Hormones and Behavior 64 (2013) 439–447

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Reproductive experience does not persistently alter prefrontal cortical-dependent learning but does alter strategy use dependent on estrous phase

Joanna L. Workman [a], Tamara Crozier [b,1], Stephanie E. Lieblich [a], Liisa A.M. Galea [a,b,c,*]

[a] Department of Psychology, University of British Columbia, Canada
[b] Neuroscience Graduate Program, University of British Columbia, Canada
[c] Centre for Brain Health, University of British Columbia, Canada

ARTICLE INFO

Article history:
Received 24 April 2013
Revised 21 June 2013
Accepted 23 June 2013
Available online 1 July 2013

Keywords:
Parity
Mothering
Maternal care
Prefrontal cortex
Behavioral flexibility
Estrus
Estrogens
Ovarian hormones

ABSTRACT

Reproductive experiences in females comprise substantial hormonal and experiential changes and can exert long lasting changes in cognitive function, stress physiology, and brain plasticity. The goal of this research was to determine whether prior reproductive experience could alter a prefrontal–cortical dependent form of learning (strategy set shifting) in an operant box. In this study, female Sprague–Dawley rats were mated and mothered once or twice to produce either primiparous or biparous dams, respectively. Age-matched nulliparous controls (reproductively-naïve females with no exposure to pup cues) were also used. Maternal behaviors were also assessed to determine whether these factors would predict cognitive flexibility. For strategy set shifting, rats were trained in a visual-cue discrimination task on the first day and on the following day, were required to switch to a response strategy to obtain a reward. We also investigated a simpler form of behavioral flexibility (reversal learning) in which rats were trained to press a lever on one side of the box the first day, and on the following day, were required to press the opposite lever to obtain a reward. Estrous phase was determined daily after testing. Neither parity nor estrous phase altered total errors or trials to reach criterion in either the set-shifting or reversal-learning tasks, suggesting that PFC-dependent cognitive performance remains largely stable after 1 or 2 reproductive experiences. However, parity and estrous phase interacted to alter the frequency of particular error types, with biparous rats in estrus committing more perseverative but fewer regressive errors during the set-shifting task. This suggests that parity and estrous phase interfere with the ability to disengage from a previously used, but no longer relevant strategy. These data also suggest that parity alters the behavioral sensitivity to ovarian hormones without changing overall performance.

Introduction

Pregnancy and motherhood (reproductive experience) comprises substantial hormonal fluctuations during pregnancy and postpartum as well as experiential changes such as offspring recognition and care. Reproductive experience exerts enduring changes in cognition and behavior, including those that are not typically considered 'maternal' but may enhance the survival of offspring. For instance, motherhood in rats enhances learning and memory across strains and hippocampus-dependent tasks (Gatewood et al., 2005; Kinsley et al., 1999, 2008; Leuner and Gould, 2010; Pawluski et al., 2006a,b; Workman et al., 2012), some of which endure long after weaning (Gatewood et al., 2005; Kinsley et al., 2012). Prior research in our laboratory demonstrated that reproductive experience enhances performance in the hippocampus-dependent spatial working/reference memory version of the radial arm maze (Pawluski et al., 2006a,b). However, less is known regarding the effects of reproductive experience on performance in cognitive tasks that do not depend on the integrity of the hippocampus. A recent study indicated that postpartum females (20–24 days after parturition) performed better in an attentional set-shifting task in which performance is dependent on the integrity of the prefrontal cortex (PFC; Leuner and Gould, 2010) but it remains unknown whether PFC-dependent cognitive enhancement endures postweaning.

Multiple reproductive experiences (multiparity) may also exert differential effects on behavior and brain plasticity compared with one reproductive experience (primiparity). For instance, after one reproductive experience, the memory for maternal behavior extends beyond the lactational period and is known as the maternal memory (Bridges, 1975; Orpen and Fleming, 1987). Further, maternal behavior may vary from first to second postpartum period (Wong et al., 2011). Parity also exerts changes in hippocampus-dependent cognitive behaviors long

* Corresponding author at: 2136 West Mall, Vancouver, BC V6T 1Z4, Canada. Fax: +1 604 822 6923.
E-mail address: lgalea@psych.ubc.ca (L.A.M. Galea).
[1] Current address: School of Nursing, University of British Columbia, T201-2211 Wesbrook Mall, Vancouver, BC V6T 2B5, Canada.

0018-506X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yhbeh.2013.06.005

after pups are weaned. Specifically, multiparous rats performed better when repeatedly tested in a spatial dry land maze compared with primiparous and nulliparous rats at 6, 12, 18, and 24 months of age (Gatewood et al., 2005). One striking example of the influence of biparity on hippocampal remodeling is that primiparous rats had significantly diminished neuron complexity (evidenced by fewer branch points and shorter dendrites) in the CA1 and CA3 regions of the hippocampus compared with both nulliparous and biparous rats (Pawluski and Galea, 2006). Further, in the same study, biparous rats had higher spine densities on basal dendrites of the CA1 region compared with nulliparous rats. In addition, hippocampal neurogenesis is reduced across the postpartum in primiparous but not biparous rats (Pawluski and Galea, 2007). Collectively, these data suggest that multiple reproductive experiences exert different effects compared with one reproductive experience and that hippocampal restructuring and sensitivity may explain parity-related differences in spatial learning and memory.

Reproductive experience also alters hormonal profiles. Specifically, corticosterone concentrations are higher in primiparous compared with biparous dams on postpartum day (PPD) 1 and corticosteroid binding globulin (CBG) is higher in biparous compared with primiparous dams on PPD 35 (Pawluski et al., 2009). Parity-related changes in glucocorticoid signaling may contribute to dendritic remodeling in the hippocampus (Pawluski and Galea, 2006). One reproductive experience also alters hormone concentrations during the course of the estrous cycle. Specifically, primiparous females in proestrus have lower concentrations of 17β estradiol compared with nulliparous females in proestrus (Bridges and Byrnes, 2006). Sensitivity of hormone and neurotransmitter systems also differs after reproductive experience. For instance, in response to estrogens, middle-aged multiparous females have higher rates of hippocampal cell proliferation compared with age-matched nulliparous females (Barha and Galea, 2011). Reproductive experience also alters opiate (Kinsley and Bridges, 1988) and dopamine (DA) systems (Byrnes et al., 2001), the latter of which is integral for executive functions such as strategy set shifting.

Attentional set shifting consists of a task that is dependent upon the medial PFC (mPFC) in which subjects or participants must learn to alter behavior in response to rewards contingent upon changing perceptual features in the task (Birrell and Brown, 2000; Monchi et al., 2001). For example, a commonly used test to assess set shifting in humans is the Wisconsin Card Sorting Task (WCST) in which a deck of cards must be sorted by particular features of images on the cards (i.e., size, shape, color, and number of objects) based on changing contingencies (Monchi et al., 2001). Lesions to or inactivation of the mPFC selectively impair set-shifting ability (Birrell and Brown, 2000; Floresco et al., 2008). As mentioned above, at the end of the postpartum period, female rats have enhanced cognitive flexibility (specifically, fewer errors and trials to reach criterion) in a set-shifting plus maze and enhanced dendritic complexity in the mPFC compared with reproductively-naïve females (Leuner and Gould, 2010). However, it is unknown whether these changes extend beyond the postpartum period or are potentially augmented with subsequent reproductive experiences, as with hippocampal-dependent learning tasks. Set shifting is also dependent upon dopamine signaling (Floresco et al., 2006b) and primiparous rats have increased D_2 receptor mRNA expression in the anterior pituitary during proestrus compared with nulliparous rats (Byrnes et al., 2001). Further, parous females (either primiparous or multiparous) have higher striatal DA and 3,4-Dihydroxyphenylacetic acid or DOPAC, a DA metabolite (Byrnes et al., 2001). Both findings may be related to substantial fluctuations of estradiol during pregnancy and the postpartum period as estradiol alters several aspects of the DA system (Becker, 1990; Jacobs and D'Esposito, 2011; Thompson and Moss, 1994).

Given that parity mediates hippocampal-dependent cognitive behaviors long after weaning and alters the sensitivity of DA systems (Byrnes et al., 2001), our goal was to determine how parity would alter attentional set shifting after the postpartum period. We predicted that biparous females would make fewer errors in an attentional set-shifting task compared with nulliparous and primiparous females after weaning of offspring because the enhancing effects of reproductive experiences on spatial cognitive performance may be additive (Gatewood et al., 2005). We used an operant box apparatus to train food-restricted females to press levers to obtain sugar pellets. Once trained to criterion, females assigned to the set-shifting task were tested in two days: the first day, rats only received a reward for pressing the lever under the illuminated light cue, which varied randomly from left to right. The second day, rats only received a reward if they pressed, for example, the right lever regardless of the light stimulus. The set-shifting task required rats to shift their strategy from one dimension to another (extradimensional shift): from a visual cue response strategy (i.e., responding to the light) to a spatial (left or right) response strategy. In the response-reversal task, rats were required to disregard the light cue on both days. On the first day, rats received a reward only after pressing the right lever (for example) and on the next day received a reward only after pressing the left lever. The reversal task assesses ability to alternate strategy use within one perceptual (i.e., left to right) dimension (intradimensional shift).

Further, because estrous phase could alter strategy use in this task (Hussain et al., 2013; Korol et al., 2004), we monitored vaginal cytology daily and predicted that estrous phase would interact with parity given changes in E2 levels with estrous phase and parity. Finally, because level of maternal care could also predict cognitive performance as it does in hippocampus-dependent memory (Pawluski et al., 2006b), we conducted correlations between maternal behaviors and performance in the operant tasks.

Methods

Animals

Eighty-two female Sprague–Dawley rats at 2–3 months of age were obtained from the University of British Columbia Animal Care Facility (Vancouver, BC Canada) and were used in this study. After arrival, rats were housed in pairs for 1 week in polyurethane cages (48 × 27 × 20 cm) with aspen chip bedding and were given Purina rat chow and tap water ad libitum. Rats were handled for 5 min/day for 7 days after arrival. Animals were maintained on a 12:12 light/dark cycle (lights on at 7:30 am) in temperature- and humidity-controlled rooms (21 ± 1 °C; respectively). In addition, 30 males (approximately 4–5 months old) were used for mating. All protocols were in accordance with ethical guidelines set by the Canada Council for Animal Care and were approved by the University of British Columbia Animal Care Committee.

Breeding

Female rats were randomly assigned to one of the following conditions: biparous (n = 26), primiparous (n = 29) and nulliparous

Table 1
Sample sizes of each group after assignment to operant task and determination of estrous phase.

Set-shifting task	Biparous	Estrus	n = 5
		Other phases	n = 12
	Primiparous	Estrus	n = 5
		Other phases	n = 13
	Nulliparous	Estrus	n = 4
		Other phases	n = 12
Response-reversal task	Biparous	Estrus	n = 3
		Other phases	n = 6
	Primiparous	Estrus	n = 2
		Other phases	n = 9
	Nulliparous	Estrus	n = 4
		Other phases	n = 7