Published in final edited form as:
J Alzheimers Dis. 2013 January 1; 34(3): 589–594. doi:10.3233/JAD-122101.

Early Reproductive Experiences in Females Make Differences in Cognitive Function Later in Life

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Abstract

Women experience dramatic changes in hormones, mood and cognition through different periods of their reproductive lives, particularly during pregnancy and giving birth. While limited human studies of early pregnancy and motherhood showed alteration of cognitive function in later life, research conducted on rodents showed a persistent improvement of learning and memory performance in females with history of giving birth (primiparous or multiparous) compared to virgin controls (nulliparous). In this mini review, we will focus on the effect of early motherhood on cognitive function later in life, which would provide insight on how reproductive experiences influence women's health during ageing.

Keywords

pregnancy; motherhood; steroids; neurogenesis; gene regulation; cognition

Introduction

Reproductive experiences in females, pregnancy and giving birth, constitute as special conditions in women's lives that affect various physiology and endocrinology systems. The reproductive hormones produced during pregnancy and postpartum period have profound and distinct effects on brain. Those changes include increasing of the size of the brain cell body, extending the length of dendritic branches, and altering of neurogenesis in several brain regions [1–3]. The effects of pregnancy and motherhood on learning and memory are associated, but different. These differences are attributed to an adaptive function in preparation for parturition, changes of associated hormones and specific brain functions. The effects are also different in human studies compared to rodent experiments. However, some of the reproductive experience induced behavioral changes last longer than the postpartum or mother care periods and may have important impacts later in life. In this mini review, we will discuss reproductive experiment associated changes in neurogenesis in different brain regions, learning and memory performances, as well as regulation of cognitive associated genes during pregnancy and postpartum period.

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Parenting and the brain

It is known that the changes in cognitive function induced by pregnancy and motherhood are partially due to dramatic fluctuations in sex hormones as well as neuropeptides, which may alter the morphology and structure of various brain regions which are directly or indirectly involved in learning and memory functions. For instance, olfaction plays a central role in numerous basic roles in many animal species as a function of social recognition. Increasing evidence in animal studies suggest that neural plasticity in the olfactory bulb is important for maternal recognition and for the production of normal maternal behaviors [4,5]. While dendritic spines have been considered as one of the cellular substrates underlying experience-related plasticity and their morphology has been related with synaptic stability and strength, a recent study using in vivo time-lapse imaging technology in rats reported a significant increase in the number of stable dendritic spines of adult-born neurons in the olfactory bulb in lactating mothers compared with naive virgins [6]. However, reproductive experiences can cause more changes in brain regions beyond the olfactory bulb. The reproductive experience-induced morphology changes are also found in cognition-associated brain regions, such as the hippocampus, medial prefrontal cortex, and medial preoptic area [7–10]. In parallel with neurogenesis observed in the olfactory blub, studies also showed an increase in the dendritic spine density in the CA1 stratum lacunosum-moleculare in late-pregnant and lactating experimental rats [11]. Compared with virgin females, postpartum rats showed more dendritic spines in the anterodorsal and fewer in the posterodorsal but no difference was found in the posteroventral area of amygdale [12], suggesting brain-region specific changes of synaptic plasticity are induced by maternal care. As shown in figure 1, we found more BrdU positive cells in the hippocampus dentate gyrus region in older female mice with history of giving birth (6–9 months after parturition with more than 1 litter) compared to the age-matched virgin mice at 12 months old. While estradiol, corticosterone and prolactin play the main roles in the maternal associated regulation of neurogenesis in various brain regions [13], our data is in line of supporting the hypothesis that although the hormone surges are transient during pregnancy and postpartum, the reproductive experience-induced changes on brain function and behavior have lifelong effects [14]. The long lasting effects of the maternal experiment is not only supported by morphological studies, but also evidenced by changes in brain function later in life. For example, the motherhood experience during early life increased sensitivity in response to estrogen treatment-induced increase in cell proliferation in the dentate gyrus of hippocampus at an older age in rats [15], a higher tolerance to stress-induced learning impairment [16], and a permanent change in the responsiveness of the nervous system [17], suggesting a long lasting neurogenesis effect of the maternal experience on brain function. These structural or morphological changes in the brain, particularly in the hippocampus are believed to lead to behavioral implications, such as improvement in learning and memory activities.

Parenting and cognitive function

As a consequence of the reproductive experience-induced brain structure changes, studies showed better learning and memory in mothers compared to virgins both in human and animal studies. The maternal experience associated behavioral changes include an improved ability for mothers to navigate in their surrounding environment [14,16,18], as well as an enhanced spatial and working cognitive function [19–21]. Part of the behavioral changes are an adaptive function for mothers who are forced to find and remember the location of food and water nearby their home (nest) in order to ensure the survival of their offspring. Behavioral changes are also demonstrated by an improved ability in preventing stress-induced learning deficits which often occur in virgins [22].

Pregnancy raises estrogen and progesterone to higher levels for much longer period of time compared to the estrous cycle. The increased hormone levels may contribute to a prolonged improvement of learning and memory. However, whether the improved learning and memory found in animal studies is related to elevated levels of steroid hormones such as estrogen and progesterone remains unknown. In addition, there is a large discrepancy between human studies and animal research. In human studies, pregnant women showed impairments in verbal memory [23], word fluency, word list learning [24,25], and performance on priming tasks and incidental learning tasks [26–28] as compared with non-pregnant controls. A recent longitudinal study of 302 women (254 pregnant and 48 non-pregnant) showed the transition of memory function from gestations during pregnancy into the postpartum period [29]. This study showed that recall memory was adversely affected during pregnancy and postpartum period while working memory was unaffected, and prenatal estradiol and cortisol levels predicted memory performance during pregnancy and into the postpartum period, suggesting that the exposure to high levels estrogen during pregnancy does not help learning and memory but causes specific memory impairment. Other human studies with a smaller sample size showed no differences in memory performance between pregnant subjects and non-pregnant controls [30,31]. However, findings from animal studies showed a different picture. The cognitive performance not only improved in pregnant rats, but the improvements also persist through postpartum period and even longer in rodents [14, 18–21]. Furthermore, rats with completed motherhood showed fewer errors and performed better than virgin rats while “pregnancy only” female rats (pups removed after parturition) failed to complete spatial learning and memory tests [14,32]. These discrepancies in findings of cognitive function between human and animal studies during pregnancy and motherhood are more likely due to different time points of examination. For human studies, examinations often occurred shortly after pregnancy or parturition while lacking further examinations of the long-term effects months or years after parturition and motherhood were completed. Another possible reason that could account for the inconsistency in the reproductive experience impact on cognitive function between human and rodents is whether birth control pills were used by the non-pregnant control subjects in human studies, as females taking oral contraceptives showed improvement of cognitive performance [33]. These discrepancies in findings of cognitive function between human and animal studies may also be related to the difference in level and change patterns of sex hormones during pregnancy, as well as very different social and living environments between human and animal [34, 35]. In contrast, the reproductive experiences are well controlled in animal studies and there are no concerns of extra hormonal treatments.

Hormones, peptides and genes

Pregnancy and postpartum periods are characterized by robust hormonal changes. By the end of the third trimester, levels of estrogen and progesterone in circulation increase dramatically and reach levels about 50-fold and 10-fold higher than the maximal menstrual cycle levels, respectively. The levels of both hormones drop sharply after parturition and in the early postpartum period. Such a drastic change of hormone levels between period of pregnancy and postpartum caused significant changes in brain functions as well as immediate behavioral changes. While estradiol is well recognized as a neurotrophic factor and promotes cell proliferation and survival in general, some studies reported that estrogen down-regulates cell proliferation in the hippocampus and subventricular zone during pregnancy in rodents [36,37]. Similarly, progesterone and its metabolites also suppress newborn cell numbers in the hippocampus [38,39]. The effects of estrogen and progesterone on brain cell proliferation might be dependent on reproductive experience, as studies in rats found no or little change in cell proliferation in the hippocampus during pregnancy while a significant decrease in hippocampal cell proliferation is reported after the parturition or early postpartum periods [13]. It is possible that the estrogen-induced changes of cell proliferation

in the hippocampus may be compromised by other hormones and peptides which promote cell proliferation. In addition, studies showed that elevated levels of estradiol during pregnancy initially increase neurogenesis in the hippocampus of the female, but repeated exposure to estradiol during later pregnancy reduces cell death [37,40]. There are other hormones and peptides that also play roles in promoting cell proliferation, such as prolactin [1], oxytocin [3] and vasopressin [41]. Indeed, in addition to reproductive hormones such as estrogen, studies also found that neuropeptides such as oxytocin and vasopressin are also responsible for social recognition. Oxytocin working through the oxytocin receptor (OTR) located in medial preoptic area (MPOA) clearly increases maternal behavior with dependency upon estrogen priming [42–44]. The interaction between oxytocin and estrogen makes maternal and social behavior especially interesting. Our preliminary data also shows an elevation of OTR protein expression in multiparous mice compared to nulliparous mice (Figure 2).

Several cognitive related genes were identified with association of the hormone changes in pregnancy and postpartum period by multiple studies. Ca2+/Calomoduline-dependent protein kinase II (CAMKII) is involved in synaptic plasticity and memory. A down-regulation of CAMKII is found in the brain of individuals with depression, Alzheimer's disease as well as in early postpartum period [45–47]. Calcineurin is a Ca2+/calmodulin-dependent protein phosphatase and is also widely recognized for its abundance in the brain and its association with cognitive function. For example, overexpression of calcineurin in young adult animals leads to altered synaptic function, memory retention deficits and inhibition of calcineurin can rescue the memory decline in a mouse model of AD at a young age [48–50]. Furthermore, the level of Thr286 phosphorylation of CAMKII in the hippocampus is associated with faster hippocampal-dependent spatial memory formation reported from animal studies [51]. Recent animal studies showed that gene expression of calcineurin increases during pregnancy and parturition [52] and the levels of calcineurin protein vanished from MPOA brain region in the postpartum period [53]. The cAMP-response element-binding (CREB) protein is a crucial transcription factor regulating expression of genes involved in neuronal growth and plasticity and takes part in neuronal survival. Studies showed that estradiol induces spine plasticity in the hippocampus via rapid membrane effects and slower transcriptional regulation via the CREB pathway [54–56]. Furthermore, the number of cells with positive immunostaining for phospho-CREB in the medial preoptic area of the hypothalamus, a key region for the expression of maternal behavior, increased about three-fold in female maternal mice exposure to pups [57]. Brain-derived neurotrophic factor (BDNF) is a small protein for neuronal survival. BDNF is known to upregulate the induction of long-term potentiation, to enhance synaptic transmission, and also to increase neuronal plasticity in the central nervous system (CNS) [43,58]. The role of BDNF in learning and memory is also evidenced by genetic approaches, such as an age-dependent deficit in learning was found in BDNF(+/−) animals [59] and BDNF(−/−) mice showed impaired motor learning performance but not spatial learning and recognition memory compared with wildtype mice suggesting a specific neocortical dysfunction [60]. The level of BDNF expression increased during the pregnant period and decreased in the early postpartum period in a hormone-stimulated pseudopregancy and postpartum rat model [47]. In sheep, in the early postpartum period, the levels of BDNF mRNA were increased in the hippocampus CA1 region and temporal frontal cortex, but no changes were found in the olfactory bulbs, suggesting an independent change in visual recognition memory from classic maternal care behavior [61,62].

Conclusion

While limited human studies have been done in cognitive function changes long after giving birth to a child, findings from animal studies show that reproductive experiences improve

learning and memory performance in mothers even long past the maternal care period. Although the molecular mechanisms of these persistent improvements in cognitive function found in primiparous or multiparous rodents remain unknown, dramatic changes of hormone levels, expression of steroid receptors, and regulation of cognitive associated genes have been identified and may contribute to the reproductive experience induced alteration of cognitive functions.

Acknowledgments

This work was supported by grants from the Alzheimer's Association IIRG-07-59510 and IIRG-09-61521, American Health Assistance Foundation Grant G2006-118, and National Institute of Health (NIH R01AG032441-01, R01AG025888-01).

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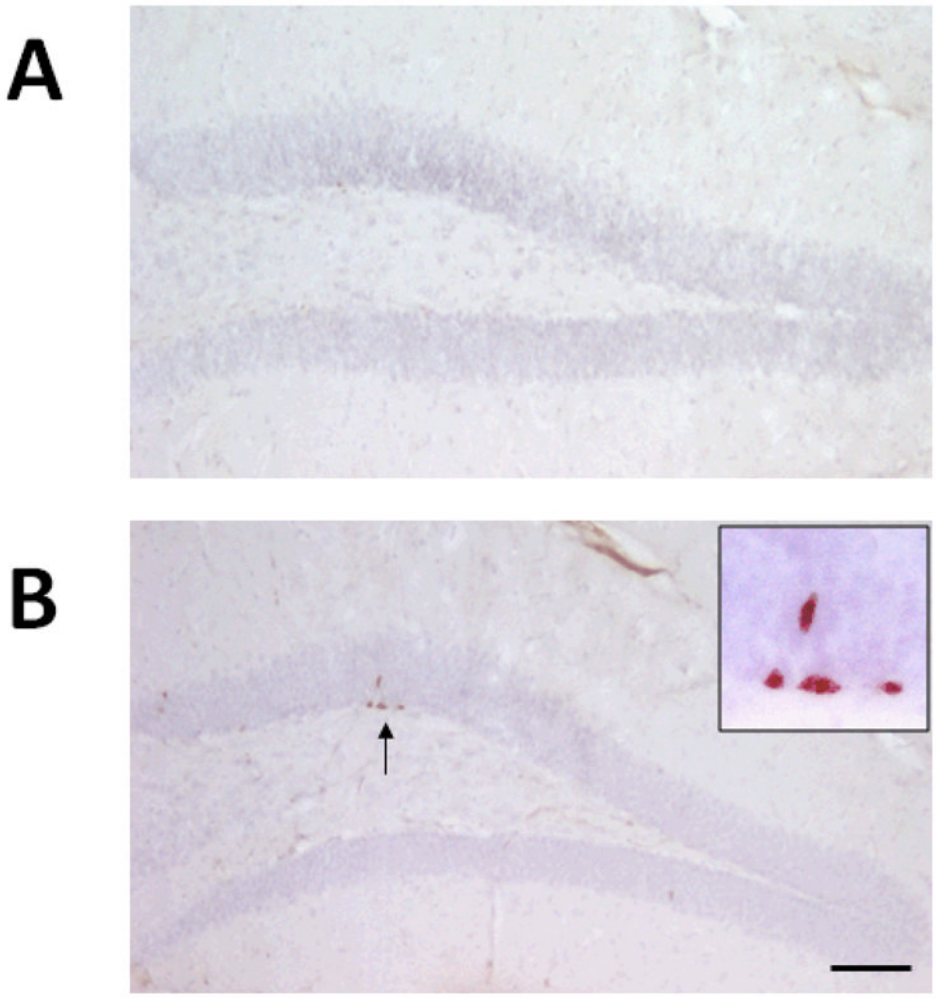

Figure 1.

Representative images show that the number of BrdU-staining positive cells located in the subgranular zone of the dentate gyrus in hippocampus from multiparous mice (B) and age-matched nulliparous littermates (A) at 12 months old. BrdU was injected intraperitoneally with 50 mg/kg 4 hrs before sacrifice. Following 2N HCl treatment in 37°C for 30 min, the primary antibody against BrdU was applied (1:500, Abcam). After DAB step the sections were counter-stained with hemotaxyin. Bar: 100 um.

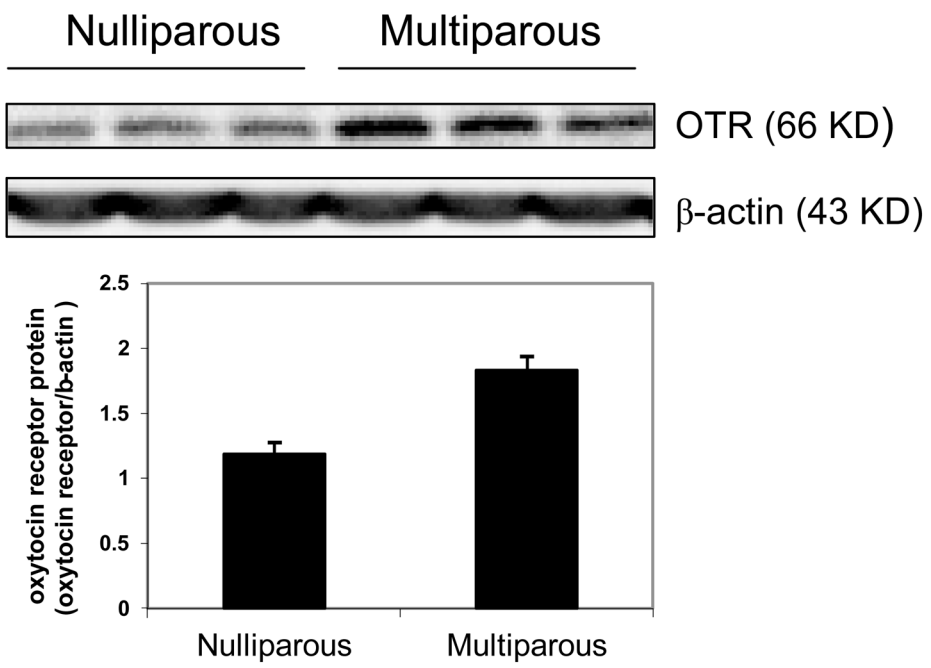

Figure 2.

Oxytocin receptor (OTR) expression in brain of nulliparious and multiparous mice at 12 months old. All multiparous mice completed their last maternal experience at least 6 months ago and had more than 1 litter. Oxytocin receptor expression was detected by polyclonal anti-oxytocin receptor antibody (1:500, Santa Cruz) and the bar graph showed density analysis of western blot image of OTR.