a potential proxy for nutritional differences (Douglas and Ross, 1964). More recent studies of academic performance show that earlier maturation is still associated with positive effect for boys in terms of academic performance, but earlier maturation is now associated with worse academic performance in girls (Dubas et al., 1991), while early maturers of both sexes reported lower career training aspirations. Dubas et al. (1991) also find that relative pubertal timing (compared to grade level peers) rather than pubertal status (independent of grade level) drives these effects suggesting that extrinsic social factors play a role in the effects of pubertal maturation on academic performance more than intrinsic biological factors.

5.5 Autobiographical memory

Associative neocortex is thought to be the site of memory storage, and a wealth of evidence suggests autobiographical memory storage changes with age. A series of investigations of autobiographical memories have found that people tend to generate more lasting autobiographical memories from late childhood and teenage period of life than later in life (Janssen et al., 2011; Koppel and Berntsen, 2015)—a phenomenon called the "reminiscence bump." The reminiscence bump was found to peak between ages 6–10 in a recent study that used neutral word cues to elicit memories and had large enough samples to use small age bins (Janssen et al., 2011). Studies that used olfactory cues also place this reminiscence bump at age 6–10 (Chu and Downes, 2000; Willander and Larsson, 2008). Interestingly, studies that use important life events to cue memories find a bump that occurs in later teenage years and into the third decade of life (age 15–28; Koppel and Berntsen, 2015). These data suggest that across development, memories are differentially encoded or encoded in a way that they can be differentially later retrieved (Rubin, 2015). Olfactory-related autobiographical memories are more readily retrieved from the time prior to puberty (Chu and Downes, 2000; Rubin, 2015; Willander and Larsson, 2008), and more general autobiographical memories are retrieved from around the peripubertal period than at later times in life (Janssen et al., 2011). We can speculate that these forms of autobiographical memory may rely more on biological processes related to greater juvenile plasticity (Fig. 1, green curve). In contrast, autobiographical memories related to important life events and life decisions peak after puberty and coincide instead with the time of important stages of early independent decision making (Koppel and Berntsen, 2015; Rubin, 2015). These forms of autobiographical memory may be related to changes in behavior and/or biological processes (Fig. 1, red inverted U curve) associated with independent exploration and the formation of new social bonds during adolescence and early adulthood.

5.6 Executive function

The frontal association cortex is the seat of executive function and continues its development into the third decade of life in humans (Gogtay et al., 2004). Executive function can be divided into sub-domains that include spatial cognition, reasoning, response inhibition, delay discounting, and flexible updating. Together, these processes support cognition and adaptive goal-directed behavior.

Changes to associative neocortex during the transition to adolescence may contribute to the altered executive function observed between juveniles and adolescents. However, subdomains of executive function develop along different trajectories, resulting in a complex pattern of maturation. Here we address how each subdomain changes during the peripubertal period and evaluate the evidence that pubertal hormones affect this development.

5.6.1 Spatial cognition—Spatial cognition includes skills such as mental rotation or perception of embedded figures thought to depend on higher neocortical association areas. Many studies find sex differences in spatial cognition that emerge after puberty. Schulz et al. (2009a) review a number of studies that show higher or lower levels of androgens due to idiopathic hypogonadotropic hypogonadism in men or congenital adrenal hyperplasia in women alters spatial cognition after puberty. Schulz et al. (2009a) suggest developmental changes in spatial cognition may be driven by organizational effects of steroid hormones. Petersen (1983) reviews a number of studies from the 70s-80s that find a decrement in spatial cognition at puberty onset or in earlier maturing children. However, in follow up Petersen (1983) finds null effects of pubertal status and grade (6–8) in a sample of high performing children.

5.6.2 Reasoning and cognitive strategy—Learning rules that guide appropriate behavior in a particular context is critical for successful development and survival. In novel situations, rules must be learned either through explicit instruction or implicitly through trial and error. A recent behavioral study showed that children (age 6–12) and adolescents (age 13–17) excel at learning rules through experience, whereas adults were biased to learn more from explicit instruction (Decker et al., 2015). Ten to eleven year olds are more likely than older adolescents (age 13–14) to use a problem solving strategy that more heavily weights personally experienced recent outcomes (Kokis et al., 2002). Additionally, performance in a feedback learning task increased from age 8–12 before reaching adult levels, but was not explained by pubertal stage, estradiol, or testosterone levels (Peters et al., 2014).

Strategic exploration, which is the purposeful choice to test the outcome of novel experiences during feedback learning, aids in actively determining a particular environment's rules. Measures of exploration and novelty seeking in both humans and rodents increase during adolescence (Spear, 2004; Steinberg et al., 2008). Within a focused sample of girls ranging from 11–13 years, no association was found between age or pubertal development and propensity for strategic exploration (Kayser et al., 2015). Similarly in rodents, there was no relationship between testosterone, estradiol, progesterone, or physical signs of sexual maturation with novelty seeking after controlling for age (Vetter-O'Hagen and Spear, 2012).

5.6.3 Response inhibition—An important aspect of cognitive control is the ability to inhibit prepotent or inappropriate responses. Numerous studies have shown that response inhibition increases from childhood through young adulthood (Bunge et al., 2002; Luna et al., 2004; Marsh et al., 2006; Rubia et al., 2006; Velanova et al., 2008; Williams et al., 1999). One study showed a transient adolescent (age 13–17) decrease in response inhibition relative to children and adults (Somerville et al., 2010), however there are considerable individual differences in performance across studies that may reflect age independent factors.

There are few longitudinal studies that have specifically spanned the peripubertal age range. An accelerated longitudinal design study of antisaccade performance in humans showed that accuracy improved most steeply between ages 10–14, but the authors did not track the pubertal status of participants (Paulsen et al., 2015). Another longitudinal antisaccade study was performed in macaque male monkeys which were tested during the pubertal transition and again as young adults, using morphometric, radiographic, and hormonal measurements to determine pubertal onset (Zhou et al., 2016). Neural recordings in the prefrontal cortex during behavior suggest that adult improvements in performance may be due to increased preparation for an alternate course of action and not due to suppression of the visual stimulus. Increased neural capacity to represent rules of the task and multiple actions may drive age related increases in task performance. A recent study by Tyborowska et al. (2016) was able to further parse the role of testosterone levels in 14 year-old adolescents' ability to avoid impulsive actions in an emotional approach-avoidance task. Higher testosterone levels were associated with greater control over emotional actions and increased recruitment of the anterior prefrontal cortex.

5.6.4 Delay discounting—Living independently requires long term planning and anticipating future events. One laboratory test for these abilities involves asking subjects to choose between a small immediate reward and a larger delayed reward. Decreased subjective value of a reward as the delay increases is called delay discounting. Delay discounting generally decreases between young childhood and adulthood, meaning children tend to choose a smaller immediate reward over a larger delayed reward (Christakou et al., 2011; de Water et al., 2014; Green et al., 1994; Olson et al., 2007; Scheres et al., 2006; Steinberg et al., 2009). However, one study found that 13–17 year olds were more willing to wait for the delayed reward compared to children (aged 6–12) and young adults (aged 18–19; Scheres et al., 2014). Pubertal stage and hormone concentrations were not significantly associated with delay discounting in either boys or girls, but prepubertal children were not included in these studies, so the effect of puberty onset could not be determined (Bromberg et al., 2015; de Water et al., 2014).

5.6.5 Flexible updating—A growing body of studies suggests that flexibility in goal-directed behavior increases during adolescence. The ability to switch between sets of simple stimuli emerges by age 5 (Espy, 1997). More complex forms of switching such as shifting between response sets based on abstract categories become adult-like as early as age 7 (Luciana and Nelson, 2002), with other studies suggesting a plateau at age 10 (Chelune and Baer, 1986; Chevalier et al., 2013; De Luca et al., 2003) or 11–12 (Huizinga et al., 2006; Huizinga and van der Molen, 2007; Somsen, 2007), gradual improvement across the teenage

years (Crone et al., 2006; Crone et al., 2008), or an inverted U in the teenage years (van der Schaaf et al., 2011). Variability in these studies may be related to aspects of study design, including the real-world motivational salience of rewards offered (Nelson et al., 2005; Vrti ka et al., 2014) and the relative amounts of punishment and reward in the task (Cohen et al., 2010; Davidson et al., 2006; van den Bos et al., 2012; van der Schaaf et al., 2011; van Duijvenvoorde et al., 2008). To our knowledge, studies have not directly addressed the relationship between the onset of puberty and behavioral flexibility in humans.

Experimental studies in animal models are well suited to ask how pubertal timing impacts behavioral flexibility because the age of pubertal onset and progression through pubertal milestones can be easily tracked. A challenge for these studies is to find a behavioral task that can be easily trained and tested before the onset of puberty. A digging-based foraging task is a naturalistic method to test behavioral flexibility and is rapidly learned by mice and rats (Birrell and Brown, 2000; Garner et al., 2006; Kim and Ragozzino, 2005). In the version of the task used in our lab, food rewards are buried in one of 4 bowls of scented wood shavings and rodents rapidly learn to forage based on the odor cues (Fig. 4). We observe that pre-pubescent juvenile mice (P26) learn the odor associations more rapidly than adults and that they more quickly update their choice behavior when the reward unexpectedly shifts to a different odor in a reversal phase of the task (Johnson and Wilbrecht, 2011). Behavioral flexibility declines with age and is adult-like after P40, just ~10 days after the onset of puberty in mice (Fig. 4). A similar task in postpubertal rats (but with 2 rather than 4 choices in the task) instead found that older adolescents were less cognitively flexible in reversal and set-shift phases of training than adults, but juveniles were not studied (Newman and McGaughy, 2011). Future studies are needed to test flexibility with greater age resolution and manipulation of puberty to directly understand puberty's role in this cognitive function.

A clear role for pubertal hormones altering executive function has not emerged from the studies reviewed in this section. However, many of these studies did not assess any pubertal measures. Due to the variability in age at pubertal onset, future studies will need to directly assay puberty while including prepubertal subjects. It is also possible that changes in executive function may instead relate to changing experience and accumulation of information, independent of biological effects of puberty. Variation in executive function phenotypes displayed in adolescence and adulthood may also reflect adaptive processes related to cues or resources in the early environment (Nettle and Bateson, 2015). Animal models and experimental manipulations of both experience and puberty will be necessary to untangle the relationships between these variables.

5.7 Effects of stress

Periods of heightened plasticity can be moments of opportunity for growth, learning, and adaptation, or periods of vulnerability, particularly to stressful experiences. Stressors occurring during sensitive periods may have profound effects on development of brain, cognition, and behavior by altering the organization of neural circuits, which in turn may lead to increased risk for psychopathology and negative health outcomes (Gilbert et al., 2009; Heim and Nemeroff, 2001; Sánchez et al., 2001). Further, early life stress can induce early vaginal opening in female rats (Grassi-Oliveira et al., 2016) and may interact with

puberty to exacerbate the rise in psychopathology during early puberty (Fig. 5; Silberg et al., 1999).

Studies assessing the effects of stress during the first weeks of life in rodents indicate that maternal separation or other disruptions to the early environment change neuronal morphology of the frontal cortex (Brenhouse et al., 2013; Bock et al., 2005; Chocyk et al., 2013; Monroy et al., 2010; Muhammad and Kolb, 2011; Yang et al., 2015). These structural changes are accompanied by changes to cognition supported by frontal circuits (Lovic and Fleming, 2004; Thomas et al., 2015; Yang et al., 2015). Interestingly, early life adversity may accelerate brain development (Callaghan et al., 2014; Hostinar and Gunnar, 2013), puberty onset (Belsky et al., 1991; Ellis et al., 1999; Grassi-Oliveira et al., 2016), maturation of fear extinction/recovery behavior (Callaghan and Richardson, 2011), attachment and avoidance learning (Moriceau et al., 2009), reversal learning (Thomas et al., 2015), and maturation of frontal-amygdala connectivity (Gee et al., 2013). This accelerated brain development following early life stress may be an adaptive mechanism that coordinates the development of neural circuits to meet the demands of an adverse environment (Callaghan et al., 2014; Hostinar and Gunnar, 2013).

Heightened responsivity to stress may continue until the period between weaning and mid-puberty in rodents. Some reviews suggest that adolescence, more than early life or adulthood, is a sensitive period for stress-induced programming of the brain (Mccormick et al., 2010), which may contribute to vulnerabilities for developing psychopathologies (Blaustein and Ismail, 2013; Dahl and Gunnar, 2009; Romeo and Mcewen, 2006). Multiple studies indicate that post-weaning social isolation (Powell et al., 2012) leads to reduced dendritic arborization and spine density in frontal cortex (Pascual et al., 2006; Silva-Gómez et al., 2003), changes in cortical dopamine (Novick et al., 2011; Watt et al., 2009; Wright et al., 2008), abnormal activity of pyramidal cells after VTA stimulation (Peters and O'donnell, 2005), and decreased parvalbumin immunoreactivity (Schiavone et al., 2009), which may directly affect plasticity (see section 8). Social isolation from P20–40 in mice disrupts medial PFC function and myelination, but later isolation from P40–60 does not (Makinodan et al., 2012). This may result in stunted social learning from lack of play behavior, which itself peaks between P28-P35 in rats (Meaney and Stewart, 1979; Thor and Holloway, 1984; Vanderschuren et al., 1997).

There is growing evidence that early life stress alters development and perhaps accelerates the development of the brain and body. The onset of puberty may change individuals' needs and expectations as well as sensitivity to different forms of stress, resulting in different responses to stress between juveniles and adolescents. Future studies that manipulate or assay puberty directly will be needed to resolve the causal role of puberty.

5.8 Effects of drugs with abuse potential

In contrast to puberty's likely role in closing a critical period for learning or stress responsivity, puberty may open a period of heightened sensitivity to drugs of abuse (Fig. 1). The peripubertal period is a time of exploration outside the home/nest in both humans and rodents, during which animals learn crucial information about the rewards (e.g. food, social contact, drugs) available in their environment. Given that reward circuitry is also developing

(Benes et al., 1996; Sinclair et al., 2014; Wahlstrom et al., 2010), it is not surprising that animal models of drug abuse reveal unique patterns of drug-related behaviors (Schramm-Sapyta et al., 2009) and heightened sensitivity to the long-term effects of drug exposure during this period (reviewed below). Pubertal hormones influence a variety of drug-related behaviors in animal models (reviewed below and in Kuhn et al., 2010), suggesting that changes in the timing of puberty may influence peripubertal sensitivity to drugs of abuse.

5.8.1 Effects of pubertal hormones on drug-related behaviors—Pubertal hormones affect or correlate with drug-related behaviors in a variety of animal models. For example, p30–50 female rats show higher levels of cocaine self-administration than p30-p50 male rats, with higher levels of estradiol correlating with higher levels of cocaine self-administration in females (Lynch, 2008). In addition, prepubertal (p25) gonadectomy produces opposite effects on cocaine-induced locomotion in adult (p65) male and female rats, suggesting that pubertal hormones play a role in regulating sex-specific responses to cocaine (Parylak et al., 2008). In the case of nicotine, sex differences in self-administration emerge at the time of puberty (p30–45), with females self-administering more than males and high estradiol to progesterone ratios correlating with higher rates of self-administration in females (Lynch, 2009). For ethanol, pre-pubertal (p23) or adult (p70) gonadectomy does not affect intake in adult female rats, though pre-pubertal gonadectomy increases ethanol preference in adult females (Vetter-O'hagen and Spear, 2011). In contrast, gonadectomy at either timepoint increases both ethanol preference and intake in male rats (Vetter-O'hagen and Spear, 2011), and testosterone replacement in adulthood (p77–93) lowers ethanol preference to control levels (Vetter-O'Hagen et al., 2011). In a separate study involving both sucrose and ethanol consumption, pre-pubertal (p20) gonadectomy increased ethanol consumption in adult male rats but decreased consumption in adult females (Sherrill et al., 2011). Thus, although specific patterns of pubertal drug preference and intake differ between drugs, pubertal hormones regulate drug-related behaviors for a variety of drugs of abuse.

Given the strong relationship between pubertal hormones and drug-related behaviors in animal models, changes in the timing of puberty may influence propensity for drug abuse in humans. For example, estradiol's activation of drug preference/intake may occur earlier in girls who experience early puberty. Early drug use is consistently associated with higher risk of developing substance use disorders (Chou and Pickering, 1992; Clark et al., 1998; DeWit et al., 2000; Grant and Dawson, 1998; Hawkins et al., 1997; Lynskey et al., 2003; O'Brien and Anthony, 2005; Prescott and Kendler, 1999; SAMHSA, 2013), suggesting that early puberty may further increase risk of drug abuse in already vulnerable populations due to their average earlier puberty onset (Downing and Bellis, 2009).

5.8.2 Peripubertal sensitivity to drug exposure—While pubertal hormones affect propensity for drug self-administration, the peripubertal period also marks a time of unique vulnerability to the long-term effects of drug exposure in a variety of animal models. For example, peripubertal sensitivity to the long-term effects of nicotine, alcohol, and THC on a variety of adult behaviors is discussed extensively in other reviews (Counotte et al., 2011; Goriounova and Mansvelder, 2012; Lisdahl et al., 2013; Malone et al., 2010; Rubino and Parolaro, 2008; Rubino and Parolaro, 2014; Schneider, 2008; Spear, 2015; Witt, 2010).

While many studies point to ages surrounding puberty as a vulnerable time for the long-term effects of drug exposure, the extent to which this vulnerability is mediated by pubertal hormones remains largely unknown.

Given that the dopamine system changes markedly during the peripubertal period (Kuhn et al., 2010; Sinclair et al., 2014; Wahlstrom et al., 2010), animals may be primed to organize their reward circuitry in a way that is adapted to the specific environmental contingencies they experience during this period of exploration. Drug-related experiences during this period may therefore impact developmental trajectories in a way that is distinct from the same experiences in childhood or adulthood. To the extent that pubertal hormones regulate the development of reward circuitry (Kuhn et al., 2010; Sinclair et al., 2014), changing the timing of puberty may affect the timing of this sensitive period for the long-term effects of drug exposure.

5.8.3 Peripubertal development of the dopamine system: a unique period of reward exploration and vulnerability to drug abuse—Given the well-established role of dopaminergic function in drug- and other reward-related behaviors, peripubertal changes in drug sensitivity are likely related to peripubertal changes in dopaminergic function (Kuhn et al., 2010). The dopamine system that innervates the frontal association cortex changes in complex ways around puberty, with distinct components showing distinct developmental trajectories (Benes et al., 1996; Kuhn et al., 2010; McCutcheon and Marinelli, 2009; Sinclair et al., 2014; Wahlstrom et al., 2010). For example, dopamine neurons in the ventral tegmental area alter their firing rates in an inverted U-shaped curve that peaks shortly after p40 in male rats (McCutcheon and Marinelli, 2009; McCutcheon et al., 2012). Dopamine receptor expression also peaks around the age of puberty, though only for specific receptor subtypes in specific neuronal populations (reviewed in (Wahlstrom et al., 2010)). For example, a greater number of accumbens-projecting PFC neurons express D1 receptors at p44 compared to p27 and p105 in male rats—a pattern that may directly relate to drug-seeking behavior in adolescent (p44) animals (Brenhouse et al., 2008).

Dopaminergic modulation of both interneurons and pyramidal cells in frontal cortex changes abruptly around the age of puberty. For example, parvalbumin positive (PV+) fast spiking and non-fast spiking interneurons in frontal cortex dramatically increase in excitation in response to the D2 agonist quinpirole between p36 and p50, while non fast spiking interneurons increase in their response to a D1 receptor agonist (Tseng and O'donnell, 2007). In PFC pyramidal neurons, co-application of NMDA and D1 receptor agonists induces plateau depolarizations resembling *in vivo* up-states in slices from post-pubertal (p45-p65) but not pre-pubertal (p29-p38) rats (Tseng and O'Donnell, 2005). Dopaminergic modulation of cortical projections to striatum also changes across adolescence, with D2 receptor activation exerting opposite effects on striatal responses to stimulation of cortical inputs in early adolescent (p23–38) compared to adult (p50–63) rats (Benoit-Marand and O'Donnell, 2008). Although it is still unknown whether pubertal hormones are necessary and/or sufficient for these changes in neural responses to dopamine receptor activation, these peripubertal alterations in dopamine modulation may have important implications for adolescent patterns of drug-seeking behavior.

While the role of pubertal hormones in many age-related changes in cortical dopamine function has not been tested, several rodent studies point to effects of pubertal estradiol and testosterone on dopaminergic function (reviewed in Becker, 2009; Kuhn et al., 2010; Sinclair et al., 2014). For example, castration or testosterone injections during mid to late adolescence (p45-p60) alter various markers of dopaminergic function in male rats (Purves-Tyson et al., 2014), though gonadal hormones are not necessary for male-specific peaks in striatal dopamine receptor expression (Andersen et al., 2002). While the stimulatory effects of estradiol on dopaminergic function are well-established for adult female rodents (Kuhn et al., 2010), evidence in pubertal females comes largely from the effects of prepubertal ovariectomy on responses to dopaminergic drugs such as cocaine (reviewed above; Parylak et al., 2008). Thus, although scant, literature on the effects of pubertal hormones on the development of the dopamine system suggests that some aspects of dopaminergic function respond to pubertal increases in circulating gonadal hormones.

We know little about the ontogenetic profiles of steroid receptor expression in the ventral tegmental area, but in adult rodents this area expresses steroid receptors in specific spatial and concentration gradients, including progesterone receptor (Frye et al., 2013; Willing and Wagner, 2016), androgen receptor (Kritzer, 1997; Kritzer and Creutz, 2008) and both estrogen receptor alpha and beta ((Creutz and Kritzer, 2002; Kritzer, 1997; Vanderhorst et al., 2005). Many of these cells also express tyrosine hydroxylase, suggesting they produce dopamine. Further, androgen receptor expressing cells in the frontal cortex project to the VTA (Aubele and Kritzer, 2012), providing the potential for puberty to initiate changes in bidirectional regulation of dopaminergic function. If these receptors are expressed during puberty, the rise in gonadal steroids likely significantly alters dopamine function throughout the brain.

Whether mediated by pubertal hormones or by other factors associated with the transition to independence, adolescent development of the dopamine system may facilitate exploration of rewards available in the environment during this time of newfound autonomy. Peripubertal peaks in dopamine neuron firing and dopamine receptor expression suggest a period of enhanced motivation, reinforcement/reward sensitivity, and peripubertal changes in neuronal responses to dopamine receptor activation may be crucial for developing the cognitive strategies appropriate for late adolescent and adult life stages. Determining the extent to which pubertal hormones mediate these changes in dopaminergic function is critical for understanding the impact of early puberty on behaviors associated with reward, exploration, and drug abuse during adolescence.

6 How does the neurobiology of the associative neocortex change during puberty?

Language, reading, mathematics, autobiographical memory, and executive function are presumably regulated, at least in part, by the plasticity of associative cortex. By examining how the various neural systems in neocortex change during development and at the onset of puberty, we hope to develop insight into the mechanisms regulating shifts in behavior and

associative neocortex function, while gaining insight into the potential negative health outcomes associated with disruptions to normal pubertal development.

6.1 Gray Matter

In humans, there are significant changes in gray matter volume in associative cortices around the time of puberty (Giedd et al., 2006; Peper et al., 2009b; Herting et al., 2015). In general, brain-wide gray matter increases during early childhood and peaks around the onset of puberty (in frontal cortex of boys and girls peak age is 11–12) before declining gradually to adult levels (Gogtay and Thompson, 2010). In frontal and parietal cortex, this peak occurs around 10–11 years of age in girls, while the peak in boys is shifted about one year later (Giedd et al., 1999), which may relate to the tendency for girls to start puberty earlier than boys (Lenroot et al., 2007). When controlling for age, both pubertal hormones and stage of puberty correlate with changes in gray matter across adolescent development in disparate regions of cortex (De Bellis et al., 2001), including in the frontal cortex (Bramen et al., 2011; Gogtay et al., 2004; Herting et al., 2014; Herting et al., 2015; Koolschijn et al., 2014; Neufang et al., 2009; Peper et al., 2009a; Raznahan et al., 2010). For example, in a longitudinal study in which adolescent girls and boys were scanned once during early puberty and a second time during late puberty, there were effects of rate of change in pubertal status and sex in various subregions of the temporal, frontal, and occipital cortices (Herting et al., 2015). Further, changes in salivary estradiol and testosterone across this time interacted with sex to predict cortical thickness changes in some of these regions (Herting et al., 2015). Another previous study also showed that puberty onset was associated with a significant decrease in frontal and parietal gray matter that was not accounted for by age (Peper et al., 2009b). Thus multiple studies strongly suggest that the rise in pubertal steroids is tied to remodeling of gray matter volume across the associative neocortex.

6.2 White Matter

Measures of adolescent reductions in gray matter volume may be reduced as white matter encroaches and changes the ratio between gray and white matter. White matter volume reflects the myelination of long-range bundles of axons, which dramatically increases the speed of neuronal transmission. Postnatal development in humans is associated with a persistent rise in white matter volume across the brain into adulthood in many white matter tracts (Barnea-Goraly, 2005; Lebel et al., 2008). In addition to age, pubertal status and hormone titers significantly interact with sex to affect white matter volume in multiple tracts in the human brain, including those connecting higher association cortices (Asato et al., 2010; Chavarria et al., 2014; De Bellis et al., 2001; Herting et al., 2012; Peper et al., 2008; Perrin et al., 2008; Perrin et al., 2009).

In rodents, frontal white matter is also affected by age and hormones in both sexes (Markham et al., 2007). Frontal white matter increases in volume in a linear fashion in male rats but jumps in females from P25–35 and then again from p45–60, suggesting specific regulation during the peripubertal period (Willing and Juraska, 2015). In rats, gonadectomy results in no change in white matter volume in male rats but does increase white matter volume in female rats in the frontal cortex (Koss et al., 2015). Further, exposure to ovarian

steroids during adolescence reduces the size of the corpus callosum in female rats (Bimonte et al., 2000).

Changes in gray matter and white matter may also reflect changes in the number and composition of cell types and the function of neurons and glia. In animal models and human postmortem tissue, each can be measured directly to better understand which gray matter components are remodeled during puberty.

6.3 Synapses

A portion of gray matter volume is made of small dendritic protrusions called dendritic spines. These are the sites of a vast majority of excitatory synapses onto pyramidal cells in the neocortex (Holtmaat and Svoboda, 2009). In humans, there is a rapid increase in synapse formation just after birth, which reaches a plateau in late childhood before declining during adolescence (Huttenlocher, 1979; Petanjek et al., 2011). In the prefrontal cortex, reduction in global synapse density occurs later than in sensory neocortex and declines at its steepest rate around the time of pubertal milestones (Huttenlocher and Dabholkar, 1997). Synaptophysin and PSD-95, markers of excitatory synapses, reach their peak in human cortex ~age 8 (group consisted of 6–10 year olds, mean age 8.3) before declining to adult levels by 18 years of age (Glantz et al., 2007). This general pattern of development has been replicated in greater temporal and spatial resolution in macaques, mice, and rats. Again, the age range in which pubertal milestones are reached is a time of decline in prefrontal cortex synapse density (Anderson et al., 1995; Bourgeois et al., 1994; Drzewiecki et al., 2016; Gourley et al., 2012; Koss et al., 2014). These correlational data suggest that synapse pruning and pubertal milestones may be co-regulated, but some experimental data suggest otherwise. Castration in a very small sample of male monkeys did not clearly impact the general pattern of synapse density decline in the prefrontal principal sulcus (Anderson et al., 1995); however, there were too few samples to draw strong conclusions.

In addition to pruning synapses, neuronal connectivity in the developing neocortex also undergoes a process of stabilization (Holtmaat et al., 2005). In mice, individual dendritic spines can be followed longitudinally using 2-photon *in vivo* imaging. By repeatedly imaging the same dendritic branch over time, the gains and losses of individual spines can be tracked over many days (Holtmaat et al., 2009). Across the mouse neocortex, rates of spine gain and spine loss (independent of spine density) decrease from peripubertal age (P30) to P60 (Chen et al., 2014; Johnson et al., 2016a; Zuo et al., 2005). Recent evidence suggests regional specificity in this effect. Pattwell et al. (2016) found that dendritic spine formation decreased on pyramidal cells between P30 and P45 in male mice in the medial prefrontal cortex but not the adjacent frontal association cortex. This means juvenile development is characterized by exuberant daily turnover of synaptic structures (Holtmaat et al., 2005; Johnson et al., 2016a; Zuo et al., 2005) that declines during puberty and into adolescence. Daily spine gain and loss in the PFC, sensory, and motor cortices are associated with potential for greater rewiring to support learning and memory (Comeau et al., 2010; Holtmaat et al., 2006; Johnson et al., 2016b; Kasai et al., 2010; Muñoz-Cuevas et al., 2013; Xu et al., 2009; Yang et al., 2010). Lower turnover that comes with age means that neurons come to sample information from fewer potential partners (Stepanyants and Chklovskii,

2005) and exhibit fewer long thin spines that have greater potential to undergo significant Hebbian strengthening (Bourne and Harris, 2007; Kasai et al., 2010). We speculate that greater levels of turnover in the juvenile neocortex allow it to more readily learn or adapt its connectivity to accommodate changing inputs and experience. To our knowledge, there is no published evidence to date that examine the impact of pubertal status or gonadal steroids on *in vivo* spine dynamics.

6.4 Cell bodies and dendritic arbors

Cell bodies and dendritic arbors also contribute to the overall gray matter volume and therefore may contribute to the age and puberty dependent decline in gray matter. In female rats, the number of neurons and glia in the frontal cortex increases early in postnatal development and then declines to adult levels within a ten day period surrounding puberty onset (Willing and Juraska, 2015). This decline can be eliminated by prepubertal ovariectomy, suggesting that pubertal gonadal steroids induce apoptosis of frontal cortex neurons in females (Koss et al., 2015). There is no age related decline in frontal cortex neuron numbers in males, nor does removing the testes before puberty result in any changes to neuron number (Koss et al., 2015; Willing and Juraska, 2015). This effect also holds true for the number of glial cell bodies in the frontal cortex (Koss et al., 2015). Manipulating ovarian hormone availability has no effect on cell number in the frontal cortex in 12 month old rats, suggesting that the frontal cortex is more sensitive to gonadal steroids earlier in life (Chisholm et al., 2012).

Time lapse imaging studies of dendritic tips in frontal cortex show that dendritic branches of pyramidal neurons are largely stable by P25 in male mice (Johnson et al., 2016a). Dendritic arborization of pyramidal neurons in frontal cortex examined by Golgi declines between P35 and P90 in female rats but not male rats (Koss et al., 2014). A similar pattern is observed in certain subtypes of dendrite in the human prefrontal cortex, which decline in arborization starting between ~10–15 years old, though it is unknown if there is a sex difference (Petanjek et al., 2008).

6.5 Inhibitory and Excitatory neurotransmission

There are also significant shifts in the molecular and electrophysiological underpinnings of excitatory and inhibitory neurotransmission in association cortex during peripubertal development. These changes could significantly alter information processing and plasticity in the frontal cortex.

6.5.1. mRNA and protein expression—Data from tissue punches in the frontal cortex suggest that adolescence is associated with shifts in markers of both excitatory and inhibitory transmission.

In rats, AMPA/Kainate receptor binding sites (Insel et al., 1990) and GluR2 protein (Murphy et al., 2012) begin to decline between ~P24-P30 and P60. NMDA receptor expression also changes during peripubertal development. In humans, mRNA and protein expression of the obligatory subunit of the NMDA receptor, NR1, peaks within the frontal cortex in the 11–15 year old age group before declining until age 21–25 (Catts et al., 2013; Henson et al., 2008).

GABA receptors in frontal cortex also demonstrate peripubertal changes that may influence cortical processing and plasticity. In humans, mRNA for GABA receptor subunits (Duncan et al., 2010; Fillman et al., 2010) and markers of inhibitory cell bodies (Fung et al., 2010) change substantially across postnatal development, with some specific subunits and markers showing either positive or negative inflections around 10 years of age.

6.5.2 Pyramidal neurons—Cell type-specific assays offer a more in-depth understanding of the peripubertal development of frontal cortex. While many measures of excitatory transmission in cortical pyramidal cells do not change across adolescence, some measures of inhibition show marked peripubertal changes (reviewed below).

Functional measures of excitatory AMPA and NMDA mediated currents in frontal cortex pyramidal neurons do not change between the juvenile and adolescent periods in macaques or mice (Gonzalez-Burgos et al., 2008; Vandenberg et al., 2015), in contrast to the reduction in dendritic spines observed at these ages (Johnson et al., 2016a; Zuo et al., 2005). Further, NMDA-mediated current does not change across adolescence in layer 5 pyramidal neurons in rat frontal cortex (Wang et al., 2008). It is possible that AMPA-mediated currents change in non-pyramidal cell types or that changes are occurring on distal dendrites that are not detectable in somatic recordings, which could explain differences in conclusions reached between protein measures and excitatory current measures.

In contrast, inhibition onto pyramidal cells increases between juvenile and adolescent/adult groups in both mice and macaques (Delevich, 2014; Gonzalez-Burgos et al., 2015; Vandenberg et al., 2015). In mice, this increase is dependent on signaling through the TrkB receptor (Vandenberg et al., 2015), which is activated by brain derived neurotrophic factor (BDNF), which itself is known to induce maturation of PV+ interneurons (Huang et al., 1999; Rutherford et al., 1997). BDNF signaling in the cortex is modulated by puberty and directly affected by gonadal steroid availability (Hill et al., 2012), suggesting a possible causal mechanistic link between inhibition and puberty.

In another study of macaques, the GABA alpha 2 subunit declined during postnatal development while the GABA alpha 1 subunit increased in the frontal cortex, resulting in a faster decay of inhibitory currents in pyramidal cells after puberty (Hashimoto et al., 2009). Further, the expression of GABA receptor subunits on layer 3 and 5 pyramidal cells in macaque dlPFC changes substantially across postnatal development, with different subunits reaching maximal levels at ages ranging from perinatal to adult (Datta et al., 2015). These data suggest that peripubertal development is more strongly associated with maturation of inhibition, which implicates changes to inhibition as one mechanism underlying peripubertal changes to cortical plasticity and function.

6.5.3 Interneurons—As reviewed above, inhibition onto pyramidal cells changes during adolescence. It appears that PV+ interneurons may be most affected by puberty onset and thus may underlie the changes in inhibition onto pyramidal cells.

In rats, excitatory postsynaptic currents change across puberty in fast spiking PV+ interneurons (Wang and Gao, 2009). This change is mediated by an increase in AMPA

currents onto PV+ interneurons, which, combined with decreased NMDA mediated currents, results in a decreased NMDA/AMPA ratio (Wang and Gao, 2009), suggesting that these neurons are more easily recruited by excitatory input but may be less plastic. Importantly, regular and low threshold spiking interneurons show little modulation of NMDA or AMPA currents with age (Wang and Gao, 2009), suggesting that there is cell type specific regulation of NMDA and AMPA currents during adolescence in frontal cortex. Finally, there is also an increase in calcium-permeable AMPA receptors in adolescent PV+ interneurons in frontal cortex, which is associated with altered short term synaptic plasticity (Wang and Gao, 2010).

In macaque prefrontal cortex, the number of PV+ synapses at the soma increases linearly from early juvenile to adult development (Erickson and Lewis, 2002) while those that cluster on the axon initial segment decrease dramatically (as visualized by parvalbumin immuno-staining) near macaque puberty onset (Anderson et al., 1995). In mice, the intrinsic electrophysiological properties of PV expressing interneurons in the frontal cortex change significantly during prepubertal development (Yang et al., 2012) and into mid adolescence (P45–49; (Cho et al., 2015)).

Together, these data highlight the continuing change in cortical circuit function across postnatal development. The maintenance of excitation coupled with the rise in inhibition demonstrated in frontal cortex likely results in altered excitatory to inhibitory balance within frontal networks, which has been associated with regulation of sensitive period plasticity. This shift in inhibition is likely mediated by PV+ interneurons, which are also thought to regulate sensitive period plasticity in sensory cortex (Davis et al., 2015; de Villers-Sidani et al., 2008; Hensch, 2005; Le Magueresse and Monyer, 2013; Werker and Hensch, 2015), and therefore are attractive candidates for pubertal regulation of association cortex plasticity.

7. Steroid Receptor Expression in the Cortex

In order to understand the role of pubertal hormones in association cortex maturation, it is critical to know which steroid hormone receptors are expressed in what cell types during development.

Androgen receptors (AR) are expressed in the cerebral cortex throughout postnatal development, including in frontal regions (McAbee and DonCarlos, 1998; Nunez et al., 2003). There is relatively little known about the peripubertal development of AR expression in cerebral cortex, but one study suggests that AR is expressed in similar density in juvenile (P21), adolescent (P42), and adult (P63) rat cortex (Monbon et al., 1974). In adults AR is expressed across the cerebral cortex, including associative cortex, in both sexes in rodents (Clancy et al., 1992; Dart et al., 2013; DonCarlos et al., 2006; Feng et al., 2010; Kritzer, 2004; Simerly et al., 1990; Young and Chang, 1998), and humans (Bezdickova et al., 2007; Puy et al., 1995; Sarrieau et al., 1990).

In rodents, the two genes that express distinct estrogen receptors, ER alpha and ER beta, are expressed in neocortex, including the frontal cortex (Shughrue et al., 1990). Their postnatal expression patterns suggest interesting and potentially important roles in ontogeny. In

neonatal rodents, ERalpha is expressed relatively abundantly in neocortex while ERbeta is mostly absent (Perez et al., 2003; Zsarnovszky and Belcher, 2001). Prior to weaning (~P18), ERalpha expression declines precipitously and shortly after ERbeta rises (Prewitt and Wilson, 2007; Wilson et al., 2011; Zsarnovszky and Belcher, 2001), resulting in higher ERbeta expression in neocortex in adults (Kritzer, 2002; Shughrue et al., 1997), which is localized primarily to inhibitory interneurons (Blurton-Jones and Tuszynski, 2002; Kritzer, 2002). In humans, antibody labeling suggests widespread expression of ERalpha in frontal (Montague et al., 2008) and temporal (Gonzalez et al., 2007) neocortex but one mRNA labeling study found low and diffuse expression of ERalpha mRNA in temporal cortex and restricted expression in deep layers of entorhinal cortex (Osterlund et al., 2000). These studies mirror a study in mice that found that while ERalpha mRNA transcript levels decrease through life, protein expression remains stable (Dietrich et al., 2015). Further studies will be required to understand the extent and ontogeny of estrogen receptor expression in humans and animal models.

The ontogeny of PR expression in the neocortex is less clear. It is unambiguously expressed in the rat frontal cortex at birth and rises in both males and females until it peaks during the second week of life, after which it significantly declines and is maintained at lower levels into adulthood (Hagihara et al., 1992; Kato and Onouchi, 1981; Kato and Onouchi, 1983; Kato et al., 1984; Lopez and Wagner, 2009; Shughrue et al., 1991; Shughrue et al., 1992). Females express more PR than males (Kato et al., 1984; Lopez and Wagner, 2009; Shughrue et al., 1991; Wagner et al., 2001), and it is likely only expressed in neurons (Lopez and Wagner, 2009; Hagihara et al., 1992).

It is difficult to infer the precise pattern of PR expression in post-weaning to adult aged animals due to the literature's poor age resolution and a diversity of techniques. However, a general theme in the literature is that PR binding decreases before weaning and is maintained at mid to low levels into adulthood (Kato and Onouchi, 1981; Kato and Onouchi, 1983; Kato et al., 1984; Parsons et al., 1982); this general pattern emerges in mRNA experiments as well (Hagihara et al., 1992; Intlekofer and Petersen, 2011). However, in one study of mRNA from homogenized tissue, differential developmental expression patterns of the two PR isoforms (A and B) was seen. They found that expression of the B isoform peaked at P8 and then declined to basal values before weaning, while the A isoform rose, resulting in total PR expression in the cortex remaining into adulthood (Kato et al., 1993).

Canonically, steroids influence cells by activating their cognate receptors that act as transcription factors to alter gene expression. However, it is important to note that steroids can also signal via non-canonical, non-genomic means, both through the familiar nuclear receptors and through novel receptor signaling. Canonical and non-canonical AR, ER, and PR, are expressed on neuronal membranes and in glial cells(Almey et al., 2014; Brinton et al., 2008; Foradori et al., 2008; Mermelstein and Micevych, 2008; Petersen et al., 2013). AR and both ERs are expressed sparsely in axons and dendrites in the frontal cortex, including on both pre and postsynaptic sites (DonCarlos et al., 2003; Wang et al., 2010) where they may directly alter synaptic signaling.

Unfortunately, data describing developmental changes in the various steroid receptors in cortex during peripubertal development is relatively sparse, particularly in association cortex. Further, we do not fully understand the role these receptors play in cortical physiology. However, the literature is sufficient to reasonably conclude the following: 1. Steroid receptors are expressed widely across the cortex, including association cortex. 2. Cortical expression of these receptors is developmentally regulated, suggesting changing function with development. 3. A complement of steroid receptors are present in association cortex (including frontal areas) during peripubertal/adolescent development. This suggests that the rise in gonadal steroids at puberty can locally influence development of association cortices.

8 Proposed Model

Given the diversity of steroid signaling mechanisms present in association cortex during development, the potential for the rise in gonadal steroids at puberty to alter associative cortex circuit function is strong. However, as we've discussed, very few studies have attempted to causally relate the pubertal rise in gonadal steroids to cortical sensitive period plasticity. We hypothesize that pubertal steroids may influence the timing and/or duration of the juvenile sensitive period in cortical circuits, primarily through their modulation of PV+ inhibitory interneurons. The following model is speculative and simplified, but provides a framework to guide future studies. Our three main lines of evidence (discussed in greater detail below) are: 1) estrogen receptors specifically localize to PV+ interneurons 2) PV+ interneurons regulate sensitive period plasticity in sensory cortices and 3) inhibitory neurotransmission in frontal association cortex increases during puberty.

1. *Estrogen receptors in frontal cortex are specifically localized to PV+ interneurons*: ERbeta, the predominant nuclear estrogen receptor expressed in cortex during puberty and adulthood (Kritzer, 2002; Pérez et al., 2003; Shughrue et al., 1998), is expressed almost exclusively in PV+ interneurons. Across various areas of cortex, including the frontal, parietal, and insular cortices, about 96% of cells that express ERbeta are PV+ interneurons, and this represents between 15–27% of total PV+ interneurons (Blurton-Jones and Tuszynski, 2002; Kritzer, 2002). It is important to note that both males and females show this pattern of estrogen receptor expression (Kritzer, 2002); Testosterone may be converted to estradiol via the aromatase enzyme, which is present in the frontal cortex (Akther et al., 2015; Mitra et al., 2015) or the testosterone metabolite, dihydrotestosterone, may be converted to 3beta-diol, which itself can activate ERbeta (Handa et al., 2008). Thus, the rise in either androgens or estrogens at puberty in both sexes may activate frontal cortex ERbeta where it may act as a transcription factor (Heldring et al., 2007) to alter gene expression that may then regulate the physiological properties of PV+ interneurons and change network inhibition.

2. *PV+ interneurons are implicated in sensitive period plasticity*: Increasing inhibition from PV+ interneurons is implicated in regulating sensitive period plasticity in primary sensory cortices (Davis et al., 2015; Heimel et al., 2011;

Hensch, 2005; Le Magueresse and Monyer, 2013; Werker and Hensch, 2015). In rodents, the age and timing of sensitive periods varies substantially throughout the cortex; in auditory and somatosensory cortex the sensitive period closes prior to the third week of life (de Villers-Sidani et al., 2007; Wen and Barth, 2011) while the sensitive period for ocular dominance plasticity in rodents closes after puberty onset (Gordon and Stryker, 1996). This suggests that the age and timing of sensitive period plasticity varies substantially throughout the cortex, and while mechanisms underlying these sensitive periods are similar, their triggers, and thus timing, vary substantially. In mice, puberty may overlap with the decline in ocular dominance plasticity, but this is not true for many other species, including ferrets (Issa et al., 1999) monkeys (LeVay et al., 1980), and humans (Sengpiel, 2014). Further, early exposure to testosterone in kittens does not close ocular dominance plasticity (Daw et al., 1987). Thus, although frontal and visual cortices may share common sensitive period plasticity mechanisms involving PV + interneurons, we only propose a role for pubertal hormones in regulating sensitive periods in associative neocortex.

3. *Inhibition increases peripubertally in the frontal cortex*: In the frontal association cortex, measures of inhibitory neurotransmission onto pyramidal neurons increases from P21–25 to P40–50 (Vandenberg et al., 2015), and inhibitory current amplitudes increase around puberty in rhesus macaque dlPFC (Gonzalez-Burgos et al., 2015). Given that PV+ axons preferentially target cell bodies (Hu et al., 2014), these increases in inhibition observed in recordings from pyramidal cell bodies may be mediated by GABA release originating from PV+ interneurons. Further, these cells are recruited differently after puberty. AMPA currents increase substantially during early puberty in PV+ interneurons (Wang and Gao, 2009), while the NMDA/AMPA ratio decreases, suggesting that these neurons may be more readily recruited, but less plastic, after puberty onset. In these same cells, activation of D2 receptors enhances excitability, but only after puberty (Tseng and O'donnell, 2007). Collectively, these changes could increase inhibition in association cortex and mediate transient enhancement and developmental reduction of plasticity (Dorrn et al., 2010; Froemke et al., 2007; Gandhi et al., 2008; Hensch, 2005; Southwell et al., 2010) in a manner similar to sensory cortex (Levelt and Hubener, 2012) . Changes in inhibitory neurotransmission of PV+ cells can potentially be explained by genomic alterations within PV+ interneurons themselves, which may feasibly be linked to activation of ERbeta receptors on PV+ interneurons.

Our model is primarily motivated by the fact that gonadal steroids appear at the right place and time to affect cortical sensitive period plasticity and that these cells exhibit the clearest cell specific changes around puberty onset. While steroid receptor expression is sparse in cortex compared to subcortical regions, PV+ interneuron axons branch extensively (Karube, 2004) and provide dense inhibition to nearby pyramidal neurons in cortical circuits (Packer and Yuste, 2011). This means that steroidal modulation of even a small portion of these neurons could exert large effects over the function of neocortex (Fig. 7). In all, this model has yet to be tested, but based on reports of steroid receptor expression we can surmise that

PV+ interneurons are very likely to be affected by the pubertal rise in circulating steroids, which could affect pubertal changes to cortical function.

Further, it is important to note that pubertal changes in frontal cortex physiology likely rely on the complex interaction of the activation of all steroid receptors present in the cortex at puberty, including ER, AR, and PR. It is also important to appreciate that steroid derivatives can act as neuromodulators; progesterone and androgen metabolites, all of which can be synthesized in the brain, are known to regulate such diverse systems as GABA and NMDA neurotransmission, myelination, and neurite growth (Compagnone and Mellon, 2000), many of which are independent of steroid receptor binding.

The role of pubertal hormones on frontal cortex development resists a simple explanation. However, the specific localization of ERbeta on a cell type that is in flux during puberty and regulates circuit plasticity is a strong candidate system by which puberty may affect some of the behavioral and phenomenological effects on plasticity reviewed above.

9 Does early pubertal maturation negatively affect adolescent cognitive and neural development?

Many neural systems shift their developmental trajectories around the time of puberty onset, but only a handful of studies have sought to causally relate the rise in pubertal steroids with these changes to development. Thus, it is impossible to determine how much of a causal role puberty plays in sensitive period plasticity and the development of associative cortex. This lack of knowledge is troubling because age at puberty onset is advancing (reviewed above), and there is reason to believe that early puberty onset may negatively impact brain development and adult outcomes.

Furthermore, the age at puberty onset may titrate the impact of gonadal steroids on brain development. Sisk and colleagues have demonstrated that the juvenile to adolescent transition is a sensitive period for steroid-induced organization of hypothalamic and limbic circuitry that regulates basic motivated behaviors, including sex and aggression (Schulz-Wilson et al., 2002; Schulz et al., 2004; Schulz et al., 2009a). They have proposed that during postnatal development, the brain gradually becomes less sensitive to the organizing effects of circulating steroids, such that earlier puberty may have greater effects on neural circuits than on-time or late puberty (Fig. 8). For example, they found that male hamsters implanted with testosterone earlier than normal puberty expressed stronger sexual behaviors than hamsters exposed to testosterone at the appropriate time (Schulz et al., 2009b). Gonadectomized hamsters implanted with testosterone later than normal puberty also displayed reduced adult sexual behavior. Together, these data suggest that the timing of puberty onset may result in long lasting effects on hormone sensitive neural circuits (Schulz et al., 2009a).

It is unknown if the associative neocortex demonstrates a similar age-related decline in sensitivity to gonadal steroids, but early puberty is associated with increased risk for depression, anxiety, negative self-body image, drug use, and symptoms of eating disorders, conduct disorder, and schizophrenia (Burt, 2006; Copeland et al., 2010; Ge et al., 2003;

Graber et al., 2004; Kaiser and Gruzelier, 1996; Kaiser and Gruzelier, 1999; Obeidallah et al., 2009; Tschann et al., 1994; Whittle et al., 2012; Zehr et al., 2007), suggesting that early exposure to gonadal steroids may affect cortical development differently than on-time exposure. Earlier maturation itself may also be an adaptive developmental response to cues or stress experienced in the early environment (Hostinar and Gunnar, 2013; Thomas et al., 2015)

Language, reading, mathematics, autobiographical memory, and executive function are complex processes resulting from the interactions of a dizzying array of neural systems in association cortex and connected brain regions. If only a portion of their constituent inputs are sensitive to hormones, then advancing puberty may change the timing and magnitude of development while some other non-hormone sensitive neural systems lag behind. Without knowing which systems are hormone sensitive and how the various systems interact, we will be unable to predict how altered pubertal timing affects associative circuit function. Further, if hormones induce larger effects at earlier ages, then hormone sensitive systems may have exaggerated responses compared to non-hormone responsive systems, possibly altering the balance of function in neural circuits for life. Differences of this kind may explain changes in functional phenotype and vulnerability to disease.

10 Conclusion

It is clear from our survey of the literature that 1) there are dramatic changes in the function of the associative neocortex at ages overlapping with pubertal milestones, and 2) these changes are accompanied by neurobiological changes in the associative neocortex itself. Some studies link these processes and changes to pubertal steroids, while others do not find relationships. The large majority of studies, however, do not manipulate puberty or assess pubertal markers. Our survey of the literature suggests PV+ interneurons are a promising candidate mediator of pubertal effects on cortical development based on their expression of steroid receptors, significant changes during peripubertal development, and their established role in regulating sensitive period plasticity in primary sensory cortices.

The onset of puberty in both humans and animal models is extremely variable, so cross-sectional studies grouping subjects by age lack the resolution to identify links with pubertal development. In order to clarify if and how gonadal steroids affect peripubertal cortical maturation, it will be necessary to use animal models to experimentally manipulate exposure to hormones during development. In humans, studies using gonadal steroid assays and tanner stage determination will be critical for linking the myriad peripubertal changes to brain and behavior with puberty onset. Further, increased emphasis on conducting longitudinal studies with collection of somatic, neural, and hormonal measures will allow researchers to much more strongly delineate puberty-dependent from puberty-independent maturation and avoid errors associated with inferring longitudinal developmental profiles from cross-sectional data (Kraemer et al., 2000). With greater investment in both manipulation and measurement of gonadal steroids, we will better understand the unique role that puberty onset plays in adolescent neocortical development. This question is particularly urgent given clear evidence that the age of puberty onset is advancing in

developed nations, and the possible connections between earlier puberty, decreased plasticity, and psychopathology.

Acknowledgments

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Highlights

- Juvenile and adolescent is demarcated by puberty, a major life-history event.

- Puberty may close a sensitive period for enhanced plasticity in associative cortex.

- PV+ interneurons may mediate effect of pubertal hormones on cortical plasticity.
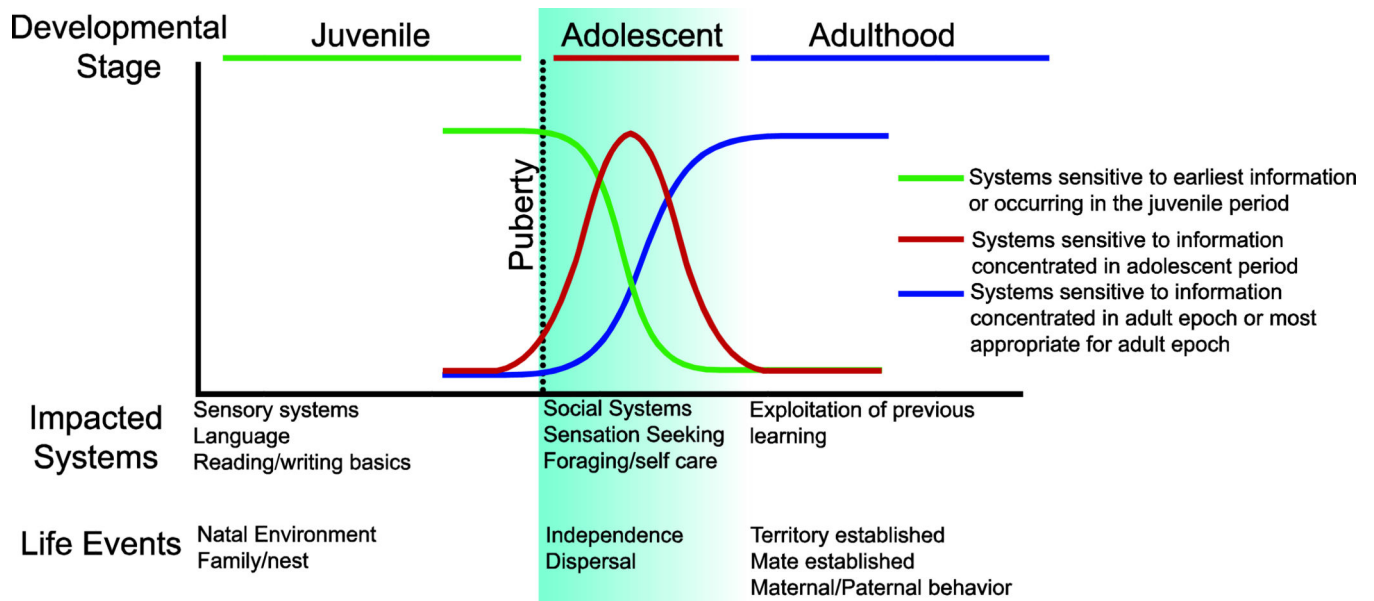
Figure 1.

Heuristic model of three distinct periods of development: juvenile, adolescent and adult. In this model the juvenile period (Green line) is when an animal is developing the foundations of sensory and cognitive/associational architectures in the brain. To facilitate this process they display enhanced experience dependent plasticity, which serves to organize neural circuits to be best adapted to their natal environment. In humans, this period is also when the basic educational foundations are established, like the ability to read and write and produce or understand language. At the start of puberty (dotted line), which marks the onset of adolescence (Red line), independence is exerted, social networks expand, and sensation seeking and the salience of social feedback increases. This period is important for humans and animals to explore their social world and learn how to survive independently. Finally, adolescents transition into adults (blue line) and exploit the knowledge they gained during childhood and adolescence, to successfully survive, mate, maintain territory, and raise young. These characteristic life stages are conserved across mammalian species.
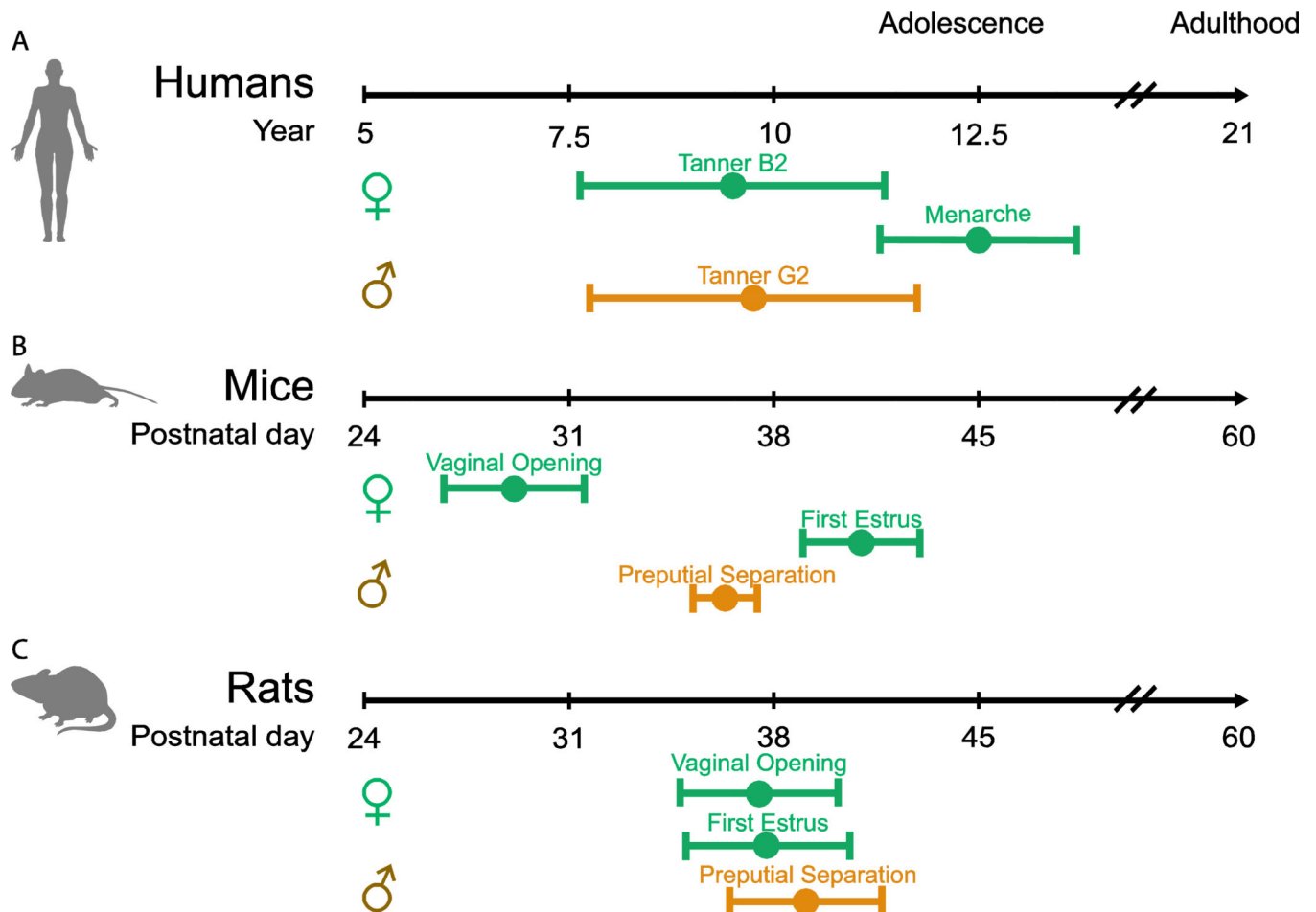
Figure 2.
Humans, mice, and rats experience analogous pubertal milestones. A) In girls (green line)
the first externally observable pubertal milestone is onset of breast development caused by
the pubertal rise in estradiol (Tanner B2; occurring at age 9.5 ± 1.85 SD) which is followed
by first menses (menarche; average age 12.5 ±1.2 SD). In boys puberty onset can be
observed by attainment of testicular volume greater than 3 ml (Tanner G2; 9.75 ± 2.0 SD).
Data for girls reproduced from (Herman-Giddens et al., 1997) and data from boys
reproduced from (Herman-Giddens et al., 2012). B) In mice the female milestones are
similar to humans. In female mice the first externally visible milestone is vaginal opening in
which estradiol causes dissolution of a film of cells covering the vagina (Vaginal opening;
29.125 ± 2.4 SD), which is followed by first estrus, the mouse equivalent of menarche (P41
± 2 SD) (Piekarski and Wilbrecht, unpublished data). Male rodents exhibit the first external
signs of puberty by the separation of the prepuce from the glans penis (Preputial separation;
P36.5 ± 1.1; (Deboer and Li, 2011). C) Finally, both female and male rats display the same
pubertal milestones as mice: Females (Vaginal opening; 37.5 ± 2.7; First Estrus; 37.8 ± 2.7;
(Clark and Price, 1981) and males (Preputial Separation; P36.5 ± 1.1; (Korenbrot et al.,
1977). NOTE: Exact age at pubertal milestones varies by strain and between experiments.
Specific ages are offered to compare progression through puberty as it relates to pubertal
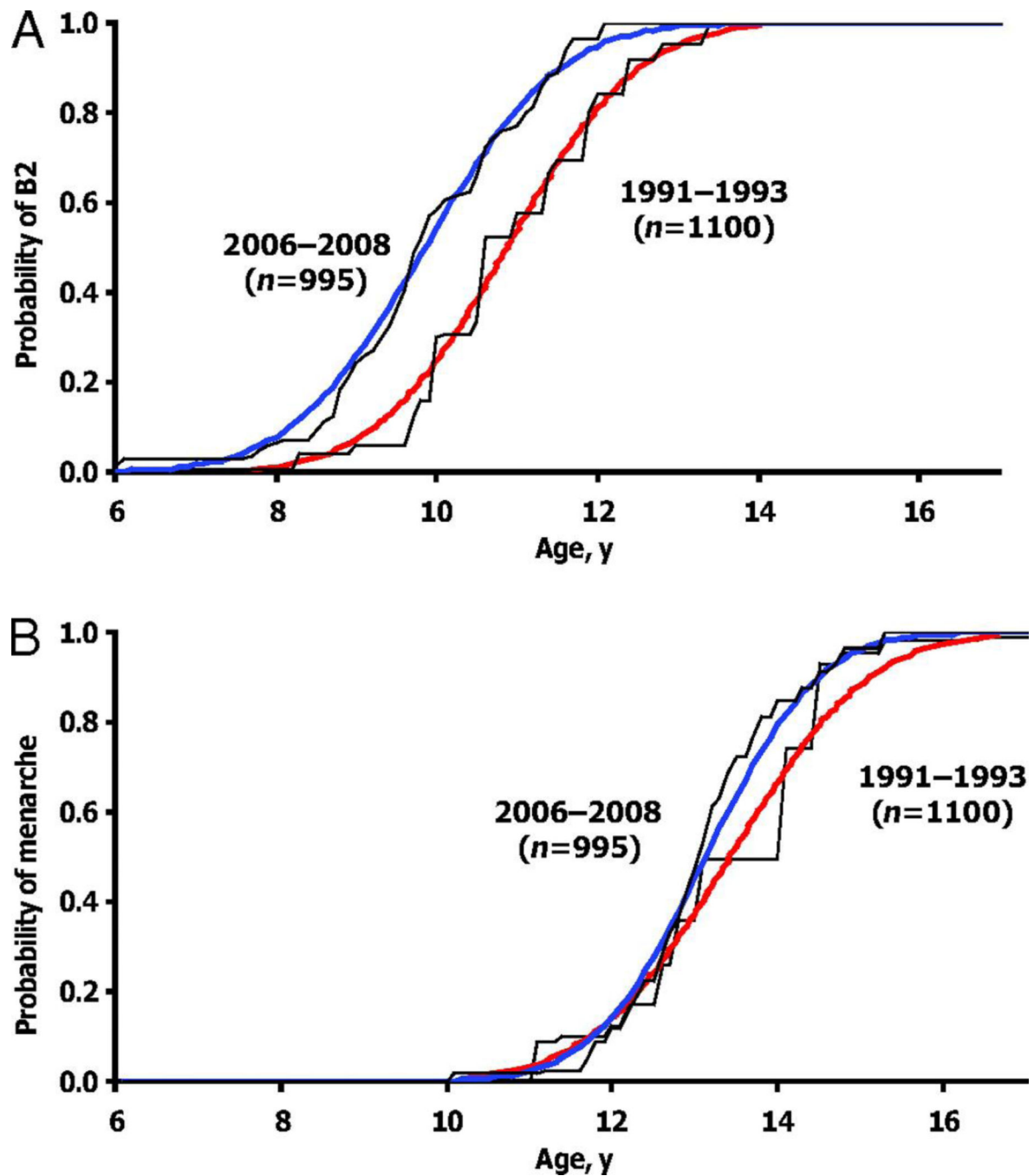milestones in each species and to provide a reference for the data reviewed below.

Figure 3.
Reprinted from Aksglaede et al. (2009) without modifications. Here, onset of breast development (Tanner breast stage 2) and menarche were collected by pediatricians. Mean age at onset of breast development advanced by 1 year (mean age 10.88 vs 9.86) while mean age at menarche advanced by approximately four months (mean ages of 13.42 vs 13.13). These differences remained significant even after adjustment for BMI.
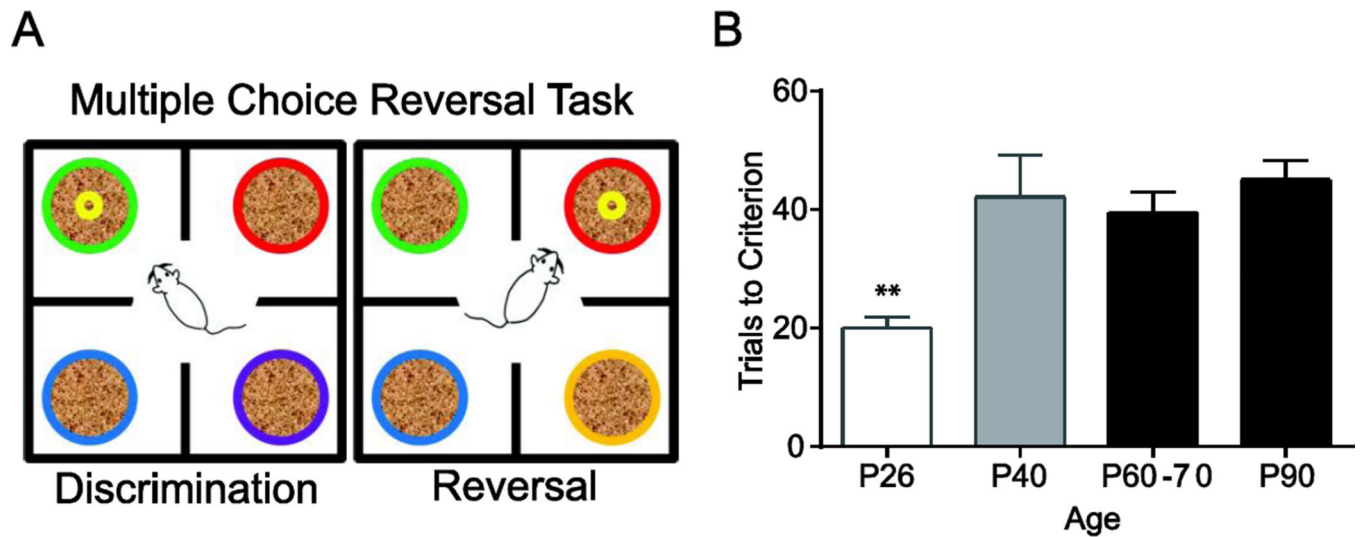
Figure 4.
Age-dependent changes in behavioral flexibility in a multiple choice reversal task. A) A schematic of the task used in our lab (Johnson and Wilbrecht, 2011). Each color represents an odor. Mice are released from a central cylinder to start a trial. In the discrimination phase mice must learn to dig in the correct odor to receive a food reward. After the mouse completes 8 out of 10 correct trials the reversal phase begins in which a previously unpaired scent predicts the food reward. B) Prepubertal (P26) mice make significantly fewer reversal errors (F3,96=12.00; p<0.01) than mid-adolescent mice (P40) or adult mice (P60–90).
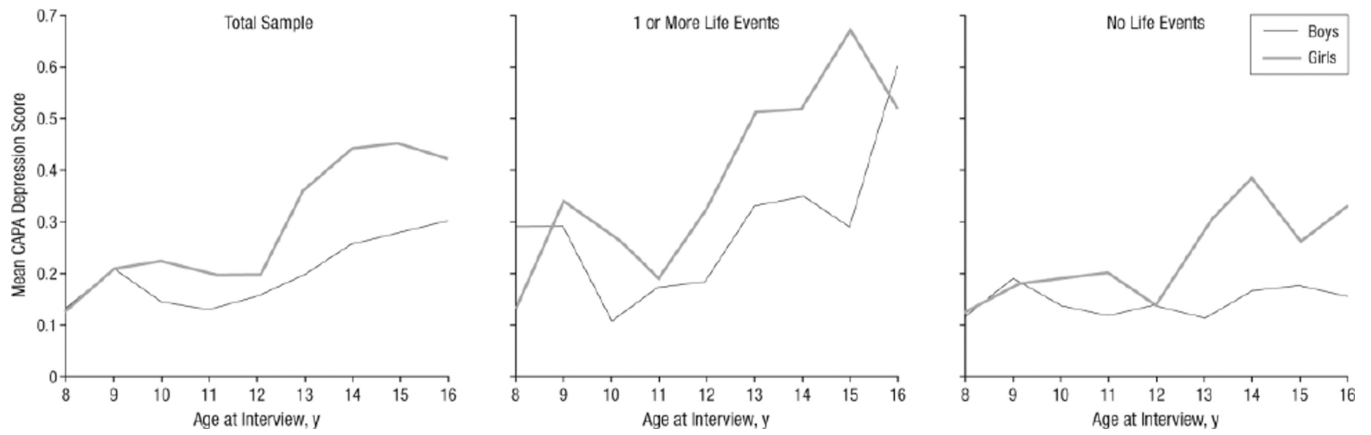
Figure 5.
Reprinted from Silberg et al., 1999 without modifications. Cohorts of 1420 boys and 1700 girls were separated by sex and whether they had experienced a stressful-life even within the past year. They found that one or more stressful life-events was associated with a significant increase in depression score starting at age 11 and that stressful life events impacted girls who had started puberty more than prepubertal girls.
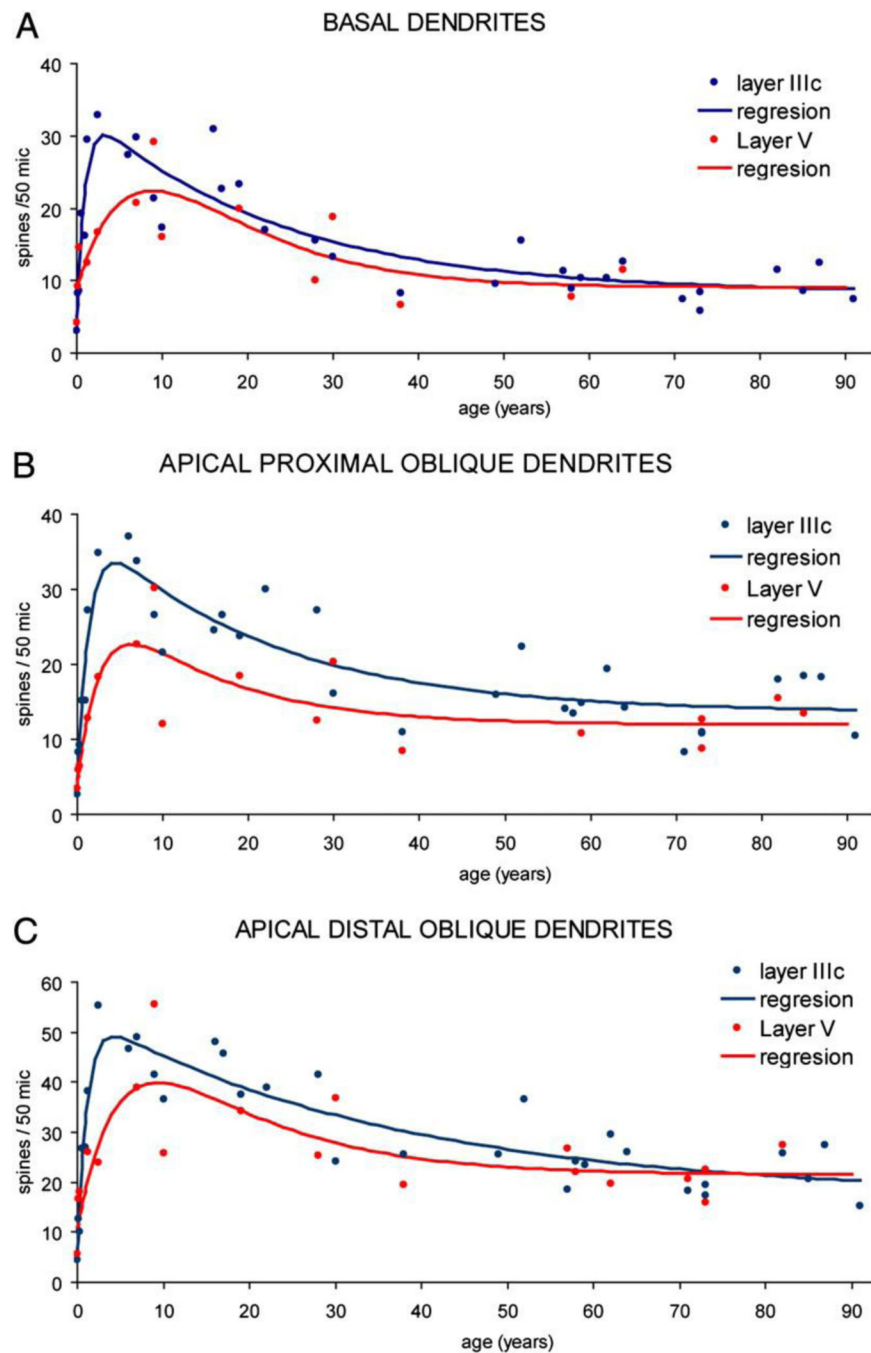
Figure 6.
Reprinted from Petanjek et al., 2011 without modification. These data were collected from human post-mortem samples of dorsolateral prefrontal cortex in both males and females. Dendritic spines on both the basal (Fig 6A) and the proximal (Fig 6B) and distal (Fig 6C) apical dendrites rise steadily throughout the first decade of life in post-mortem samples of human brain before gradually declining in density in the frontal cortex. This decline began at peripubertal age ranges in these mixed sex samples.
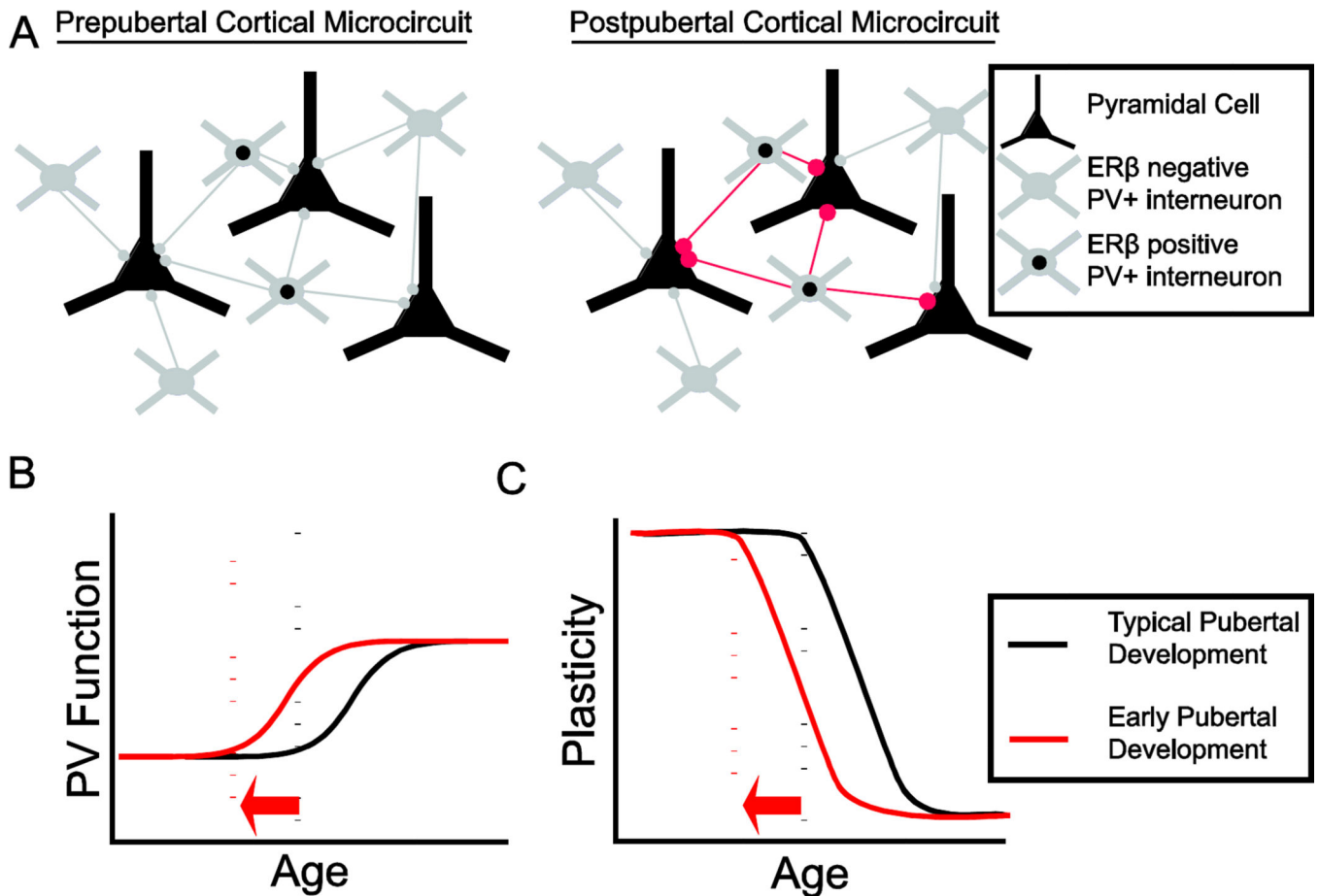
Figure 7.
Model for the mechanism by which pubertal hormones may increase inhibition in the frontal cortex and close the sensitive period. This model is adapted from work conducted in primary sensory cortices implicating PV expressing interneurons in regulation of sensitive period plasticity. A) Before puberty circulating gonadal steroids are low. At puberty onset, circulating gonadal steroids rise, and estradiol (either produced in the ovaries or locally synthesized from circulating testosterone) binds to estrogen receptor beta (ERβ), which is expressed in a subset of PV+ interneurons. Estrogen receptors beta then acts as a transcription factor to increase these cells' inhibitory output (red axons and terminals). Because of their dense connectivity, increased inhibition from a minority of PV+ interneurons could affect all local pyramidal cells. B) In this model, early puberty results in earlier increases in PV function and C) premature closure of juvenile plasticity.
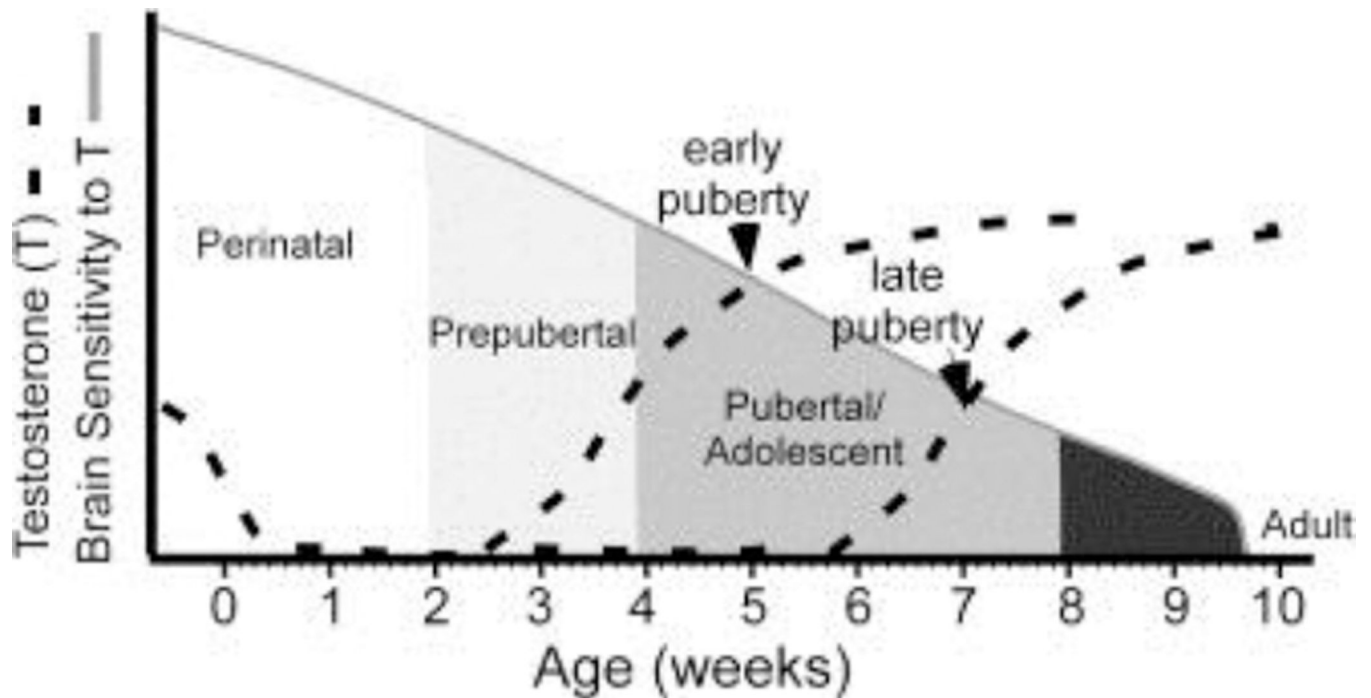
Figure 8.
Reprinted from Schulz et al., 2009 without modification. In this schematic, put forward by Schulz et al., 2009, the brain's sensitivity to the organizing effects of gonadal steroids declines continuously across postnatal development and into adulthood. In this case, altering the age at the pubertal rise in gonadal steroids would alter the extent of organization of neural circuits at puberty. These data are supported by behavioral studies that show sexually dimorphic male behaviors are more strongly expressed in males treated with androgens earlier than typical puberty compared to those treated with androgens later. It is unknown if the same declining sensitivity to hormones manifests in the neocortex, but if it does, early puberty may exaggerate organization of cortical regions sensitive to steroids. This provides a biological mechanism by which early puberty could impact sensitivity to the development of psychopathology or cognitive dysfunction at puberty.