



Multiparity-induced enhancement of hippocampal neurogenesis and spatial memory depends on ovarian hormone status in middle age



Cindy K. Barha^{a,1}, Stephanie E. Lieblich^a, Carmen Chow^a, Liisa A.M. Galea^{a,b,c,*}

^a Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada

^b Graduate Program in Neuroscience, University of British Columbia, Vancouver, British Columbia, Canada

^c Brain Research Centre, University of British Columbia, Vancouver, British Columbia, Canada

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ABSTRACT

Menopause is associated with cognitive decline, and previous parity can increase or delay the trajectory of cognitive aging. Furthermore, parity enables the hippocampus to respond to estrogens in middle age. The present study investigated how previous parity and estrogens influence cognition, neurogenesis, and neuronal activation in response to memory retrieval in the hippocampus of middle-aged females. Multiparous and nulliparous rats were ovariectomized (OVX) or received sham surgery and were treated with vehicle, 17 β -estradiol, 17 α -estradiol, or estrone. Rats were trained on the spatial working and reference memory versions of the Morris water maze. Multiparous rats had a significantly greater density of immature neurons in the hippocampus, enhanced acquisition of working memory, but poorer reference memory compared with nulliparous rats. Furthermore, OVX increased, while treatment with estrogens reduced, the density of immature neurons, regardless of parity. OVX improved reference memory only in nulliparous rats. Thus, motherhood has long-lasting effects on the neuroplasticity and function of the hippocampus. These findings have wide-ranging implications for the treatment of age-associated decline in women.

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1. Introduction

Pregnancy and motherhood (parity) are associated with dramatic changes in hormones and behavior, which are necessary to ensure the survival of offspring (Kinsley and Lambert, 2008). There are long-term changes in the maternal circuit (including medial preoptic area and nucleus accumbens) that ensure maternal responsiveness to pups after parturition (Numan and Stolzenberg, 2009). For example, maintenance of maternal memory involves increased mesolimbic dopamine release into the shell region of the nucleus accumbens from the medial preoptic area (Champagne et al., 2004). Other regions not traditionally part of the maternal circuit, such as the hippocampus, are also affected in the postpartum period by reproductive experience (for review, see Galea

et al., 2014). For example, primiparity is associated with reduced dendritic branching in the CA1 and CA3 regions of the hippocampus (Pawluski and Galea, 2006) and reduced neurogenesis in the early and late postpartum (Pawluski and Galea, 2007). However, there are few studies that have examined whether parity affects neuroplasticity and function of the hippocampus during aging.

The integrity of the hippocampus is important for cognition, and the volume of the hippocampus has been used as a proxy for overall brain health during aging (Fotuhi et al., 2012). The hippocampus is of particular interest with respect to aging as it retains a remarkable degree of plasticity throughout life, contains a large amount of steroid hormone receptors, and is implicated in age-associated dementia (Barha and Galea, 2010; Foster, 2012). There is evidence to indicate that previous reproductive experience has long-lasting effects on hippocampal plasticity in middle age. Multiparity (4–6 litters) increased expression of brain-derived neurotrophic factor in the CA1 region (Macbeth et al., 2008) and increased cell proliferation in response to estrogens in the dentate gyrus (DG) (Barha and Galea, 2011). Furthermore, biparity (2 litters) reduced the amount of amyloid precursor protein in the CA1 region and DG of the hippocampus of middle-aged rats (Gatewood et al., 2005). Together, these results suggest that reproductive experience affects

* Corresponding author at: Department of Psychology, University of British Columbia, 2136 W Mall, Vancouver, British Columbia, Canada V6T 1Z4. Tel.: +604 822 6536; fax: +604 822 3697.

E-mail address: lgalea@psych.ubc.ca (L.A.M. Galea).

¹ Current address: Faculty of Health Sciences, Simon Fraser University, 8888 University Dr, Burnaby, British Columbia, Canada.

hippocampal neuroplasticity; however, to date, no study has examined the impact of multiparity on hippocampal neurogenesis or neuronal activation in response to spatial memory retrieval.

Studies are equivocal on the effects of parity and aging on hippocampus-dependent cognition. Although some studies have found that increasing parity is associated with cognitive impairment (McLay et al., 2003), others have found no association (Ryan et al., 2009) or associations only after a relatively high number of pregnancies (Heys et al., 2011; Rasgon et al., 2005). The opposing effects of parity on cognition in older women may be dependent on amount of parity, age of first pregnancy, or whether the studies screened for dementia as findings with an association of parity and changes in cognition did not exclude cognitively impaired individuals (Heys et al., 2011; McLay et al., 2003). In rodents, primiparity compared with nulliparity has little effect on spatial working memory in middle age (Zimmerknopf et al., 2011). In spatial reference memory tasks, studies have found that parity is associated with both enhanced and impaired performance (Cui et al., 2014; Gatewood et al., 2005; Lemaire et al., 2006; Love et al., 2005; Zimmerknopf et al., 2011), dependent on age at testing, the amount of parity, and perhaps previous testing. Previous work has shown that separately both parity and treatment with estradiol result in differential effects on working versus reference memory, with primiparity and low-dose estradiol facilitating working memory, but biparity and high-dose estradiol having no significant effects on reference memory (Holmes et al., 2002; Pawluski et al., 2006a, 2006b). Working memory relies on the hippocampus and prefrontal cortex, whereas reference memory relies on the hippocampus and caudate nucleus (Burgess et al., 2002; Floresco et al., 1997). Thus, it is possible that differences between studies are because of task differences in assessing working and reference memory.

Preclinical research supports the possible use of estrogens as therapeutic agents to treat cognitive decline in postmenopausal women (Sherwin, 2012). In a meta-analysis, estrone-based hormone therapies (HTs) had more detrimental effects (or fewer positive outcomes) on cognitive function and AD risk compared with estradiol-based HTs, which had more cognitive enhancing effects (Hogervorst et al., 2000; Ryan et al., 2008). This was dependent on when HTs were prescribed (early or late in menopause). These findings suggest that the type of estrogen within the HT can significantly affect cognition and neuroprotection. We have previously found that estrone impairs, while estradiol enhances, cognition and neuroplasticity in young adult female rodents (Barha et al., 2010; McClure et al., 2013). Most studies have focused on the effects of estradiol to examine whether estrogens can prevent normal age-associated cognitive decline in middle-aged rodents with equivocal results (Mennenga and Bimonte-Nelson, 2013). Although estradiol treatment can improve, impair, or have no effect on cognition in later life (Chisholm and Juraska, 2013), there is ample evidence to suggest that estradiol administered early after ovariectomy (OVX) is beneficial for cognition in middle age (Daniel, 2013). However, to our knowledge, studies have yet to directly examine the impact of different estrogens and parity on cognition in middle age, and the present study aims to fill this gap.

The aim of the present study was to determine the effects of multiparity and different estrogens on spatial working and reference memory, neurogenesis, and neuronal activation in response to spatial memory retrieval in the DG of middle-aged rats. Rats were treated with 1 of 3 estrogens (17 β -estradiol [E₂ β], 17 α -estradiol [E₂ α], and estrone) and tested on 2 different versions of the Morris water maze to test spatial working and reference memory acquisition and retention. Hippocampal neurogenesis and activation of neurons in the DG via immediate early gene (IEG) expression were assessed after 21 days of hormone treatment. We hypothesized that

previous parity and estrogens would interact to affect spatial working and reference memory and neurogenesis in the hippocampus of middle-aged female rats.

2. Methods

2.1. Subjects

Multiparous Sprague-Dawley retired breeder rats ($n = 82$) and nulliparous Sprague-Dawley rats ($n = 80$) weighing approximately 300 grams were used (Harlan Laboratories, Indianapolis, IN, USA). Multiparous retired breeder rats had approximately 4–5 confirmed litters. Rats were age matched and were approximately 8 months old at the time of their arrival at the Department of Psychology at the University of British Columbia where they were housed in pairs in opaque polyurethane bins (48 × 27 × 20 cm) with aspen chip bedding and were given Purina rat chow containing 0.1%–0.15% isoflavones by weight (laboratory diet 5012) and tap water ad libitum. Rats were maintained under a 12:12-hour light:dark cycle (lights on at 7:30 AM). Multiparous and nulliparous rats were housed in separate colony rooms.

At approximately 12 months of age, rats underwent surgery and were either bilaterally OVX ($n = 130$) or sham operated ($n = 32$) as previously described (Barha and Galea, 2011; Barha et al., 2009, 2010; McClure et al., 2013). Surgery was performed under isoflurane gas (5% induction and 2.5% maintenance). Rats were given 5 mg/kg Anafen immediately before and again 24 and 48 hours after surgery. One week after surgery, multiparous and nulliparous females were assigned to 1 of 5 treatment groups: OVX vehicle control (OVX control), sham-operated vehicle control (sham control), E₂ β , E₂ α , or estrone (all hormone groups were OVX; for doses, see below). Furthermore, some of the multiparous and nulliparous rats were assigned to be behaviorally tested in the Morris water maze ($n = 52$ multiparous and 50 nulliparous), whereas the remaining rats ($n = 30$ per parity group) were kept behaviorally naive and were treated as cage controls. Beginning in middle age (between 10 and 12 months of age), female rats show alterations in the length and nature of the estrous cycle, transitioning from regularly cycling to irregularly cycling, culminating in acyclicity and persistent estrus, and/or persistent diestrus (LeFevre and McClintock, 1988). Therefore, throughout the duration of the study, estrous cycles were monitored in the sham-operated vehicle control multiparous and nulliparous rats. Vaginal cells were collected by lavage, and rats were classified as either regularly or irregularly cycling (presence of consecutive cycles varying in length). Out of the 21 sham rats, 10/21 showed irregular cycling, and an additional rat was in constant estrus. All experiments were conducted in accordance with the ethical guidelines set by the Canada Council on Animal Care and were approved by the University of British Columbia Animal Care Committee. All efforts were made to reduce the number and suffering of animals.

2.2. Apparatus

The maze used in the present study was a circular pool (180 cm in diameter and 60 cm in height) filled to a 33-cm depth with 21 °C water rendered opaque with nontoxic white tempura paint (Reeves and Poole Group, Toronto, Ontario, Canada). A 10-cm wide white platform was hidden 3 cm below the surface of the water in the center of a quadrant. Multiple large black distal cues were placed on the beige walls around the dimly lit testing room and remained stable throughout testing. The movements of the rats within the pool during testing were tracked and recorded by a camera mounted above the pool and connected to a desktop computer and the program ANY-maze (Stoelting Co, Wood Dale, IL, USA).

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