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Author manuscript

*Brain Res.* Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

*Brain Res.* 2017 January 01; 1654(Pt B): 87–94. doi:10.1016/j.brainres.2016.04.012.

## Pubertal onset as a critical transition for neural development and cognition

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### Abstract

Adolescence, broadly defined as the period between childhood and adulthood, is characterized by a variety of neuroanatomical and behavioral changes. In human adolescents, the cerebral cortex, especially the prefrontal cortex, decreases in size while the cortical white matter increases. Puberty appears to be an important factor in both of these changes. However, the white matter continues to grow beyond what is thought to be adolescence, while the grey matter of the cortex stabilizes by young adulthood. The size changes that are the manifestation of cortical reorganization during human adolescence are also seen in cellular reorganization in the rat cortex. The prefrontal cortex loses neurons, dendrites and synapses while myelination in the white matter continues to increase. All of this reorganization is more marked in female rats, and there is evidence both from puberty timing and from removal of the ovaries that puberty plays an important role in initiating these changes in females. The maturation of behavioral functions of the prefrontal cortex, such as inhibitory control, occurs in both humans and rats across adolescence. There is also evidence for puberty as a major factor in decreasing perseveration in rats, but few studies have been done using pubertal status as an experimental variable, and the role of the gonadal steroids in modulating behavior throughout life makes clear effects more difficult to document. In all, puberty appears to be so essential to the changes occurring during adolescence that it should be recorded when possible, especially given the sex difference in pubertal timing.

### Keywords

prefrontal cortex; adolescence; puberty; neuron number; inhibitory control

### Introduction

Adolescence is the period between childhood and adulthood, characterized by neural maturation and changes in a variety of cognitive behaviors in addition to reproductive

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The authors have no conflicts of interest to report.

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behavior. While it is obvious that libido and sexual behavior are set into motion by puberty, it is less apparent that pubertal onset is also involved in the maturation of the cerebral cortex and executive functions that occur during adolescence. It is difficult to establish the role of puberty in these changes in human adolescents where pubertal indices unfold over many years (Marshall and Tanner, 1969; 1970). In addition, specific information regarding pubertal status is often unavailable, especially for autopsy tissue where the cellular underpinnings of the loss of cortical volume can be examined. We will focus on cortical development and work from our laboratory in this review. We will present evidence from both human and animal models that puberty is an important event for many of the neural and behavioral changes that occur during adolescence.

## Neural development during adolescence

### Humans

Several MRI studies have indicated that the human cerebral cortex decreases in size during adolescence (Jernigan et al., 1991; Giedd et al., 1999; Sowell et al., 1999). While this appears to occur across many cortical areas, the prefrontal cortex (PFC) has the most reliably large decrease (Sowell et al., 2003; Gogtay et al., 2004), and this is especially interesting given that behaviors mediated by the PFC in particular undergo maturation during this time (Durstun & Casey, 2006). There was a report that synaptic density in the PFC decreases during adolescence although the number of subjects and ages examined are very small (Huttenlocher, 1979). Still there is some supporting data from macaques (Bourgeois et al, 1994) and through quantification of the synaptic marker, synaptophysin, in the human PFC with Western blots (Glantz et al., 2007). While all of these studies contained both male and female subjects, only Giedd et al. (1999) described different trajectories in cortical maturation between the sexes. Giedd et al. noted the peak of cortical size could be affected by puberty; other investigators did not have the statistical power to draw such inferences.

### Rats

The volume of the medial (m) PFC peaks and decreases across adolescence (Van Eden and Uylings, 1985) in rats as it does in humans, and thus rats have been the subjects for more detailed cellular analyses of neuroanatomical changes in the PFC. Adolescence has been previously defined as postnatal days (P) 28-42 (Spear, 2000). Spear admitted that this definition is arbitrary, and we would argue on the basis of the timing of puberty and its importance for adolescence (the topic of this review) that it be extended beyond P42. This is especially true for male rats where puberty occurs between P40 and P48 (Willing and Juraska, 2015; Korenbrot et al., 1977). Work from our laboratory has found several types of pruning between the adolescent period and adults that vary in degree with sex. Markham et al. (2007) found that the number of neurons decreased between P35 and P90, as did the volume of the mPFC in females. It should be noted that this was the total number of neurons, not just neuron density. The calculation of the number of neurons is the density of neurons, obtained with the optical disector, multiplied by the volume of the mPFC from cytoarchitectonic parcellation. Both sexes lost neurons in the mPFC but females had considerably greater losses than males. Interestingly, the adjacent anterior cingulate showed

no differences in either sex between P35 and P90, indicating that not every cortical area loses cells during adolescence. The large decrease in the number of neurons after P35 in females was further confirmed in Willing and Juraska (2015) where a significant decrease in the number of neurons in the mPFC occurred between P35 and P45 (Figure 1A).

Dendritic pruning has also been found between adolescence and adulthood in layer 5 pyramidal neurons in the mPFC (Koss et al., 2014). Both males and females had a decrease in dendritic spine density between P35 and P90 (Figure 2), and females also lost dendritic branches, indicating an even greater decrease in the total number of dendritic spines. Interestingly, both dendritic spines and the total length of the dendritic tree increased in both sexes between P20 (the juvenile period) and P35. Thus the dendritic capacity is at a peak during adolescence in comparison to both juvenile and adult animals. The loss of synapses was confirmed across the whole mPFC in females through quantification of synaptophysin, a synaptic marker, which decreased between P35 and P45 in females (Drzewiecki et al., 2015; submitted). Changes in afferent and efferent projections between the mPFC and basolateral amygdala (BLA) have also been examined during adolescence in males. The number of neurons projecting from the PFC to the basal amygdala decreases from P45 to P90 in male rats, and concomitantly the number of mPFC axons in the basal amygdala decreases (Cressman et al., 2010). It is not clear whether this is due to neuron pruning during adolescence or to pruning of axon collaterals. This occurs while the number of axons from BLA within the mPFC is increasing from the juvenile period into adulthood without a discernable peak in adolescence (Cunningham et al., 2002).

There are also changes in transmitter levels as well as their receptors during adolescence in the mPFC, but the picture is not yet a coherent one. The investigation of transmitter systems has mainly been done in males, and both NMDA receptor binding (from P28 to <P60) and dopamine receptor (D1 and D2) densities (P40 to P80) were found to be higher in the periadolescent period than in adults in the rat PFC (Insel et al, 1990; Andersen et al, 2000). Additionally, the electrophysiological response to dopamine within the male mPFC changes during adolescence (O'Donnell, 2010) with D2 agonists causing mild inhibition prepubertally (P36) but strong excitation after puberty (P50). Lastly, the GABA receptor also alters its composition during adolescence (Smith, 2013), and this topic will be reviewed elsewhere in this issue (Shen et al., 2016 this issue). Thus the adolescent rat mPFC undergoes considerable cellular reorganization much, but not all of which, is pruning.

In addition to local changes in cortical structure, the white matter carrying cortical afferents and efferents, including the white matter under the PFC, steadily increases during adolescence in humans and in rat models with males showing larger increases than females in both species (Giedd et al., 1999; Perrin et al., 2009; Markham et al., 2007; Willing and Juraska, 2015). The cellular basis for this increase appears to be continuing myelination which is supported by evidence from diffusion tensor imaging of humans (Herting et al., 2012). Electron microscopic quantification of axons in the splenium of the corpus callosum from the visual cortex confirms that the number of myelinated axons increases during adolescence (Figure 3). This occurs in both sexes but more axons are myelinated in males (Kim and Juraska, 1997) while there is no change in axon caliber within a class (myelinated vs unmyelinated). This implies that myelination is the basis for the increases in the size of

all of the cortical white matter. Myelination extends to middle age, albeit at a slower rate, in both humans (Bartzokis et al., 2001; Courchesne et al., 2000) and rats (Nunez et al., 2000; Yates and Juraska, 2007) and is not a unique feature of adolescence.

## Hormonal effects during adolescence

### Hormone receptors

One obvious question is which hormone receptors are present peripubertally in the cerebral cortex, particularly within the mPFC. This very relevant topic has not been directly explored in the existing literature. In the adult human temporal cortex, both males and females have moderate levels estrogen receptor (ER)  $\alpha$  and ER $\beta$  (Gonzalez et al., 2007). It is not known if these receptors are present in the PFC or if they are expressed during the pubertal transition. Like estrogen receptors, androgen receptors (AR) are also expressed in the primate and rat prefrontal cortex in adulthood (Finley & Kritzer, 1999; Aubele & Kritzer, 2012). In adult female rats, Shughrue et al. (1997) found moderate levels of ER $\beta$  in the mPFC. Although it is not known if they appear peripubertally, Westberry and Wilson (2012) found that in mice of both sexes, ER $\alpha$  decreases between P4 and P25 in the mPFC while ER $\beta$  increases. This indicates that ER $\beta$  may play a role in the mPFC during puberty. It also should be noted that progesterone receptors in the mPFC decrease after 10 days of age in rats and reach very low levels by P25 (Willing & Wagner, 2015). Thus while the information is incomplete, ER $\beta$  is the most likely candidate for mediating effects in the rodent mPFC.

### Hormonal effects in humans

In order to understand the mechanisms behind the numerous cellular changes occurring during adolescence, an essential question is whether these changes are directly due to pubertal hormones or simply chronological age, independent of hormonal activity. There are indications that puberty is necessary for many neuroanatomical changes, although the evidence is circumstantial. Puberty is a protracted event in humans that continues for years. It is assessed through Tanner stage (either physical examination or self-report) and hormone levels, each of which has its limitations (see the discussion in Peper et al., 2011 and Herting et al., 2015). The Tanner stages indicate the long term continuation of rising hormones that may direct prolonged alterations in neural organization. These neural changes are difficult to discern except within an individual in longitudinal studies that include the pre-pubertal period. Additionally, hormone levels are not only generally increasing over time but also vary on a daily basis, in addition to the obvious monthly time frame for females. This makes hormone levels even more unreliable as an indicator of pubertal status.

Nonetheless, the studies that have tracked pubertal status have found that it is often an important factor for several measures. The progression in Tanner stages over a 2 year period marked a thinning of portions of the frontal cortex in both males and females (Herting et al., 2015). Tanner stage also predicted decreases in other cortical regions in a sex-specific manner. There were effects of hormone levels but they were less definitive than pubertal status (Herting et al., 2015). Likewise, both increasing levels of testosterone and dehydroepiandrosterone (DHEA), an adrenal androgen, across adolescence are associated with decreasing cortical thickness in both sexes (Nguyen et al., 2013). Taking a different

approach, Raznahan et al. (2010) found that a more efficient androgen receptor allele was associated with more cortical thinning during adolescence in both sexes, even while sex differences persisted in the rate of frontal maturation. The increase in size of both the subcortical white matter in males (Perrin et al., 2009) and the corpus callosum in both males and females (Chavarria et al., 2014) correlated with testosterone levels. Lastly, the rate of cerebral blood flow has been found to vary with self-reported Tanner stage in a sex-dependent fashion (Satterthwaite et al., 2014). In total, these studies indicate that puberty is an important component in the reorganization of the cerebral cortex that can be documented with MRI in humans.

### Hormonal effects in rats

The cellular basis for the effects of puberty can be explored more precisely in rat models since many of the gross size changes found in humans are also seen in rats, such as decreases in cortical volume and increases in white matter volume (Markham et al., 2007). Puberty can be directly prevented by removing the gonads during the juvenile period which preclude puberty, while avoiding the organizational effects of gonadal hormones during early development. Puberty in rats is relatively rapid with clear somatic markers: vaginal opening that coincides with increased luteinizing hormone output in females (Castellano et al., 2011) and preputial separation that marks increased testosterone secretion in males (Korenbrod et al., 1977). Although there are individual and strain differences in the exact day that puberty is reached, we have found that there is virtually no overlap in the range between males and females within a set of litters born in the same season under the same conditions. This helps disentangle the effects of age from those due to puberty and allows for studies in which monitoring of the pre- and post-pubertal period are clearly delineated.

There is considerable evidence that removal of the ovaries before the onset of puberty, usually at P20, stops that pruning within the cortex that occurs in intact females. Ovariectomy (OVX) before puberty resulted in increased numbers of both neurons and glia compared to control females in both the visual cortex and mPFC (Nunez et al., 2002; Koss et al., 2015) (Figure 4). There was no evidence of effects of gonadectomy in males in either of these cortical regions. Pre-pubertal OVX also halted the pruning of dendritic spines in the visual cortex of females (Muñoz-Cueto et al., 1990). Females ovariectomized before puberty had a greater volume of cortical white matter under the frontal cortex than intact controls (Koss et al., 2015), and OVX females had more myelinated axons in the corpus callosum (Yates and Juraska, 2008) which appears to be the basis for the increased volume since there was no change in the number of axons.

The results from tracking puberty have supported the findings with OVX that the rises in ovarian steroids are the primary cause of many neural changes. The number of neurons in the mPFC of intact females decreases between P35 and 45 (Figure 1A), and the average age of puberty in these females was P35 (range P32-38) (Willing and Juraska, 2015). Counts of GABA immunoreactive interneurons indicated that proportionately more non-GABAergic (pyramidal) neurons were lost than GABAergic were lost in these animals between P35 and P45. Neuron number, in general, was stable before and after the pubertal transition. Consistent with the findings of Koss et al. (2015), males had only statistically marginal

decreases across adolescence with no marked change during puberty (average age P45) (Figure 1B).

There were indications of synaptic pruning, visualized with synaptophysin, in both sexes during the pubertal transition in the mPFC, although the data from females was more definitive (Drzewiecki et al., 2015; submitted). Synapse quantification came from the same brains as the neuron counts in Willing and Juraska (2015) and indicates that synapses can be lost without a significant loss of neurons. A different pattern was found in these brains with TH staining of afferent axons. TH is the rate limiting step in dopamine synthesis and the amount of dopamine can covary with TH levels (Masserano and Weiner, 1983). In primates, the upper layers of the PFC show some peripubertal pruning of TH fibers (Rosenberg and Lewis, 1995). This contrast with rats where TH increased in both males and females linearly in the mPFC between P25 and P90 with females showing proportionately more of an increase between P25 and P35 than males (Willing et al., 2015; unpublished data; Susan Andersen, personal communication). This indicates that puberty, although important for cellular reorganization, is not the sole mechanism of neural change during the adolescent period.

## Behavioral changes and hormone effects

### Adolescence

The adolescent period in humans is known to be associated with changes in performance on a variety of tasks, especially those that are PFC-dependent. Notably, cognitive control, defined as situationally appropriate behavioral responses in the face of conflicting ones, improves considerably between the juvenile period and adulthood (see Durston & Casey, 2006 for review). Included within this definition is behavioral inhibition and cognitive flexibility, which coincide with a decrease in perseverative behavior. In humans, performance on tasks measuring cognitive control improves from childhood to adulthood (reviewed in Lourenco & Casey, 2013; Taylor et al., 2013; Davidson et al., 2006; Casey, 2015). In general, these improvements manifest in laboratory tasks as increases in social cognition, concept formation, task-switching, working memory, and the inhibition of inappropriate responses that were formerly rewarded. It is unclear whether these abilities are improving across adolescence without pubertal influence or are either dependent upon or influenced by the neural reorganization of puberty.

Both humans and mice show attenuated fear extinction during adolescence compared to juveniles and to adults (Pattwell et al., 2012). This task, which involves the PFC, is an illustration of the uniqueness of adolescence that goes across species. There are other examples of increased performance on PFC-dependent tasks between adolescence and adulthood in rats. Compared to adults, adolescent rats display a learning deficit on a delayed alternation task and commit a greater number of perseveration errors (Koss et al., 2011). Additionally, across several tasks, adolescent rats are less sensitive to extinction or reward devaluation compared with adults (Sturman et al., 2010; Andrzejewski et al., 2011; Naneix et al., 2012; Hammerslag & Gulley, 2014), suggesting an impairment in impulse control and behavioral inhibition. These studies collectively suggest that in both humans and rats, PFC maturation during adolescence coincides with decreases in perseverative responding and



inhibitory control, functions that are dependent on PFC interactions with other parts of the limbic system such as the basolateral amygdala.

## Puberty

Though not typically examined as an experimental variable, there is some evidence that pubertal status plays a role in behaviors that mature during human adolescence (reviewed in Blakemore et al., 2010). Pubertal onset, in particular, seems to trigger an increase in behavioral responsiveness to emotionally salient stimuli, which is correlated with changes in functional connectivity between the PFC and subcortical limbic regions (Ladouceur, 2012; Klapwijk et al., 2013). Additionally, pubertal status has been shown to acutely affect performance on the PFC-dependent match-to-sample task, where pubertal onset actually induced a transient decrease in performance (McGivern et al., 2002), possibly reflecting ongoing functional changes in PFC anatomy or connectivity. A rise in pubertal testosterone in males has been found to be associated with an increase in mental rotation performance (Vuoksima et al., 2012), which also relies on PFC activity. Lastly in male rhesus macaques, pre-pubertal gonadectomy was associated with increases in pre-pulse inhibition responses (Morris et al., 2010), which is dependent on integrated cortical activity including the PFC.

In rats, it has been widely found that steroid hormones in both males and females contribute to performance on learning and memory tasks (reviewed in Juraska & Rubinow, 2008; Luine, 2008; Frick et al., 2010). However, there is little evidence thus far that puberty itself directly results in developmental changes in cognitive behavior. Evidence for a direct role for pubertal onset in cognition has been particularly difficult to elucidate using certain cognitive tasks given that puberty has been shown to alter learning strategies in spatial memory/navigation paradigms (Kanit et al., 2000; Rodriguez et al., 2013). In a recent study from our laboratory (Willing et al., in press), we used pubertal onset as a factor to explore changes in performance in male and female rats on the water maze and also on a reversal task that assessed cognitive flexibility. Pubertal status did not have an effect on short or long-term spatial memory for the location of an escape platform in the initial training. This is consistent with Schenk (1985) who found that adolescent rats performed at the same level as adults in the water maze task. However, when we moved the location of the platform, pre-pubertal males and females had an increased path length compared to post-pubertal animals (Figure 5). Additionally, during these trials, pre-pubertal rats spent more time in the quadrant of the maze where the platform was originally located, which may be indicative of perseverative behavior, than recently post-pubertal and adult animals. No differences were seen for any measure between recently post-pubertal and adult rats. This subtle yet significant effect of pubertal onset suggests that puberty leads to relatively rapid changes in cognitive behavior that may be linked with the neuroanatomical alterations mediated by puberty. Interestingly, with non PFC-dependent tasks, such as basic conditioning and spatial memory, pre-pubertal animals are not different than adults (Stanton & Freeman, 2000; Raineke et al., 2009; Vorhees et al., 2005; Brown et al., 2005; Wojnusz et al., 2013) and in place avoidance pubertal females are impaired (Shen et al., 2010; Shen et al., 2016 this issue). Future studies examining cognitive behavior during adolescence should account for pubertal status and for the sex difference in the age of pubertal onset, since pubertal status may be at least as important as chronological age.

## Conclusions

There is considerable evidence that puberty is a central event in the reorganization of the cortex, especially the prefrontal cortex, during adolescence in both humans and rats. The evidence for the role of pubertal onset in the maturation of the functions of the cortex is less definitive, given the paucity of studies done where puberty was used as an experimental variable. Still, many types of behavior are influenced by gonadal steroids throughout life, suggesting that puberty could affect neural reorganization as well as the onset of hormonal modulation of behavior. Because these are not easily separable in humans, we suggest more work in rodents is needed to investigate the effects of pubertal onset on the development of higher order behavioral functioning.

## Acknowledgments

The recent unpublished work was supported by NIH MH099625 to JMJ and NIH Training Grant T32 ES007326 currently supports JW.

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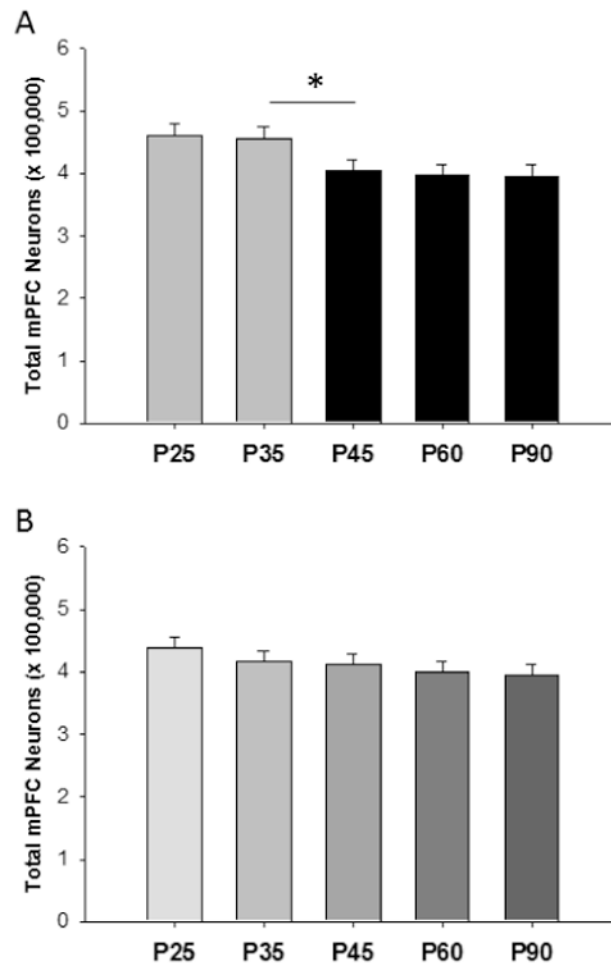
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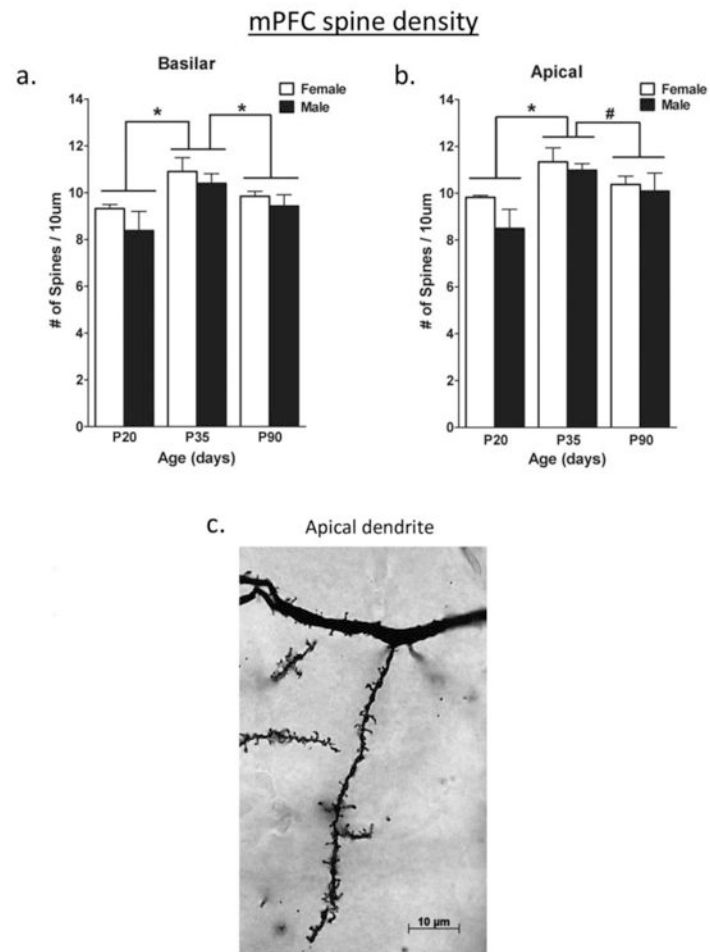
**Highlights**

- Pruning occurs in the prefrontal cortex of adolescent humans and rats
- White matter increases throughout adolescence
- Evidence indicates that pubertal onset affects reorganization in the cortex
- Puberty may also impact the development of inhibitory control
- Documentation of pubertal status is valuable when studying adolescence



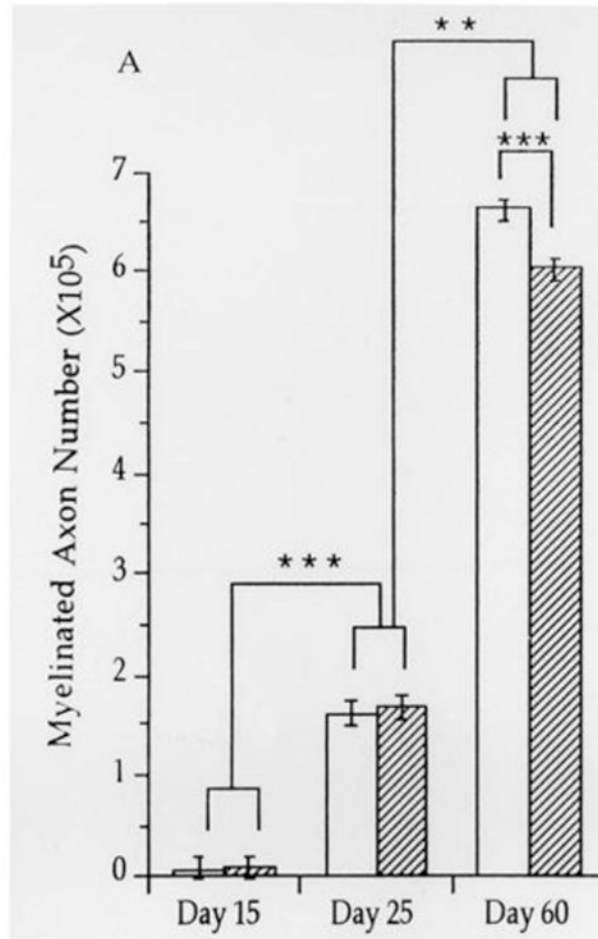
**Figure 1.** The number of neurons in the rat mPFC at postnatal ages that encompass adolescence. (A) Females lost neurons between P35 and P45, and the average age of pubertal onset was P35. \* $p < .05$ . (B) Unlike the females, males only showed a nonsignificant trend ( $p < .08$ ) for age. From Willing and Juraska, 2015.





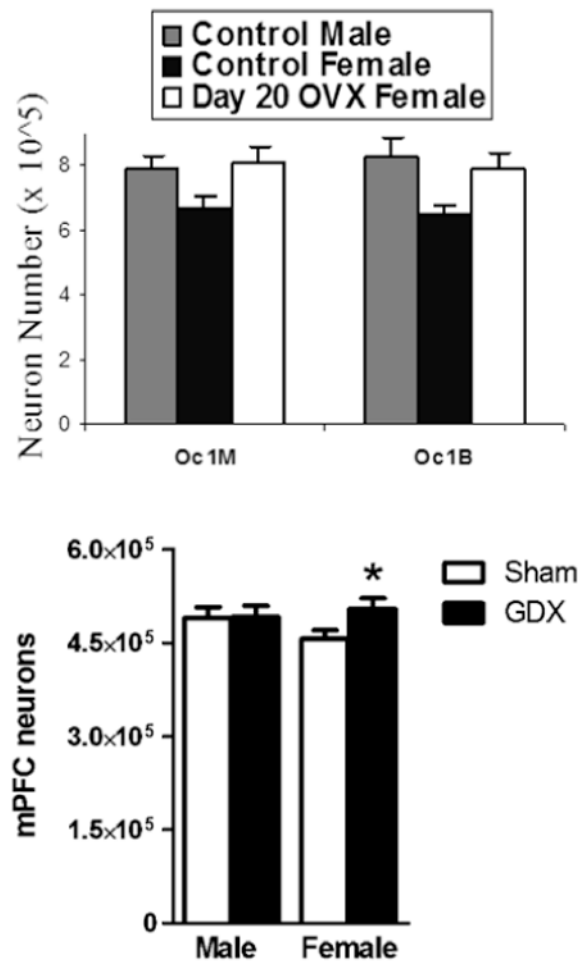
**Figure 2.**

The density of dendritic spines at postnatal ages on layer V pyramidal neurons in the mPFC a) on the basilar dendrites and b) on the apical dendrites. Spines were pruned between P35 and P90. There were no sex differences. c) A photograph of dendritic spines visualized with a Golgi Cox stain. \* $p < .05$ ; # $p < .08$  From Koss et al. (2014).



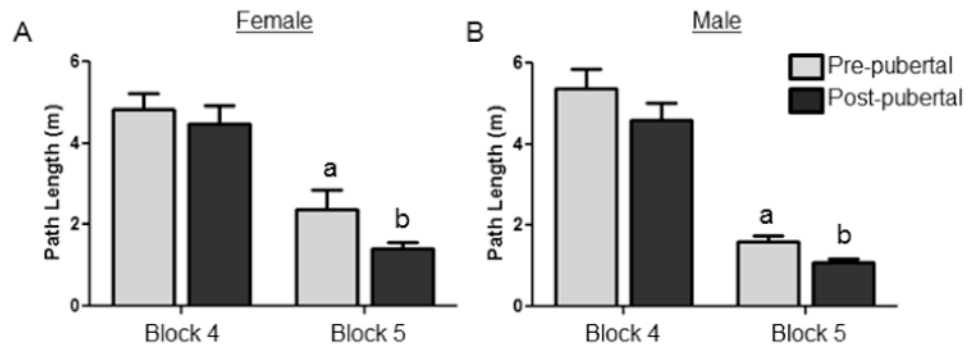
**Figure 3.**

The number of myelinated axons in the splenium of the corpus callosum quantified from electron micrographs. Females are clear bars and males striped bars. \*\*p<.005; \*\*\*p<.0005 From Kim and Juraska, 1997.



**Figure 4.**

a) The number of neurons in the two subdivisions of the rat primary visual cortex (Oc1M and Oc1B) in adult rats. The control females had significantly ( $p < .05$ ) fewer neurons in both divisions than control males and day 20 OVX females. Modified from Nunez et al., 2002. b) The number of neurons in the mPFC in adult rats. Gonadectomy (GDX) had occurred at P20. \* $p < .05$  From Koss et al., 2015.



**Figure 5.** Path length to reach the novel platform location in the Morris water maze. Path length was significantly lower in post-pubertal males and females in comparison to prepubertal after the location of an escape platform was moved. a>b p<03 Modified from Willing et al., in press.