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BRIEF COMMUNICATION

A Role for Puberty in Water Maze Performance in Male and Female Rats

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Adolescence is characterized by neuroanatomical changes that coincide with increased cognitive performance. This developmental period is particularly important for the medial prefrontal cortex (mPFC), which mediates higher-order cognitive functioning. The authors' laboratory has shown that puberty is associated with sex-specific changes in neuron number and the dendritic tree in the rat mPFC, but the effects of pubertal onset on cognitive performance remain relatively unexplored. Here, we use a water maze task to assess spatial memory for the location of an escape platform, followed by a test of reversal learning, when the platform is moved to an alternate quadrant in the maze. For both males and females, 2 groups of prepubertal animals were tested (postnatal day [P]30 and P33 for females, P40 and P43 for males), along with 1 group of newly (2 days) postpubertal animals and 1 group of young adults (P60). There were no group differences in learning the initial location of the platform or when the platform location changed, although grouping pre- and postpubertal ages did result in significantly better performance in postpubertal animals. In addition after the platform location changed, individual prepubertal males and females spent a significantly greater percentage of time in the quadrant of the maze where the platform was formerly located than the postpubertal animals. This collectively implies that pubertal onset in both males and females coincides with improved performance on a reversal task, which may be linked with the neuroanatomical changes occurring in the mPFC during this time.

Keywords: adolescence, cognitive flexibility, prefrontal cortex, sex differences

Human adolescence is a period characterized by a variety of neuroanatomical changes that are accompanied by the maturation of many cognitive functions (Casey, Giedd, & Thomas, 2000; Steinberg, 2005; Varlinskaya, Vetter-O'Hagen, & Spear, 2013). Rodent studies also show increases in cognitive performance between adolescence and adulthood, particularly on tasks that use the prefrontal cortex (PFC) (Sturman, Mandell, & Moghaddam, 2010; Koss, Franklin, & Juraska, 2011; Andrzejewski et al., 2011; Naneix, Marchand, Di Scala, Pape, & Coutureau, 2012). The PFC is primarily involved in executive function and emotional regulation, and adolescence is a critical period of development for this region. The onset of puberty, which is associated with increases in circulation of steroid hormones, may play a role in PFC maturation and subsequent increases in cognitive performance in a sex-specific manner.

Several studies imply a direct role for pubertal onset in the development of the PFC. In human subjects, pubertal increases in estradiol levels in females are associated with decreased PFC gray matter density, whereas increases in testosterone in males have no such effect (Peper et al., 2009). Likewise, female rats lose neurons in the medial prefrontal cortex (mPFC) between Postnatal Day (P)35 and P45 (Willing & Juraska, 2015), which corresponds with the pubertal period in females. Interestingly, this neuronal loss is prevented following ovariectomy during the juvenile period (Koss, Lloyd, Sadowski, Wise, & Juraska, 2015), suggesting that pubertal ovarian hormones play a role in this phenomenon. Between P35 and P90, both males and females lose dendritic spines on mPFC pyramidal neurons, and there is pruning of basilar dendrites in females (Koss, Belden, Hristov, & Juraska, 2014). In addition, there is evidence that synaptic pruning in the mPFC may be directly related to pubertal onset in both males and females (Drzewiecki, Willing, & Juraska, 2015). These studies collectively suggest sex-specific effects of puberty on distinct cellular facets of PFC development.

Although there is a paucity of research exploring a direct role for puberty in the development of cognitive ability, there is evidence that steroid hormones affect performance on learning tasks. The role of gonadal steroids in cognitive performance of adults has been well-documented in human and animal models (Frick, Fernandez, & Harburger, 2010; Juraska & Rubinow, 2008). Estradiol

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can act locally in the PFC to affect performance on PFC-mediated tasks (Uba, Rummel, Floresco, & Galea, 2012; Almey et al., 2015), and female rats treated with estradiol prior to puberty performed better than controls on a Morris water maze task during adolescence (Wartman, Keeley, & Holahan, 2012). There is also evidence for changes in cognitive strategies between pre- and postpubertal rats, particularly on tasks involving spatial navigation (Kanit et al., 2000; Rodriguez, Chamizo, & Mackintosh, 2013), yet a direct role for pubertal onset in changes in cognition has not been described. Although the mPFC is less involved in tasks requiring spatial learning and memory than other neural regions, mPFC lesions have been shown to negatively impact performance on reversal components of spatial tasks (de Bruin et al., 1994; Lacroix, White, & Feldon, 2002). Here, we use an adapted Morris water maze task to compare both spatial memory and reversal learning in prepubertal, recently postpubertal and young adult male and female rats.

Methods

Animals

Subjects were the offspring of Long-Evans hooded rats obtained from Harlan Laboratories (Indianapolis, IN) and bred in the vivarium in the Psychology Department at the University of Illinois. All animals were weaned on P24 and housed with same-sex littermates in pairs or triplets before and during behavioral testing. Both age and pubertal onset were determined to delineate experimental groups. Vaginal opening was used as a marker for puberty in females, as this coincides with surges of estrogen and luteinizing hormone (Castellano et al., 2011). Preputial separation was used for determining puberty in males, since this coincides with a surge in androgen secretion (Korenbrot, Huhtaniemi, & Weiner, 1977). For each sex, four groups were run based on age and pubertal status. For female groups ($n = 10$ per group), testing started on P30 (prepubertal), P33 (prepubertal), 2 days after pubertal onset (postpubertal) or at P60 (young adults). For males ($n = 9$ per group), testing began on P40 and P43 for the two prepubertal groups, or two days after pubertal onset or at P60. All groups were equally counterbalanced across litters, with one animal from each litter being assigned to each group. All animals were kept on a 12:12-h light–dark cycle with ad libitum access to food and water. All procedures were approved by the University of Illinois Institutional Care and Use Committee and adhere to the National Institute of Health guidelines on the ethical use of animals.

Experimental Procedures

Pretraining. The first day of testing, termed *pretraining*, was conducted in a different room than the testing procedures. The pretraining maze was a wading pool 122 cm in diameter with a 36 cm depth. The water was kept clear and maintained at 26°C. A visible escape platform was placed in the maze, and each animal underwent four trials in which the latency to reach the platform was recorded. If the subject did not reach the platform within 60 s, they were manually placed on it for a period of 10 s. In between trials, animals were placed into a holding cage with a dry towel for one minute.

Testing. Testing commenced 24 hr after pretraining. Procedures for this adapted water maze test were adopted from Karatsoreos, Bhagat, Bloss, Morrison, and McEwen (2011) to assess both spatial memory and cognitive flexibility in rodents. Testing was conducted in a plastic tank (175 cm in diameter, 74 cm deep) filled with water (26°C) made opaque with nontoxic white tempera paint. An escape platform (10 square cm) was placed 2 cm below the water level. All trials were recorded using ANY-maze behavior-tracking software (Stoelting, Wood Dale, IL). Using this software, the maze was divided into four equal quadrants (A–D).

The task consisted of five trial "blocks" (four trials per block) that occurred over two consecutive days. Blocks 1 and 2 took place on the first day and were separated by a 20-min interval. Blocks 3, 4, and 5 took place on the second day and were also separated by 20 min each. For Blocks 1–3, the escape platform was in the same location. In Blocks 4 and 5, the location of the platform changed to an alternate quadrant of the maze. Both the initial and novel locations for the escape platform were kept uniform for all animals. In each trial, the distance traveled (path length) and the latency to reach the platform was recorded with a maximum latency of 60 s. Animals were led to the platform if it was not found in 60 s. Intertrial intervals within the block were 1 min. Path length and latency to the platform on Blocks 1–3 assesses spatial memory. These measures in Blocks 4 and 5 test reversal learning, the ability to learn the position of the new platform location while inhibiting the tendency to revert back to the first location of the platform. Within each animal, path lengths were averaged for each block. In addition, to analyze individual trials that vary in distance between the start point and platform, ANY-maze software was used to calculate an efficiency score for each trial (distance between the starting point and the escape platform divided by the actual distance swam). This measure is similar, but not identical, to that used by Gallagher, Burwell, & Burchinal (2015). Lastly, the percentage of time spent in each of the four quadrants of the maze was scored during the trials in Block 5.

Statistical Analyses

Differences in the path length to the platform across blocks were analyzed for each sex using two-way repeated measures analysis of variance (ANOVA; Age × Block), with litter used as a cofactor. Separate repeated measures ANOVAs were run for Blocks 1–3 and for Blocks 4–5. A one-way ANOVA was conducted for the percentage of time spent in the original quadrant for Block 5 as an indicator of perseveration. Latency to reach the platform and average swim speed were also analyzed. At the request of a reviewer, groups of pre- and postpubertal animals were pooled for a secondary analysis for measures of efficiency score for Blocks 4 and 5, with a higher efficiency score reflecting greater performance. Because of differences in the timing of puberty, males and females were analyzed separately for all ANOVAs.

Results

Initial Platform Location

Pubertal status did not affect performance on spatial memory for the initial location of the escape platform (see Figure 1). There were no effects of age on path length, latency, and swim speed for

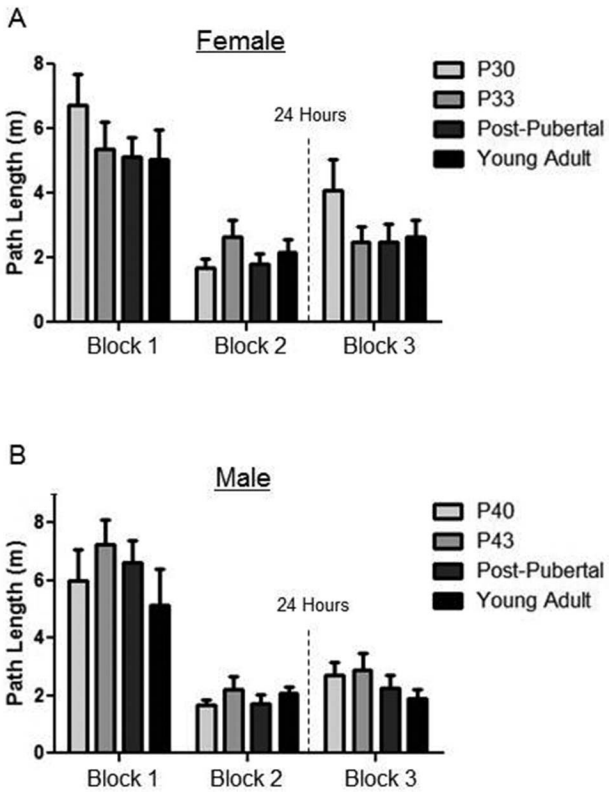

Figure 1. Age/pubertal status had no effect on learning the location of an escape platform in males or females. There was a significant effect of trial block on path length to reach the escape platform in its initial location in (A) females and (B) males ($p < .001$). Post hoc tests revealed a difference between the first and second trial blocks ($p < .001$), but not between trial Blocks 2 and 3 in either sex.

both males and females in Blocks 1–3, nor were there any significant interactions. The repeated measure for block was significant for path length, $F(2, 107) = 11.89$, $p < .001$, and latency, $F(2, 107) = 11.36$, $p < .001$, in males, as well as path length, $F(2, 119) = 10.36$, $p < .001$), and latency, $F(2, 119) = 12.27$, $p < .001$, in females.

New Platform Location

In Blocks 4–5, there was another main effect of block on path length in both females (Figure 2A), $F(1, 79) = 8.22$, $p < .001$, and males (Figure 2C), $F(1, 71) = 18.27$, $p < .001$. There was also an effect of block on latency in males, $F(1, 71) = 23.13$, $p < .001$, and females, $F(1, 79) = 4.59$, $p = .008$, but there was no significant effect of age in either males, $F(3, 71) = 1.71$, $p = .183$, or females, $F(3, 79) = 1.23$, $p = .313$ (Figure 2A and 2C). There were no significant interactions between block and age for any measure of path length for the initial and new location. Similarly, there was no effect of age/pubertal status on latency to reach the platform or Blocks 4–5.

When an individual trial analysis was run with pre- and postpubertal ages pooled for the changed platform location (Trials 13–20), females (Figure 2B) had a main effect of pubertal status on efficiency score, $F(1, 304) = 3.98$, $p = .039$; an effect of trial, $F(7, 304) = 21.23$, $p < .001$; and no significant interaction, $F(7, 304) = 0.44$, $p = .880$). In males (Figure 2D), there was a significant effect of pubertal status, $F(1, 272) = 6.19$, $p = .013$; a main effect of trial, $F(7, 272) = 30.42$, $p < .001$; and no interaction, $F(7, 272) = 0.91$, $p = .492$.

Analysis of the percentage of time spent in the former quadrant location during Block 5 showed an effect of age in females, $F(3, 39) = 3.26$, $p = .033$, and males, $F(3, 35) = 3.38$, $p = .031$; Figure 3A and 3D). Post hoc comparisons (Fisher's LSD) between individual groups revealed that both prepubertal males and prepubertal females spent a greater amount of time in this quadrant than their postpubertal and young adult counterparts ($p < .05$). There was no effect of age on percentage of time spent in the novel quadrant in females ($p = .17$; mean/*SEM*; P30: 43.5/2.9, P33: 38.5/2.7, postpubertal: 44.9/2.2, young adult: 41.2/2.7) or males ($p = .64$; mean/*SEM*; P40: 42.3/2.7, P43: 42.1/2.5, postpubertal: 45.8/1.6, young adult: 41.8/3.1). There were also no differences between ages on the percentage of time spent in the other two quadrants in females ($p = .27$; mean/ *SEM*; P30: 24.5/1.5, P33: 21.7/2.6, postpubertal: 24.3/1.6, young adult: 26.3/1.8) or males ($p = .52$; mean/ *SEM*; P40: 24.6/3.4, P43: 28.1/2.4, postpubertal: 28.0/3.3, young adult: 28.4/3.0).

Discussion

In the present study, there were no effects of pubertal status on the ability to learn the initial location of an escape platform in a Morris water maze task. Both male and female pre- and postpubertal animals had significantly reduced path lengths between the first and second blocks, suggesting a fairly rapid acquisition of the spatial task. Despite the decreased spine density in males (Meyer, Ferres-Torres, & Mas, 1978) and females (Yildirim et al., 2008) associated with puberty in the hippocampus, pubertal onset did not significantly improve spatial memory after 20 min or 24 hour interblock intervals. It is possible that these neuroanatomical changes may affect learning strategies, which are known to change after puberty (Kanit et al., 2000; Rodriguez et al., 2013) but do not manifest into observable changes in performance on a simple spatial task.

Analysis across individual trials revealed that postpubertal males and females had significantly increased path efficiency to the platform after its location was moved to an alternate quadrant of the maze. They also spent less time in the former quadrant of the maze where the platform was previously located. It is likely that the impairments in prepubertal animals in the present study were due to an immature prefrontal cortex. Previous studies have shown that mPFC lesions do not lead to deficits in spatial learning but do impair reversal learning (de Bruin et al., 1994; Lacroix et al., 2002). Though the deficits in prepubertal animals were subtle and less pronounced than the deficits found after lesioning the mPFC, results from the present study suggest that pubertal onset does play a role in mPFC-mediated reversal learning.

In addition, prepubertal animals of both sexes spent a greater percentage of time in the initial quadrant, suggesting that the deficit in reversal in prepubertal subjects might be characterized as a deficit in cognitive flexibility. This is consistent with a study in which presumably prepubertal males (P28–42) committed more perseveration errors than adults on an extinction task (Sturman et al., 2010). The present study suggests that pubertal onset may be

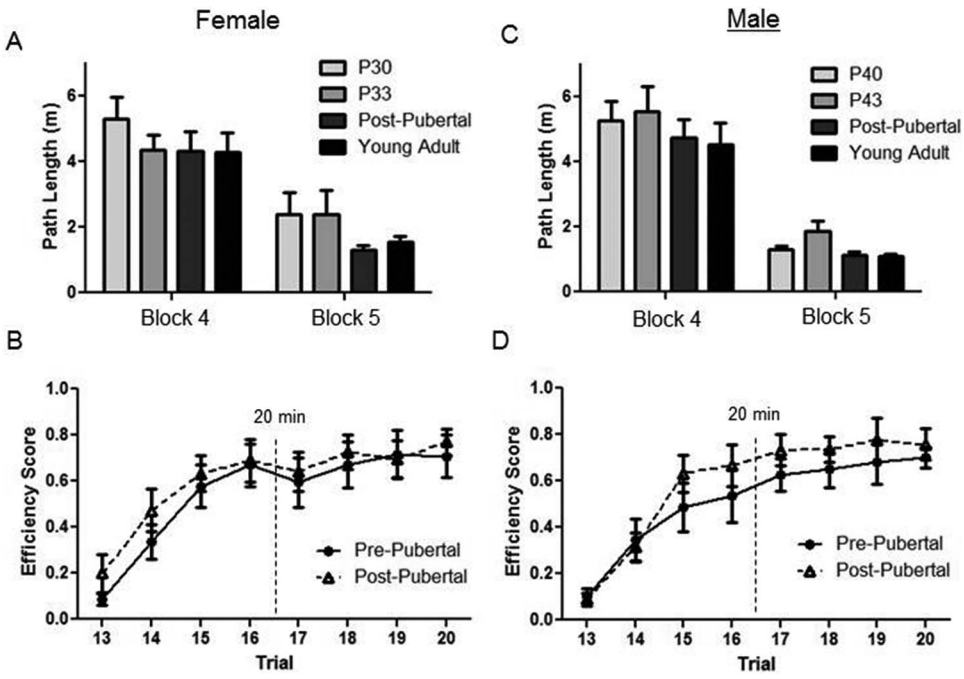

Figure 2. Prepubertal rats of both sexes showed a deficit in reversal learning when the escape platform was switched to a novel location. There was a significant effect of trial block on path length in both sexes, $p < .001$ (A,C). There was a reduction in path length between blocks 4 and 5 in females and males ($p < .001$). When animals were grouped between pre- and postpuberty, path efficiency score (higher score reflective of greater efficiency) was also reduced in postpubertal females, $p = .039$, and males, $p = .013$, across Trials 13–20 in Blocks 4 and 5 (B,D).

associated with rapid changes in cognitive behavior, which may accompany the neuroanatomical changes in the mPFC. Previous data from our laboratory show that a variety of these changes occur during the pubertal period. In females, there is a reduction in the number of mPFC neurons (Willing & Juraska, 2015) and a loss of basilar dendrites on mPFC pyramidal neurons (Koss et al., 2014). In addition, both males and females lose dendritic spines on mPFC neurons during adolescence (Koss et al., 2014) and changes in synapse number in the mPFC coincide with pubertal onset (Drzewiecki et al., 2015). Thus there may be an association between increased cognitive performance and pruning in the mPFC.

Additional neuroanatomical and neurochemical changes have been described during adolescence. Increases in tyrosine hydroxylase fibers in the PFC occur during this period (Naneix et al., 2012; Willing, Brodsky, Cortes, Kim, & Juraska, 2015), and have been thought to play a role in enhanced cognition (Naneix et al., 2012). This period is also associated with changes in neuronal firing patterns involving D1 dopamine and NMDA receptors (Tseng & O'Donnell, 2004), and there are substantial changes in dopamine receptor (D1 and D2) density across adolescence in both the PFC and striatum (Andersen et al., 2000). Furthermore, there are peripubertal increases in myelination (Kim & Juraska, 1997;

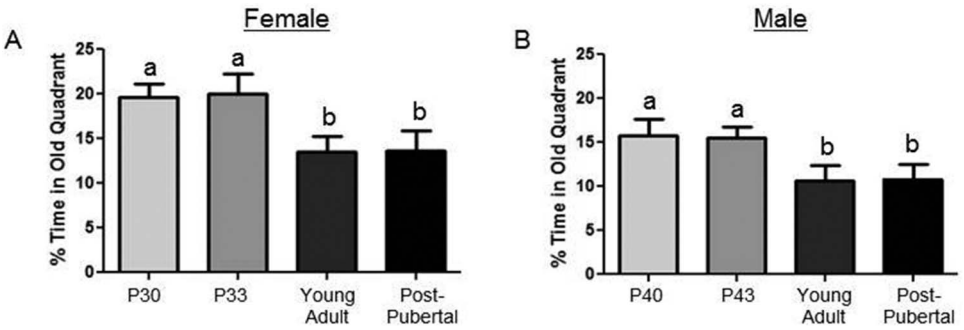

Figure 3. Prepubertal rats of both sexes spent more time in the initial quadrant of the maze in Block 5. In both (C) female ($p = .033$) and (D) male ($p = .031$) groups that had reached puberty, less time was spent in the original quadrant than prepubertal groups.

Matsuoka et al., 2010) and expression of cortical NMDA receptors (El-Rawas et al., 2009).

Future studies should further elucidate the mechanisms by which pubertal onset affects cognitive performance, particularly assessing whether better cognitive performance is a result of steroid hormone actions during puberty on neural connectivity, or a direct result of acute local effects of hormones on already mature circuits. In addition, a more complicated task might be able to more easily parcel out the changes in cognitive performance that occur during and after the pubertal period. Regardless of the mechanism, the present study provides evidence that the pubertal period in males and females is a critical developmental window when nonreproductive behavior changes rapidly. Furthermore, it supports the notion that adolescence is not uniform, and studies exploring adolescent development should account for pubertal onset for both males and females.

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