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The effects of pregnancy, lactation, and primiparity on object-in-place memory of female rats

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ABSTRACT

Maternal physiology and behavior change dramatically over the course of pregnancy to nurture the fetus and prepare for motherhood. Further, the experience of motherhood itself continues to influence brain functioning well after birth, shaping behavior to promote the survival of offspring. To meet these goals, cognitive abilities, such as spatial memory and navigation, may be enhanced to facilitate foraging behavior. Existing studies on pregnant and maternal rats demonstrate enhanced cognitive function in specific spatial domains. We adopted a novel object-in-place task to assess the ability of female rats to integrate information about specific objects in specific locations, a critical element of foraging behavior. Using a longitudinal design to study changes in spatial memory across pregnancy and motherhood, an advantage in the object-in-place memory of primiparous female rats compared to nulliparous females emerged during lactation not during pregnancy, and was maintained after weaning at 42 days postpartum. This enhancement was not dependent on the non-mnemonic variables of anxiety or neophobia. Parity did not affect the type of learning strategy used by females to locate a cued escape platform on a dual-solution water maze task. Results indicate that the enhancement of object-in-place memory, a cognitive function that facilitates foraging, emerged after pregnancy during the postpartum period of lactation and persisted for several weeks after weaning of offspring.

Introduction

Pregnancy exacts extreme changes in hormone synthesis, release, and action, affecting every bodily system studied to date. These comprehensive shifts in the hormonal milieu maintain an optimal environment for fetal growth and eventual delivery of the offspring, and profoundly remodel the maternal body and brain to prepare for motherhood (Brunton and Russell, 2008; Kinsley and Lambert, 2008; Nelson, 2005). While the changes to the body are obvious, less obvious and less understood, are the changes to the brain and the consequences for behavior throughout pregnancy and motherhood. In rats, most literature indicates that pregnancy and motherhood are associated with enhanced cognition, particularly on tasks that assess spatial learning and memory (Macbeth and Luine, 2010). Because effective and efficient foraging is highly dependent on spatial ability, these cognitive enhancements logically would improve the chances of offspring survival (Pawluski et al., 2006).

Although a number of studies have tested the cognitive functions of primiparous rats (single litter) and multiparous rats (multiple litters) after weaning, only a few studies have actually tested cognitive performance *during* pregnancy and *during* lactation. For example, on an object placement task, pregnant rats displayed better spatial working memory in the first and third weeks of pregnancy than nulliparous females, which had never been pregnant (Macbeth et al., 2008). Similarly, on water maze tasks modified to assess spatial working memory, pregnant rats had shorter latencies and traveled shorter distances when learning to reach a submerged escape platform compared to nulliparous females (Bodensteiner et al., 2006; Galea et al., 2000). Together these studies indicate a modest, but significant, improvement in spatial working memory during pregnancy in rats. Although there have been no reports on the cognitive effects of lactation on spatial working memory, primiparous rats displayed impaired spatial reference memory when learning a conventional water maze task during the first week of lactation compared to nulliparous females (Darnaudery et al., 2007). However, on a subsequent retention trial administered 10 days later, these primiparous females explored the probe quadrant significantly more than nulliparous females, displaying better long-term spatial reference memory.

Interestingly, cognitive effects persist beyond pregnancy and lactation. Two weeks after weaning, primiparous female rats displayed better spatial memory on a land maze task compared to nulliparous females, sensitized nulliparous females, or primiparous females whose pups had been removed within 24 h of birth (Lambert et al., 2005). Further, primiparous females spent more time by the baited well on a probe trial than all other groups. On a cued version of this same task, both primiparous females and sensitized nulliparous females found the reward

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faster than nulliparous and primiparous females whose pups had been removed (Lambert et al., 2005). Similarly, on a radial arm maze task administered one month after weaning, primiparous females made fewer working memory errors than nulliparous females, sensitized nulliparous females, and multiparous females (Pawluski et al., 2006). In the same study, females that had experienced pregnancy, but not motherhood, failed to complete the task significantly more often than all other groups and displayed longer latencies to traverse the arms of the maze implicating non-mnemonic factors. Even post-weaning, the combined effects of pregnancy and mothering improved spatial performance more than pregnancy or mothering independently (Pawluski et al., 2006). In contrast, non-spatial working memory does not seem to be improved after pregnancy and lactation. On an object recognition task administered two weeks after weaning, primiparous rats were no different from nulliparous rats in distinguishing a novel object after either a 4-hour or 24-hour delay interval (Lemaire et al., 2006). Therefore, cognitive changes associated with pregnancy and motherhood are selective, with overall improvements in spatial ability but no reported effects on non-spatial ability.

Motherhood also confers life-long benefits in place navigation. Two weeks after weaning, primiparous rats traveled shorter distances to reach the submerged escape platform on a water maze task (Lemaire et al., 2006). This improvement was maintained throughout life. When tested at 22 months of age, these primiparous rats again performed better than nulliparous controls. Moreover, the performance of primiparous rats at 6 and 22 months of age was comparable, whereas nulliparous controls had significantly worse performance at 22 months of age compared to 6 months of age (Lemaire et al., 2006). Similarly, 4 months after weaning, primiparous rats continued to display better working memory on the water maze task than nulliparous controls (Kinsley and Lambert, 2008). Consequently, the combination of pregnancy and motherhood exert effects on the spatial ability of female rats that can persist throughout the lifespan (for comprehensive reviews, see Kinsley and Lambert, 2008; Macbeth and Luine, 2010).

We recently reported that biological sex and hormonal status influenced the ability of adult rats to remember the locations of objects on the novel object-in-place task that combines elements of traditional measures of object recognition and object location (Cost et al., 2012). Regardless of biological sex or hormonal condition, rats were able to recognize those objects that had been repositioned in new locations after a brief delay interval of 5 min between the sample phase and the test phase. When the delay interval was increased further to 60 min, only ovariectomized females treated with estradiol and progesterone demonstrated intact object-in-place memory, while ovariectomized females and gonadally-intact males treated with vehicle were unable to distinguish moved from unmoved objects. These results indicated a female advantage in the performance of the object-in-place task that was dependent on elevated levels of ovarian hormones (Cost et al., 2012).

The current study was intended to extend the literature on the effects of pregnancy, lactation, and motherhood on spatial ability of rats using a longitudinal design across pregnancy, lactation, and post-weaning stages. Because we found previously that ovarian hormones enhanced object-in-place memory in female rats, we predicted that the high levels of hormones associated with pregnancy and lactation would lead to enhancements in performance on the novel object-in-place task. Additionally, as previous studies have found improved spatial ability in primiparous rats, we investigated whether there are effects of pregnancy and maternity on the type of navigational strategy used to learn a dual-solution water maze task because the preference for a place strategy over a stimulus–response strategy may mediate improved spatial ability.

Methods

Experimental design

Cognitive performance was evaluated using the object-in-place task, which assesses memory for the identity and location of objects in space. In a repeated measures design, primiparous female rats (n = 13) were tested at five time points, including prior to mating, during pregnancy, during lactation on post-delivery day (PDD) 14, and twice following weaning of their litters at PDD 28 and PDD 42. For comparison, nulliparous female rats in diestrus (n = 19) were tested at the same five corresponding time points. In addition, following completion of the five tests of object-in-place memory, all rats completed the cued platform water maze task on PDD 44, to assess the type of strategy used to locate a cued escape platform in a standard water maze.(Fig. 1).

Subjects

Subjects were 32 female adult Long-Evans rats procured from Harlan Laboratories, Inc. (Indianapolis, IN) at 55–60 days of age and pair-housed. An additional 6 males served as breeders. Rats were maintained at an ambient room temperature of 21 °C ±1° on a 12:12 h light–dark cycle with lights on at 1100 h. Harlan 2016 Teklad Global 16% Protein Rodent Diet and water were available *ad libitum*. Thirteen females were time-mated at 75 days of age by the male breeders with each female receiving three ejaculations on the first day of gestation. All animals were nulliparous at the beginning of the study. All rats in the primiparous group (n = 13) experienced their first pregnancy and lactation over the course of the experiment. Upon delivery of pups, litters were not culled to allow for the possibility that the total number of pups or the number of male pups may influence cognitive performance in pregnancy or the postpartum period. All animal usage was approved by the *Tulane University Institutional Animal Care and Use Committee* in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals (1996)*.

Estrous cycle monitoring

The estrous cycles of all females were monitored by vaginal swabbing daily beginning two weeks prior to behavioral testing and throughout behavioral testing. Vaginal cells were stained with toluidine blue and viewed under a microscope to monitor changes in vaginal cytology across the estrous cycle. Females were tested only during the metestrus or diestrous stage of their cycles, when ovarian steroid levels are low. Pregnant and lactating females were handled similarly to cycling females to control for the effects of daily handling.

Cognitive measures

The object-in-place task was administered at five separate time points spanning eight days prior to pregnancy to three weeks after weaning of litters. The cued platform water maze task was administered once one day after the final session of the object-in-place task.

Object-in-place task

The object-in-place task is a procedure developed to test rodent memory that combines the elements of traditional measures of object recognition and object placement (Barker and Warburton, 2009; Barker et al., 2007; Dix and Aggleton, 1999). To perform successfully, rodents must remember the features and locations of four distinct objects in an open field during a delay interval. Rodents prefer novelty, therefore memory for the original arrangement of the objects is indicated by increased time spent investigating the two objects that were relocated after the delay interval. Rats were tested in an open field constructed of matte black Plexiglas (90 cm × 90 cm × 45 cm) elevated 65 cm above the floor and surrounded by a rich assortment of visual cues. Prior to testing of object memory, rats were habituated to the open field for 10 min each day for three or four consecutive days. Habituation began in the late diestrous or early proestrous stage of the cycle so that the test day, when the rat would be in the metestrus or diestrus stage, would immediately follow the habituation days. Our initial subject numbers were purposefully high to allow for attrition due to the