Published in final edited form as:
J Neuroendocrinol. 2014 October ; 26(10): 641–648. doi:10.1111/jne.12177.

Hippocampal plasticity during the peripartum period: Influence of sex steroids, stress and ageing

Liisa A.M. Galea[1,#], **Benedetta Leuner**[2,#], and **David A. Slattery**[3,#,*]

[1]Department of Psychology, The University of British Columbia, Vancouver, BC, CANADA

[2]Departments of Psychology and Neuroscience, The Ohio State University, Columbus, OH, USA

[3]Department of Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Germany

Abstract

The peripartum period is accompanied by dramatic changes in hormones and a host of new behaviors in response to experience with offspring. Both maternal experience and maternal hormones can have a significant impact on the brain and behavior. This review outlines recent studies demonstrating modifications in hippocampal plasticity across the peripartum period, as well as the putative hormonal mechanisms underlying these changes, and their modulation by stress. In addition, the impact of reproductive experience on the aging hippocampus will be discussed. Finally, we consider how these changes in hippocampal structure may play a role in postpartum cognitive function and mood disorders as well as age-related cognitive decline.

Keywords

lactation; postpartum; neurogenesis; corticosterone; cognition; depression

Introduction

There are dramatic fluctuations of steroid and peptide hormones during gestation and the postpartum period, with some of the highest concentrations of these hormones seen during these stages of the female lifespan. In women, high levels of estrogen, progesterone and cortisol are sustained for weeks and months at a time during gestation, while at parturition these steroid hormones plummet with the expulsion of the placenta resulting in a hypogonadal state (1). Gestation and lactation are physiologically demanding and thus it perhaps should not be so surprising that there are changes in disease risk after pregnancy. For example, there is not only a decreased risk for many reproductive cancers after giving birth but an increased risk to develop depression, anxiety, psychosis and obsessive compulsive disorder (2–5); in this issue see (6, 7). In addition, the peripartum period is accompanied by changes to the brain (in this issue see (7)) and in cognition. For example,

*Corresponding author: David A. Slattery, Department of Behavioural and Molecular Neurobiology, Universitaetsstraße. 31, University of Regensburg, Regensburg, Germany, Tel: +49 9419433076 Fax: +49 9419433052, david.slattery@ur.de.
#All authors contributed equally.

overall brain volume decreases across gestation by as much as 8% and returns to preconception size within 6 months postpartum (8). Intriguingly, the reduction in brain volume coincides with a decline in cognitive function across pregnancy (9) and early postpartum (10). The mechanisms for these changes across the peripartum period are not known but may be related to modifications in hippocampus morphology that occur in response to fluctuations in steroid and peptide hormones during gestation and postpartum.

In rodents, there are a host of neural and behavioural changes that occur with pregnancy and mothering across the maternal circuit (reviewed in (11, 12); in this issue see (13)). However, there are also changes that occur in the hippocampus of the maternal brain, an area that is not traditionally considered to be part of the maternal circuit. The integrity of the hippocampus is critical for spatial ability as well as some forms of memory and has also been implicated in the regulation of mood, functions which are often disrupted with motherhood (14, 15). In addition, the hippocampus exhibits a great degree of plasticity in adulthood and contains receptors for steroid and peptide hormones that are altered during the peripartum period. Coupled with the fact that neuroplastic changes in the hippocampus are seen in response to many of these hormones (14, 16–18), the hippocampus is an attractive region to study in response to reproductive experience.

The dentate gyrus of the hippocampus retains the ability to produce new neurons throughout adulthood in most mammalian species, including humans. Neurogenesis in the hippocampus of adult rodents contributes at least in part to some forms of learning and memory (14, 19) and has been proposed to play a role in mood disorders (14, 15). Neurogenesis is comprised of four stages: cell proliferation, migration, differentiation and cell survival. There are endogenous and exogenous proteins that can be used to examine these stages. Probably the most common exogenous marker is bromodeoxyuridine (BrdU), which labels any cells in the synthesis phase (within 2 hours after injection) and its progeny. Hence, BrdU can be used as either a marker of cell proliferation or the survival of these new cells depending on the timeline of administration and perfusion (14, 20). The reader is directed to reviews on neurogenesis for more details (14, 20). In addition to neurogenesis, mature neurons in the hippocampus exhibit plasticity in the form of dendritic and synaptic remodeling which may also play a role in cognitive function and mood (14). This review will outline changes seen in adult neurogenesis and other forms of hippocampal plasticity across the peripartum period, the contribution of steroid hormones, stress and aging to these processes and their potential functional significance.

Cognitive function across the peripartum period

Pregnancy and the postpartum period are associated with alterations in hippocampus-dependent cognition in both rodents and women (see (21) and (22) for review). In rodents, spatial abilities are most often assessed and overall these studies demonstrate that early pregnancy is associated with improved cognition, while late pregnancy and early postpartum are associated with impaired hippocampus-dependent spatial cognition as compared to nulliparous controls (10, 21). In women, pregnancy is similarly associated with cognitive deficits in various domains including verbal memory, an effect which is still evident at three months postpartum and which increases with parity (9). Although the reason for impaired

cognition during late pregnancy and early postpartum is not known, at least in rodents the reduction in spatial abilities may be related to the better survival of offspring, as greater reproductive success is seen in female meadow voles that have smaller home range sizes (23).

There are also effects of motherhood on hippocampus-dependent learning that extend beyond the early postpartum period. In rodents, Craig Kinsley and others have shown enhanced spatial memory late postpartum as well as positive effects of reproductive experience on spatial cognition *after* weaning (14, 21, 24, 25). These effects are attributable to mothering and persist throughout the lifespan into aging (14, 24, 25). There is limited evidence for similar long term positive effects of motherhood on cognition in women but the majority of studies have only followed cognitive changes up to 24 months postpartum (26). For example, Vanston et al. examined parous women until menstruation resumed (which was up to 18 month after parturition) and found an enhancement over nulliparous women on working memory tasks, but only if they had been pregnant with a boy (10). However, it is important to note that the enhancing effects of motherhood on memory are not universally seen with aging in either women or rodents (27, 28) (also see aging and motherhood section).

Hippocampal plasticity across the peripartum period: dendritic architecture and dendritic spines

Coupled with the changes in rodent hippocampus-dependent cognition are time- and experience-dependent alterations in hippocampus structure and plasticity. For example, in the CA1 region of the hippocampus, increased dendritic spine density has been observed during the early (29) and late (30) postpartum periods of primiparous female rats. Spine density does not remain elevated in primiparous female rats after weaning, indicating that enhanced dendritic spine density might be transient and dependent on the presence of offspring (31). Another possibility is that the persistence of dendritic spines may be modulated by reproductive experience. Consistent with this are data showing that unlike primiparous female rats, multiparous females after weaning have more dendritic spines on CA1 basal dendrites compared to nulliparous females (31). Although spines are not altered, primiparous females after weaning do exhibit structural alterations characterized by decreased dendritic length and fewer dendritic branch points on pyramidal neurons in both the CA1 and CA3 regions of the hippocampus (22).

Changes in hippocampal morphology have been linked to cognitive capacity in rats, although these effects are sex dependent (14, 32). In virgin females, when levels of CA1 spine density are high (ie during proestrous) (33), spatial ability is reduced (34, 35). Furthermore, while chronic restraint stress is associated with CA3 dendritic atrophy in female rats (36) perhaps paradoxically it is also associated with better spatial working memory (37). Likewise, early postpartum is characterized by increased spine density and impaired spatial abilities, while improved spatial abilities late postpartum are associated with reduced CA3 dendritic complexity (21, 29, 31). However, changes in dendritic architecture and spines are not always linked to cognitive changes during the peripartum period suggesting other mechanisms may be involved.

Hippocampal plasticity across the peripartum period: adult neurogenesis

Along with peripartum associated modifications in dendritic spines and dendritic architecture are changes in hippocampal neurogenesis. Although cell proliferation does not seem to be altered during pregnancy in female rats (38–40), a number of investigators have noted reduced cell proliferation in the dentate gyrus of the hippocampus during the early postpartum period (41–43). This effect is transient such that by the time of weaning cell proliferation is no longer reduced in postpartum mothers (42). Moreover, the early postpartum reduction in cell proliferation does not seem to be modulated by reproductive experience since it occurs in both primiparous and multiparous females (43). In contrast, Pawluski and Galea (43) found that the number of new neurons surviving across the postpartum period was reduced only in primiparous rats. This reduction in neurogenesis was related to pregnancy alone as female rats that were pregnant but did not receive mothering experience also showed the reduction in neurogenesis. Interestingly, mothering alone has the opposite effect and increases neurogenesis in the hippocampus as demonstrated in studies using ‘foster’ mothers (nulliparous rats given rat pups for 21 days; (43)).

Although the function of adult neurogenesis in the hippocampus is not completely known, it has been linked to hippocampus-dependent tasks (14, 44, 45), with lower levels of neurogenesis correlated with poorer performance. Thus, reduced production of new neurons early postpartum may contribute to impaired spatial abilities seen at this time (41). It may seem counterintuitive that hippocampal neurogenesis is decreased during the peripartum period; a time of significant plasticity in many regions. But it is important to consider that lactation is energetically expensive and thus it may be beneficial for the system to have adapted a reduced capacity to exhibit behaviors that are not deemed necessary. Indeed, as indicated above, reproductive success has been linked to smaller home range sizes and thus the female physiology may have evolved to limit spatial ability (23).

Hormonal mechanisms underlying hippocampal plasticity during the peripartum period

As previously indicated, the peripartum period is accompanied by vast endocrine changes and these have the capacity to modulate hippocampal plasticity during this time (17, 46). These include changes in the steroid hormones, corticosterone and estradiol, as well as peptides hormones necessary for lactation such as oxytocin (in this issue see (6, 47)) and prolactin. Importantly, receptors for these hormones are expressed within the hippocampus (16, 18, 40, 48). Moreover, each has been shown to affect various aspects of hippocampal plasticity in virgin rats. Specifically, high levels of corticosterone decrease dendritic arbors in the CA3 region of the hippocampus (36, 49) and reduce adult neurogenesis (50, 51) while estradiol increases dendritic spine density in area CA1 and enhances neurogenesis (33, 52, 53). Oxytocin and prolactin also promote neurogenesis in the hippocampus (16, 18, 54), although their effects on dendritic spines and morphology have not been investigated.

Leuner et al. demonstrated that the early postpartum reduction in cell proliferation coincides with lactation-induced elevations in basal glucocorticoid levels (41) and both were prevented by removal of nursing pups (42). Moreover, eliminating increased basal

corticosterone (CORT) levels in postpartum rats by means of adrenalectomy and low dose CORT replacement blocked the reduction in cell proliferation (42). Thus, offspring interactions and lactation inhibit hippocampal cell production in postpartum female rats via increases in glucocorticoids. However, elevated circulating levels of CORT are not the only hormonal factor mediating these effects. The postpartum period is also accompanied by a decrease in estradiol levels (41) and it has been shown that manipulating estradiol using a hormone-simulated pregnancy regimen produces a similar decrease in cell proliferation to that found during the early postpartum period in rats (55). Taken together these data suggest that both ovarian and adrenal steroids likely contribute to reductions in hippocampal cell production during the postpartum period. In contrast, the increase in new neuron production in nulliparous female rats following pup exposure (43) might reflect environmental enrichment in the absence of hormonal changes associated with lactation and the postpartum period. Indeed, environmental enrichment is known to stimulate hippocampal neurogenesis in the dentate gyrus of virgin male and female rodents (14). In lactating females, however, it appears that the possible enriching effects of pup exposure are secondary to the effects of the postpartum hormonal environment.

The hippocampus is not a homogenous structure but instead exhibits differences in function and connectivity along the dorsal-ventral axis (56). While the dorsal hippocampus is most implicated in learning and memory, the ventral hippocampus is more generally thought to be involved in anxiety regulation and unlike the dorsal hippocampus is interconnected with various regions involved in maternal care and neuroendocrine function (56). Given these differences, it is conceivable that there are regional variations in hippocampal neurogenesis during the postpartum period. Indeed, the postpartum reduction in cell proliferation occurs predominantly within the dorsal dentate gyrus whereas cell proliferation in the ventral dentate gyrus is unaltered (B. Leuner and E. Gould, unpublished data). These data suggest that not all areas of the hippocampus are equally affected and that perhaps neurogenesis in the dorsal region may be most vulnerable to hormonal environment of the postpartum period whereas the neurogenesis in the ventral region may be resilient. In this regard, oxytocin and prolactin both prevent the adverse effects of stress and/or glucocorticoids on neurogenesis in the hippocampus with oxytocin having a specific effect in the ventral dentate gyrus where receptors for this peptide are most abundant (16, 48). Future studies are necessary to assess the involvement of these neuropeptides on the observed regional differences in postpartum hippocampal neurogenesis.

The hormonal mechanisms underlying alterations in other aspects of hippocampal morphology during the postpartum period have yet to be determined. High levels of circulating glucocorticoids during the postpartum period may contribute to hippocampal dendritic remodeling observed in primiparous females after weaning (31) since they have been associated with dendritic atrophy of pyramidal cells in the hippocampus of nulliparous rats (14). The early postpartum increase in CA1 spine density on the other hand likely involves pregnancy-related changes in estrogen and progesterone because nulliparous female rats treated with these hormones in a regimen that mimics pregnancy were found to undergo similar changes in spine number (29). Another possibility is that postpartum increases in spine density result from the enriching effects of maternal experience given that

environmental enrichment is also known to have a beneficial effect on dendritic spines in the hippocampus (14).

Importantly, there are some notable differences in hippocampal plasticity between primiparous and multiparous rats (31, 43). Although the mechanisms for these changes are not known, hormonal variations with increasing parity have been documented. For example, multiparity is associated with higher estradiol and lower prolactin during gestation compared to primiparity (57, 58). Furthermore, primiparous rats have higher corticosterone and lower corticosteroid binding globulin at various time points during the postpartum than multiparous rats (59). In addition, there are alterations in opioid receptors in the medial preoptic area with parity (60). Therefore, it remains to be determined whether hormonal variations in primiparous versus multiparous females may also contribute to the differential effects of parity on hippocampal plasticity that have been reported (43, 57, 59, 60). Even in cases where primiparous and multiparous females exhibit the same response (ie reduced cell proliferation) it will be necessary to determine whether similar or different mechanisms are involved. Regardless of the exact mechanisms, when taken together these data suggest that peripartum period is a time of significant plasticity and structural reorganization of the hippocampus.

Neurogenesis and stress-related disorders

Women exhibit a higher susceptibility to stress-related illnesses, such as mood and anxiety disorders than men (61). During the peripartum period, women are at great risk to develop several psychiatric disorders such as postpartum depression (in this issue see (6, 7)), which affects 15–20 % of mothers (3). Further, the greatest incidence for depression in women is during the reproductive years (62). A number of risk factors have been identified that may increase the risk of postpartum depression in mothers including previous depressive episodes, antepartum depression, the dramatic fluctuation in sex steroids across the peripartum period social factors such as marital and economic status and smoking. (63–66). Stress exposure is another risk factor for postpartum depression, which can easily be modelled in rodent studies (67). While it is unlikely that a specific rodent model of a postpartum mood or anxiety disorder is achievable, assessment of the behavioral, physiological, molecular and neuroendocrine alterations caused by such factors in basic research can provide a better understanding of the etiology of the disorders.

In addition to the peripartum-associated changes described above, there are profound sex differences in neurogenesis processes (31, 43, 65, 68). Intriguingly, neurogenesis has been repeatedly implicated in the pathogenesis of stress-related disorders, such as depression, and in the mechanism of action of current antidepressants (15, 69, 70). Thus, given that sex steroids and stress exposure have been implicated in both postpartum depression and alterations in neurogenesis in the hippocampus, a number of animal models, designed to mimic the withdrawal of sex steroids or to interfere with HPA axis function in the peripartum period have been investigated in relation to hippocampal plasticity.

Animal models of postpartum depression based on steroid hormones

As stated above, the prevalence of postpartum depression is approximately 15–20% but up to 80% of women experience postpartum blues (3). Two animal models of postpartum depression were created based on steroid hormones (71, 72). One was based on ovarian steroid withdrawal after birth (71) and the other one was based on administering high levels of CORT to the dam postpartum (72). In terms of hippocampal plasticity, cell proliferation in the dentate gyrus was decreased following withdrawal from pregnancy-related hormones (55). Furthermore high levels of CORT to the dam during either gestation (40 mg/kg) or high or low levels of CORT (10 or 40 mg/kg) to the dam during the postpartum reduced cell proliferation in the female hippocampus at the time of weaning compared to oil-injected primiparous rats (73). In addition, dendritic branching in the basal region of the CA3 pyramidal cells was reduced in CORT-treated postpartum dams (74), consistent with a study showing 3 weeks of chronic restraint stress resulted the same basal region in nulliparous female rats (36). Perhaps paradoxically dams treated with high CORT postpartum also showed an increase in mushroom spine density (74) at weaning but this finding was consistent with a study showing that chronic restraint stress increased spine density in the CA3 region of male rats (75). The reader is directed to a review of steroid hormone involvement in postpartum depression for further information (66).

Animal models of postpartum depression based on stress exposure

As mentioned above, stress during pregnancy represents one of the most prominent risk factors for the development of postpartum mood disorders and is known to have differential effects on neurogenesis in male and female rodents (76, 77). Although most studies that employ maternal stress are primarily interested in the effect of such stress on the offspring (in this issue see (78)), stress during both pregnancy and lactation has repeatedly been shown to change maternal behavior, anxiety- and depression-like behavior as well as HPA axis activity (see (65, 67, 77) for reviews). In addition to the peripartum-associated elevated basal CORT levels, there are numerous alterations that act in concert to decrease the response of HPA axis to external stressors (79, 80). This raises the interesting possibility that stress during the peripartum period may affect neurogenesis in a different fashion to that observed in male and female (virgin) rodents.

Repeated restraint stress from pregnancy days 11 to 17 (three times a day for 45 min) increased cell proliferation in the hippocampus compared with controls as assessed using Ki67, an endogenous protein expressed during most stages of the cell cycle, on pregnancy day 21. This stress protocol also increased Ki67 staining in virgins, suggesting that this may more related to females rather than the peripartum period *per se*. There was no effect of stress on BrdU+ cell survival in either virgin or pregnant rats (BrdU injected on pregnancy day 0; (77)). In a follow-up study, repeated restraint stress for 1h a day during the last two weeks of pregnancy (e.g. pregnancy day 8 – 21) caused apical dendritic atrophy in CA3, but not CA1, pyramidal cells in both virgin and pregnant rats. The reduction in dendritic length and branches was more severe in pregnant rats and, of note; the dendritic complexity of these cells was also reduced by pregnancy alone (49). Further, even early life environment

has been shown to affect peripartum-associated hippocampal plasticity when the offspring become pregnant (72, 81).

David Slattery's group has recently performed a study investigating the effect of repeated restraint stress during the first weeks of lactation (lactation days 2 – 13; 2h per day), which provides the first direct evidence that both hippocampal morphology and neurogenesis are effected differentially during this period (82). The lactation-associated reduction in absolute and relative brain weight, which has also been shown in humans (8) was shown to reversed by exposure to the stress paradigm. This reversal was also reflected in hippocampal neurogenesis, as the lactation-associated decrease in dentate gyrus cell proliferation 24 h after the end of stress exposure (i.e. lactation day 14)) was also prevented by stress exposure; despite an increase in basal CORT levels. In this study, BrdU+ cell survival was also investigated by injecting BrdU during the first 4 days of stress (lactation days 2 – 5) and assessing the number of BrdU+ cells on lactation day 21 (i.e. immediately prior to weaning). While BrdU+ cell survival was not affected, stress exposure reduced neuronal differentiation (82).

Taken together, these studies, as well as those described above following exogenous CORT administration, suggest that the hippocampus may be more vulnerable to the effects of stress during the peripartum period compared with virgins. Moreover, they suggest that CORT levels are only partly involved in the regulation of adult hippocampal neurogenesis under stress conditions during the peripartum period. Thus, fluctuations in other hormones that occur classically during the peripartum period may also play a major role, such as oxytocin and prolactin, which, as mentioned above, have been shown to influence hippocampal neurogenesis (16, 18). Alternatively differential interactions with pups after restraint stress may contribute to the lack of pregnancy/lactation-induced decrease cell proliferation since as pointed out earlier, pup exposure can increase cell proliferation in nulliparous rats (43, 83). In support of this, restraint stress during the first weeks of lactation increased active nursing behavior in dams for the first two hours after stress compared with control dams (82). Clearly high maternal CORT or stress can adversely affect the offspring, for a review on the effects of early life stress and environment on offspring development see reviews in this issue (78, 84, 85).

Animal models of postpartum depression based on selective breeding

Selective breeding models such as animals bred for high or low anxiety- related behavior (HAB and LAB, respectively) or depressive-like behavior, namely the Flinders Sensitive Line (FSL) have been investigated during the peripartum period. While HAB rat and mouse mothers have been repeatedly demonstrated to display elevated nursing behavior, LAB and FSL rat dams show decreased maternal care towards their offspring (86–89). HAB females have been shown to display reduced cell proliferation and survival compared with non-selected CD-1 mice, while prenatal stress decreased cell survival only in HAB offspring (90, 91). Similarly, FSL rats display decreased hippocampal volume and neuron and glial numbers in various hippocampal subregions (92). Although, it has not been studied to date in dams, these findings suggest that hippocampal plasticity may be further altered in HAB and FSL dams and play a role in their maternal phenotype.

Aging and motherhood

Given the profound changes a woman's body goes through to carry a fetus successfully it is perhaps not surprising that there may be long-lasting effects of motherhood on the female brain. There is a growing body of evidence to indicate that previous motherhood can affect the aging brain in both rodents and humans. Previous reproductive experience increased cell proliferation in the hippocampus to estrogens (93), and brain derived neurotrophic factor levels in the hippocampus (94), while it reduced the age-related decline in spatial memory and levels of amyloid precursor protein in the hippocampus (95) in middle-aged rats. However perhaps in contrast, parity is associated with an increased risk to develop Alzheimer's disease (96, 97), and parous women present with dementia at an earlier age (96, 98). The effect of parity on the age of onset of Alzheimer's disease is modulated by the apolipoprotein E genotype (99) and by the genetic variation in the CYP19 gene (100). An earlier age of onset of Alzheimer's disease in parous women was seen if they possessed the TT allele of the rs4646 genotype but remarkably this same relationship was not seen in nulliparous women (100). These findings suggest that genotype interacts with reproductive experience to affect earlier age of onset of Alzheimer's disease in women. In addition, one study found increased levels of Alzheimer's-related neuropathology (senile plaques) in women with increasing parity (101). Intriguingly a recent study may reconcile these seemingly contradictory findings of aging and parity on brain health from the human and rodent literature. Rena Li and colleagues found that reproductive experience differentially affected cognition along with cortical and hippocampal synaptophysin levels depending on the genotype of the female mouse (wildtype or APP23 (an Alzheimer's mouse model); (27)). The normal cognitive enhancement seen with reproductive experience in 12 month old mice was not apparent in the APP23 mice in either the Y maze or spontaneous alternation behavior (27). Furthermore reproductive experience increased synaptophysin levels in wildtype female mice but reduced synaptophysin levels in APP23 female mice. In addition, reproductive experience increased the number of plaques seen in the cortex and hippocampus in the APP23 mice compared to nulliparous APP23 mice. A somewhat similar finding was observed in women as nulliparity was associated with less cognitive decline in aging women (28). Cindy Barha and Liisa Galea (93) examined the effects of acute injections of various estrogens on cell proliferation in middle-aged female rats that had either no reproductive experience or were retired breeders (having had at least 4 litters). They found that all estrogens tested were sufficient to increase the level of cell proliferation in retired breeder females (those females with reproductive experience) but none of the estrogens significantly influenced cell proliferation in middle-aged females without reproductive experience. Furthermore, ovariectomy in middle-aged female rats reduced cell proliferation of reproductively-experienced female compared to sham controls, a similar finding is seen in young adults (52). These studies illustrate that the aging maternal hippocampus responds differently to ovarian hormones compared to the non-maternal hippocampus and may have implications for treatment and disease risk especially for sex-related neurological diseases. It is important to note that these are early days in understanding the significance of reproductive experience on aging in the female brain. Researchers are just beginning to explore the interactions between parity, genes, and hormone exposure on age-related dementias.

Conclusions

In this review, we have highlighted the dramatic changes that a mother undergoes during the peripartum period, which include substantial changes in hippocampal plasticity and hippocampus-based cognition. Thus, in the hippocampus of the mother cell proliferation, neurogenesis and dendritic architecture are reduced during the peripartum period. In more detail, while increased spine density has been observed in the CA1 region during the postpartum period, primiparous rats show decreased dendritic length and branch points in both the CA1 and CA3 regions compared with virgins. The decreases in dendritic length and branch points are still observed after weaning whereas spine density normalizes; except in multiparous females. These changes coincide with alterations in both ovarian and adrenal steroids in the mother and appear to require the presence of the pups. Interestingly, pup exposure in nulliparous rats leads to increased hippocampal neurogenesis suggesting that the hormonal profile of the mother may be the driving factor in her hippocampal plasticity. It should be noted that in biparental species significant changes in hormones as well as alterations in neuroplasticity are seen in fathers (as reviewed in this issue, see (85, 102)).

Such changes in hippocampal plasticity as those observed in the peripartum period have been implicated in stress-related disorders and this time represents a risk factor for woman to develop psychiatric disorders such as postpartum depression. Indeed, it has been demonstrated that withdrawal from pregnancy-related hormones and daily administration of high-doses of CORT during either pregnancy or lactation reduce cell proliferation in the hippocampus. Further, postpartum CORT administration also reduced dendritic branching of CA3 pyramidal cells, which reflects similar stress-related effects observed at the end of pregnancy. Stress during pregnancy and the postpartum period have also been shown to increase proliferation while not affecting new cell survival; although neuronal differentiation was reduced by stress in the postpartum period. However, whether these changes play a causal role in postpartum mood disorders remains to be determined.

Ageing is another factor known to affect hippocampal plasticity and reproductive experience has been shown to enable estrogens in later life to increase cell proliferation in the dentate gyrus. While reproductive experience reduces the age-related decline in spatial memory this effect appears to be offset in animal models of Alzheimer’s disease. However, the effects of reproductive experience on the onset of Alzheimer’s disease appear are more controversial and influenced by genetic variation in the CYP19 gene.

Taken together, these studies show that hippocampal architecture undergoes substantial peripartum-associated plasticity and interference with these processes by ovarian and/or adrenal steroid alterations may play a role in postpartum mood disorders. Finally, reproductive experience continues to affect hippocampal plasticity later, which impact on cognition and Alzheimer’s disease.

Acknowledgments

The work by LAMG was funded by operating grants from NARSAD, Coast Capital Depression Fund and CIHR. The work by DAS was funded by the Deutsche Forschungsgemeinschaft (DFG SL141/4-1). The work by BL was funded by grants from NARSAD and NIH (MH084148).

References

1. Brett M, Baxendale S. Motherhood and memory: a review. Psychoneuroendocrinology. 2001; 26(4): 339–62. [PubMed: 11259856]
2. Kobayashi S, Sugiura H, Ando Y, Shiraki N, Yanagi T, Yamashita H, Toyama T. Reproductive history and breast cancer risk. Breast cancer. 2012; 19(4):302–8. [PubMed: 22711317]
3. O'Hara MW, McCabe JE. Postpartum depression: current status and future directions. Annual review of clinical psychology. 2013; 9:379–407.
4. Russell EJ, Fawcett JM, Mazmanian D. Risk of obsessive-compulsive disorder in pregnant and postpartum women: a meta-analysis. The Journal of clinical psychiatry. 2013; 74(4):377–85. [PubMed: 23656845]
5. Yang CY, Kuo HW, Chiu HF. Age at first birth, parity, and risk of death from ovarian cancer in Taiwan: a country of low incidence of ovarian cancer. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2007; 17(1):32–6. [PubMed: 17291228]
6. Lonstein JS, Maguire J, GM, Neumann ID. Emotion and mood adaptations in the peripartum female: complementary contributions of *gamma*-aminobutyric acid and oxytocin. Journal of neuroendocrinology. this issue.
7. Moses-Kolko E, Horner, Phillips, Hipwell, Swain. In search of neural endophenotypes of postpartum psychopathology and disrupted maternal caregiving. Journal of neuroendocrinology. in this issue.
8. Oatridge A, Holdcroft A, Saeed N, Hajnal JV, Puri BK, Fusi L, Bydder GM. Change in brain size during and after pregnancy: study in healthy women and women with preeclampsia. Ajnr. 2002; 23(1):19–26. [PubMed: 11827871]
9. Glynn LM. Giving birth to a new brain: hormone exposures of pregnancy influence human memory. Psychoneuroendocrinology. 2010; 35(8):1148–55. [PubMed: 20304563]
10. Vanston CM, Watson NV. Selective and persistent effect of foetal sex on cognition in pregnant women. Neuroreport. 2005; 16(7):779–82. [PubMed: 15858424]
11. Slattery DA, Neumann ID. No stress please! Mechanisms of stress hyporesponsiveness of the maternal brain. The Journal of physiology. 2008; 586(2):377–85. [PubMed: 17974588]
12. Barrett J, Fleming AS. Annual Research Review: All mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. Journal of child psychology and psychiatry, and allied disciplines. 2011; 52(4):368–97.
13. Dobolyi, A.; Grattan, DR.; Stolzenberg, DS. Preoptic inputs and mechanisms that regulate maternal responsiveness. in this issue
14. Leuner B, Gould E. Structural plasticity and hippocampal function. Annual review of psychology. 2010; 61:111–40. C1–3.
15. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature. 2011; 476(7361):458–61. [PubMed: 21814201]
16. Leuner B, Caponiti JM, Gould E. Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. Hippocampus. 2012; 22(4):861–8. [PubMed: 21692136]
17. Pawluski JL, Brummelte S, Barha CK, Crozier TM, Galea LA. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. Frontiers in neuroendocrinology. 2009; 30(3):343–57. [PubMed: 19361542]
18. Torner L, Karg S, Blume A, Kandasamy M, Kuhn HG, Winkler J, Aigner L, Neumann ID. Prolactin prevents chronic stress-induced decrease of adult hippocampal neurogenesis and promotes neuronal fate. J Neurosci. 2009; 29(6):1826–33. [PubMed: 19211889]
19. Winocur G, Becker S, Luu P, Rosenzweig S, Wojtowicz JM. Adult hippocampal neurogenesis and memory interference. Behavioural brain research. 2012; 227(2):464–9. [PubMed: 21669236]
20. Taupin P. BrdU immunohistochemistry for studying adult neurogenesis: paradigms, pitfalls, limitations, and validation. Brain research reviews. 2007; 53(1):198–214. [PubMed: 17020783]
21. Workman JL, Barha CK, Galea LA. Endocrine substrates of cognitive and affective changes during pregnancy and postpartum. Behavioral neuroscience. 2012; 126(1):54–72. [PubMed: 21967374]

22. Kinsley CH, Lambert KG. Reproduction-induced neuroplasticity: natural behavioural and neuronal alterations associated with the production and care of offspring. Journal of neuroendocrinology. 2008; 20(4):515–25. [PubMed: 18266940]
23. Sheridan M, Tamarin RH. Space use, longevity, and reproductive success in meadow voles. Behavioral Ecology and Sociobiology. 1988; 22(2):85–90.
24. Kinsley CH, Madonia L, Gifford GW, Tureski K, Griffin GR, Lowry C, Williams J, Collins J, McLearie H, Lambert KG. Motherhood improves learning and memory. Nature. 1999; 402(6758): 137–8. [PubMed: 10647003]
25. Lemaire V, Lamarque S, Le Moal M, Piazza PV, Abrous DN. Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. Biological psychiatry. 2006; 59(9):786–92. [PubMed: 16460692]
26. Buckwalter JG, Buckwalter DK, Bluestein BW, Stanczyk FZ. Pregnancy and post partum: changes in cognition and mood. Progress in brain research. 2001; 133:303–19. [PubMed: 11589139]
27. Cui J, Jothishankar B, He P, Staufenbiel M, Shen Y, Li R. Amyloid Precursor Protein Mutation Disrupts Reproductive Experience-Enhanced Normal Cognitive Development in a Mouse Model of Alzheimer's Disease. Molecular neurobiology. 2013
28. McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. The Journal of neuropsychiatry and clinical neurosciences. 2003; 15(2):161–7. [PubMed: 12724456]
29. Kinsley CH, Trainer R, Stafisso-Sandoz G, Quadros P, Marcus LK, Hearon C, Meyer EA, Hester N, Morgan M, Kozub FJ, Lambert KG. Motherhood and the hormones of pregnancy modify concentrations of hippocampal neuronal dendritic spines. Hormones and behavior. 2006; 49(2): 131–42. [PubMed: 16005000]
30. Leuner B, Gould E. Dendritic growth in medial prefrontal cortex and cognitive flexibility are enhanced during the postpartum period. J Neurosci. 2010; 30(40):13499–503. [PubMed: 20926675]
31. Pawluski JL, Galea LA. Hippocampal morphology is differentially affected by reproductive experience in the mother. Journal of neurobiology. 2006; 66(1):71–81. [PubMed: 16216005]
32. Luine V, Villegas M, Martinez C, McEwen BS. Repeated stress causes reversible impairments of spatial memory performance. Brain research. 1994; 639(1):167–70. [PubMed: 8180832]
33. Woolley CS, Gould E, Frankfurt M, McEwen BS. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci. 1990; 10(12):4035–9. [PubMed: 2269895]
34. Warren SG, Juraska JM. Spatial and nonspatial learning across the rat estrous cycle. Behavioral neuroscience. 1997; 111(2):259–66. [PubMed: 9106666]
35. Chesler EJ, Juraska JM. Acute administration of estrogen and progesterone impairs the acquisition of the spatial morris water maze in ovariectomized rats. Hormones and behavior. 2000; 38(4):234–42. [PubMed: 11104641]
36. Galea LA, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabhar FS. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. Neuroscience. 1997; 81(3):689–97. [PubMed: 9316021]
37. Bowman RE, Zrull MC, Luine VN. Chronic restraint stress enhances radial arm maze performance in female rats. Brain research. 2001; 904(2):279–89. [PubMed: 11406126]
38. Banasr M, Hery M, Brezun JM, Daszuta A. Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus. The European journal of neuroscience. 2001; 14(9):1417–24. [PubMed: 11722603]
39. Furuta M, Bridges RS. Gestation-induced cell proliferation in the rat brain. Brain research Developmental brain research. 2005; 156(1):61–6. [PubMed: 15862628]
40. Pawluski JL, Barakauskas VE, Galea LA. Pregnancy decreases oestrogen receptor alpha expression and pyknosis, but not cell proliferation or survival, in the hippocampus. Journal of neuroendocrinology. 2010; 22(4):248–57. [PubMed: 20136685]
41. Darnaudery M, Perez-Martin M, Del Favero F, Gomez-Roldan C, Garcia-Segura LM, Maccari S. Early motherhood in rats is associated with a modification of hippocampal function. Psychoneuroendocrinology. 2007; 32(7):803–12. [PubMed: 17640823]

42. Leuner B, Mirescu C, Noiman L, Gould E. Maternal experience inhibits the production of immature neurons in the hippocampus during the postpartum period through elevations in adrenal steroids. Hippocampus. 2007; 17(6):434–42. [PubMed: 17397044]
43. Pawluski JL, Galea LA. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. Neuroscience. 2007; 149(1):53–67. [PubMed: 17869008]
44. Clelland CD, Choi M, Romberg C, Clemenson GD Jr, Fragniere A, Tyers P, Jessberger S, Saksida LM, Barker RA, Gage FH, Bussey TJ. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science. 2009; 325(5937):210–3. [PubMed: 19590004]
45. Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus. 2006; 16(3):296–304. [PubMed: 16411241]
46. Leuner B, Glasper ER, Gould E. Parenting and plasticity. Trends in neurosciences. 2010; 33(10): 465–73. [PubMed: 20832872]
47. Kenkel W, Yee J, Carter CS. Is Oxytocin a Maternal-Fetal Signaling Molecule at Birth? Implications for Development. in this issue.
48. Liberzon I, Young EA. Effects of stress and glucocorticoids on CNS oxytocin receptor binding. Psychoneuroendocrinology. 1997; 22(6):411–22. [PubMed: 9364620]
49. Pawluski JL, Valenca A, Santos AI, Costa-Nunes JP, Steinbusch HW, Strekalova T. Pregnancy or stress decrease complexity of CA3 pyramidal neurons in the hippocampus of adult female rats. Neuroscience. 2012; 227:201–10. [PubMed: 23036618]
50. Brummelte S, Galea LA. Chronic high corticosterone reduces neurogenesis in the dentate gyrus of adult male and female rats. Neuroscience. 2010; 168(3):680–90. [PubMed: 20406669]
51. Wong EY, Herbert J. Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. Neuroscience. 2006; 137(1):83–92. [PubMed: 16289354]
52. Tanapat P, Hastings NB, Reeves AJ, Gould E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. J Neurosci. 1999; 19(14): 5792–801. [PubMed: 10407020]
53. McClure RE, Barha CK, Galea LA. 17beta-Estradiol, but not estrone, increases the survival and activation of new neurons in the hippocampus in response to spatial memory in adult female rats. Hormones and behavior. 2013; 63(1):144–57. [PubMed: 23063473]
54. Mak GK, Weiss S. Paternal recognition of adult offspring mediated by newly generated CNS neurons. Nature neuroscience. 2010; 13(6):753–8.
55. Green AD, Galea LA. Adult hippocampal cell proliferation is suppressed with estrogen withdrawal after a hormone-simulated pregnancy. Hormones and behavior. 2008; 54(1):203–11. [PubMed: 18423635]
56. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron. 2010; 65(1):7–19. [PubMed: 20152109]
57. Bridges RS, Felicio LF, Pellerin LJ, Stuer AM, Mann PE. Prior parity reduces post-coital diurnal and nocturnal prolactin surges in rats. Life sciences. 1993; 53(5):439–45. [PubMed: 8336523]
58. Paris JJ, Frye CA. Estrous cycle, pregnancy, and parity enhance performance of rats in object recognition or object placement tasks. Reproduction. 2008; 136(1):105–15. [PubMed: 18390689]
59. Pawluski JL, Charlier TD, Lieblich SE, Hammond GL, Galea LA. Reproductive experience alters corticosterone and CBG levels in the rat dam. Physiology & behavior. 2009; 96(1):108–14. [PubMed: 18817795]
60. Bridges RS, Hammer RP Jr. Parity-associated alterations of medial preoptic opiate receptors in female rats. Brain research. 1992; 578(1–2):269–74. [PubMed: 1324763]
61. Kessler RC. Epidemiology of women and depression. Journal of affective disorders. 2003; 74(1): 5–13. [PubMed: 12646294]
62. Gutierrez-Lobos K, Scherer M, Anderer P, Katschnig H. The influence of age on the female/male ratio of treated incidence rates in depression. BMC psychiatry. 2002; 2:3. [PubMed: 11860609]
63. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. The American journal of psychiatry. 2000; 157(6):924–30. [PubMed: 10831472]

64. Bloch M, Rubinow DR, Schmidt PJ, Lotsikas A, Chrousos GP, Cizza G. Cortisol response to ovine corticotropin-releasing hormone in a model of pregnancy and parturition in euthymic women with and without a history of postpartum depression. The Journal of clinical endocrinology and metabolism. 2005; 90(2):695–9. [PubMed: 15546899]
65. Hillerer KM, Neumann ID, Slattery DA. From stress to postpartum mood and anxiety disorders: how chronic peripartum stress can impair maternal adaptations. Neuroendocrinology. 2012; 95(1): 22–38. [PubMed: 22042058]
66. Brummelte S, Galea LA. Depression during pregnancy and postpartum: contribution of stress and ovarian hormones. Progress in neuro-psychopharmacology & biological psychiatry. 2010; 34(5): 766–76. [PubMed: 19751794]
67. Perani CV, Slattery DA. Using Animal Models to study Postpartum Psychiatric Disorders. British journal of pharmacology. 2014
68. Levy F, Gheusi G, Keller M. Plasticity of the parental brain: a case for neurogenesis. Journal of neuroendocrinology. 2011; 23(11):984–93. [PubMed: 21824205]
69. Fuchs E. Neurogenesis in the adult brain: is there an association with mental disorders? European archives of psychiatry and clinical neuroscience. 2007; 257(5):247–9. [PubMed: 17554474]
70. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003; 301(5634):805–9. [PubMed: 12907793]
71. Galea LA, Wide JK, Barr AM. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. Behavioural brain research. 2001; 122(1):1–9. [PubMed: 11287071]
72. Brummelte S, Pawluski JL, Galea LA. High post-partum levels of corticosterone given to dams influence postnatal hippocampal cell proliferation and behavior of offspring: A model of post-partum stress and possible depression. Hormones and behavior. 2006; 50(3):370–82. [PubMed: 16780843]
73. Brummelte S, Galea LA. Chronic corticosterone during pregnancy and postpartum affects maternal care, cell proliferation and depressive-like behavior in the dam. Hormones and behavior. 2010; 58(5):769–79. [PubMed: 20688070]
74. Workman JL, Brummelte S, Galea LA. Postpartum corticosterone administration reduces dendritic complexity and increases the density of mushroom spines of hippocampal CA3 arbours in dams. Journal of neuroendocrinology. 2013; 25(2):119–30. [PubMed: 22935038]
75. Sunanda, Rao MS, Raju TR. Effect of chronic restraint stress on dendritic spines and excrescences of hippocampal CA3 pyramidal neurons--a quantitative study. Brain research. 1995; 694(1–2): 312–7. [PubMed: 8974660]
76. Hillerer KM, Neumann ID, Couillard-Despres S, Aigner L, Slattery DA. Sex-dependent regulation of hippocampal neurogenesis under basal and chronic stress conditions in rats. Hippocampus. 2013; 23(6):476–87. [PubMed: 23504963]
77. Pawluski JL, van den Hove DL, Rayen I, Prickaerts J, Steinbusch HW. Stress and the pregnant female: Impact on hippocampal cell proliferation, but not affective-like behaviors. Hormones and behavior. 2011; 59(4):572–80. [PubMed: 21376727]
78. Maccari S, Krugers HJ, Morely-Fletcher S, Szyf M, Brunton PJ. The consequences of early life adversity: neurobiological, behavioural and epigenetic adaptations. Journal of neuroendocrinology. in this issue.
79. Altemus M, Deuster PA, Galliven E, Carter CS, Gold PW. Suppression of hypothalmic-pituitary-adrenal axis responses to stress in lactating women. The Journal of clinical endocrinology and metabolism. 1995; 80(10):2954–9. [PubMed: 7559880]
80. Brunton PJ, Russell JA, Douglas AJ. Adaptive responses of the maternal hypothalamic-pituitary-adrenal axis during pregnancy and lactation. Journal of neuroendocrinology. 2008; 20(6):764–76. [PubMed: 18601699]
81. Akbari EM, Chatterjee D, Levy F, Fleming AS. Experience-dependent cell survival in the maternal rat brain. Behavioral neuroscience. 2007; 121(5):1001–11. [PubMed: 17907831]

82. Hillerer KM, Neumann ID, Couillard-Despres S, Aigner L, Slattery DA. Lactation-induced reduction in hippocampal neurogenesis is reversed by repeated stress exposure. Hippocampus. 2014
83. Ruscio MG, Sweeny TD, Hazelton JL, Suppatkul P, Boothe E, Carter CS. Pup exposure elicits hippocampal cell proliferation in the prairie vole. Behavioural brain research. 2008; 187(1):9–16. [PubMed: 17913255]
84. Haller J, Harold G, Sandi C, Neumann ID. Effects of adverse early-life events on aggression and anti-social behaviours in animals and humans. Journal of neuroendocrinology. in this issue.
85. Braun K, Champagne FA. Paternal Influences on Offspring Development: Behavioural and Epigenetic Pathways. Journal of neuroendocrinology. in this issue.
86. Bosch OJ. Maternal nurturing is dependent on her innate anxiety: The behavioral roles of brain oxytocin and vasopressin. Hormones and behavior. 2011; 59(2):202–12. [PubMed: 21094649]
87. Kessler MS, Bosch OJ, Bunck M, Landgraf R, Neumann ID. Maternal care differs in mice bred for high vs. low trait anxiety: Impact of brain vasopressin and cross-fostering. Social neuroscience. 2011:1–13.
88. Lavi-Avnon Y, Shayit M, Yadid G, Overstreet HD, Weller A. Immobility in the swim test and observations of maternal behavior in lactating Flinders sensitive line rats. Behavioural brain research. 2005; 161(1):155–63. [PubMed: 15904722]
89. Lavi-Avnon Y, Weller A, Finberg JP, Gispan-Herman I, Kinor N, Stern Y, Schroeder M, Gelber V, Bergman SY, Overstreet DH, Yadid G. The reward system and maternal behavior in an animal model of depression: a microdialysis study. Psychopharmacology. 2008; 196(2):281–91. [PubMed: 17928996]
90. Sah A, Schmuckermair C, Sartori SB, Gaburro S, Kandasamy M, Irschick R, Klimaschewski L, Landgraf R, Aigner L, Singewald N. Anxiety- rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. Translational psychiatry. 2012; 2:e171. [PubMed: 23047242]
91. Lucassen PJ, Bosch OJ, Jousma E, Kromer SA, Andrew R, Seckl JR, Neumann ID. Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: possible key role of placental 11beta-hydroxysteroid dehydrogenase type 2. The European journal of neuroscience. 2009; 29(1):97–103. [PubMed: 19032587]
92. Kaae SS, Chen F, Wegener G, Madsen TM, Nyengaard JR. Quantitative hippocampal structural changes following electroconvulsive seizure treatment in a rat model of depression. Synapse. 2012; 66(8):667–76. [PubMed: 22389166]
93. Barha CK, Galea LA. Motherhood alters the cellular response to estrogens in the hippocampus later in life. Neurobiology of aging. 2011; 32(11):2091–5. [PubMed: 20034703]
94. Macbeth AH, Scharfman HE, Maclusky NJ, Gautreaux C, Luine VN. Effects of multiparity on recognition memory, monoaminergic neurotransmitters, and brain-derived neurotrophic factor (BDNF). Hormones and behavior. 2008; 54(1):7–17. [PubMed: 17927990]
95. Gatewood JD, Morgan MD, Eaton M, McNamara IM, Stevens LF, Macbeth AH, Meyer EA, Lomas LM, Kozub FJ, Lambert KG, Kinsley CH. Motherhood mitigates aging-related decrements in learning and memory and positively affects brain aging in the rat. Brain research bulletin. 2005; 66(2):91–8. [PubMed: 15982524]
96. Colucci M, Cammarata S, Assini A, Croce R, Clerici F, Novello C, Mazzella L, Dagnino N, Mariani C, Tanganelli P. The number of pregnancies is a risk factor for Alzheimer's disease. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2006; 13(12):1374–7. [PubMed: 17116223]
97. Ptok U, Barkow K, Heun R. Fertility and number of children in patients with Alzheimer's disease. Archives of women's mental health. 2002; 5(2):83–6.
98. Sobow T, Kloszewska I. Parity, number of pregnancies, and the age of onset of Alzheimer's disease. The Journal of neuropsychiatry and clinical neurosciences. 2004; 16(1):120–1. [PubMed: 14990773]
99. Corbo RM, Gambina G, Ulizzi L, Monini P, Broggio E, Rosano A, Scacchi R. Combined effect of apolipoprotein e genotype and past fertility on age at onset of Alzheimer's disease in women. Dementia and geriatric cognitive disorders. 2007; 24(2):82–5. [PubMed: 17565217]

100. Corbo RM, Gambina G, Ulizzi L, Moretto G, Scacchi R. Genetic variation of CYP19 (aromatase) gene influences age at onset of Alzheimer's disease in women. Dementia and geriatric cognitive disorders. 2009; 27(6):513–8. [PubMed: 19478482]

101. Beeri MS, Rapp M, Schmeidler J, Reichenberg A, Purohit DP, Perl DP, Grossman HT, Prohovnik I, Haroutunian V, Silverman JM. Number of children is associated with neuropathology of Alzheimer's disease in women. Neurobiology of aging. 2009; 30(8):1184–91. [PubMed: 18079025]

102. Saltzman W, Ziegler T. Functional Significance of Hormonal Changes in Mammalian Fathers. Journal of neuroendocrinology. in this issue.