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The long and short term effects of motherhood on the brain

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ABSTRACT

Becoming a mother is associated with dramatic changes in physiology, endocrinology, immune function, and behaviour that begins during pregnancy and persists into the postpartum. Evidence also suggests that motherhood is accompanied by long-term changes in brain function. In this review, we summarize the short (pregnancy and postpartum) and long-term (beyond the postpartum and into middle age) effects of pregnancy and motherhood on cognition, neuroplasticity, and neuroimmune signalling. We also discuss the effects of previous history of pregnancy and motherhood (parity) on brain health and disease (neurodegenerative diseases and stroke outcomes) and on efficacy of hormone and antidepressant treatments. Finally, we argue that pregnancy and motherhood are unique female experiences that need to be taken into account to better understand female brain function and aging.

1. Introduction

The transition to motherhood is associated with extraordinary physiological and behavioural changes to the mother (Fig. 1). During pregnancy and the postpartum, there are dramatic fluctuations in the levels of many circulating hormones. Sex steroid hormones, estrogens and progesterone, increase to maintain pregnancy, ensure safe delivery, and initiate maternal behaviour in rodents, and possibly humans (Brunton and Russell, 2010; Glynn et al., 2016; Kinsley et al., 2015). However, hormonal fluctuations are not the only dramatic changes that occur during pregnancy as cardiac, haematological (blood volume), renal, respiratory outputs change, increasing or decreasing by 20–50%, and there are numerous immune system adaptations in order to accommodate the growth of the fetus (Mor and Cardenas, 2010; Soma-Pillay et al., 2016). In the blood, expression of genes related to oxygen transport, the immune system, and host response to bacteria change over the course of a healthy pregnancy (Knight et al., 2018). Thus, a multitude of unprecedented changes are occurring in a women's body to ensure successful growth and delivery of the fetus, and it is becoming increasingly clear that there are lifelong repercussions from these impressive physiological changes (Fig. 1).

During pregnancy and postpartum, the brain is exposed to escalating levels of a number of hormones, due mainly to the placenta, which also releases novel hormones that women have not experienced prior to pregnancy. It is important to recognize that the temporal patterns of hormones during pregnancy differ between humans and rodents, although in general estradiol, progesterone, and corticosterone increase during gestation and levels drop around the time of labour or parturition (Fig. 2). We and others have shown that many of these hormones regulate neuroplasticity, neuroinflammation, and behaviour (e.g., recently reviewed in Calcia et al., 2016; Galea et al., 2017; Klein and Flanagan, 2016; Leuner and Sabihi, 2016; Lucassen et al., 2015; Mahmoud et al., 2016b). Therefore it is not surprising that there are alterations in brain function that come with pregnancy and motherhood. The purpose of this review is to highlight the effects of motherhood on cognition and associated brain plasticity and inflammation changes, particularly within the hippocampus. We focus on the hippocampus because it is an area well known to regulate learning and memory (Sweatt, 2004), the stress response (Sapolsky et al., 1985), and mood (Campbell and Macqueen, 2004), functions which change during motherhood. Further, the hippocampus is very plastic throughout adulthood as it produces new neurons throughout life in all mammalian species, including humans (Kempermann et al., 2018). Alterations in neurogenesis have been linked to aging, cognition, and the focus of this review, pregnancy and motherhood. In addition, hippocampal volume is used as a proxy for brain health as it is correlated with memory and dementia risk (Apostolova et al., 2006). Lastly the hippocampus is affected by neurodegenerative and psychiatric disorders that

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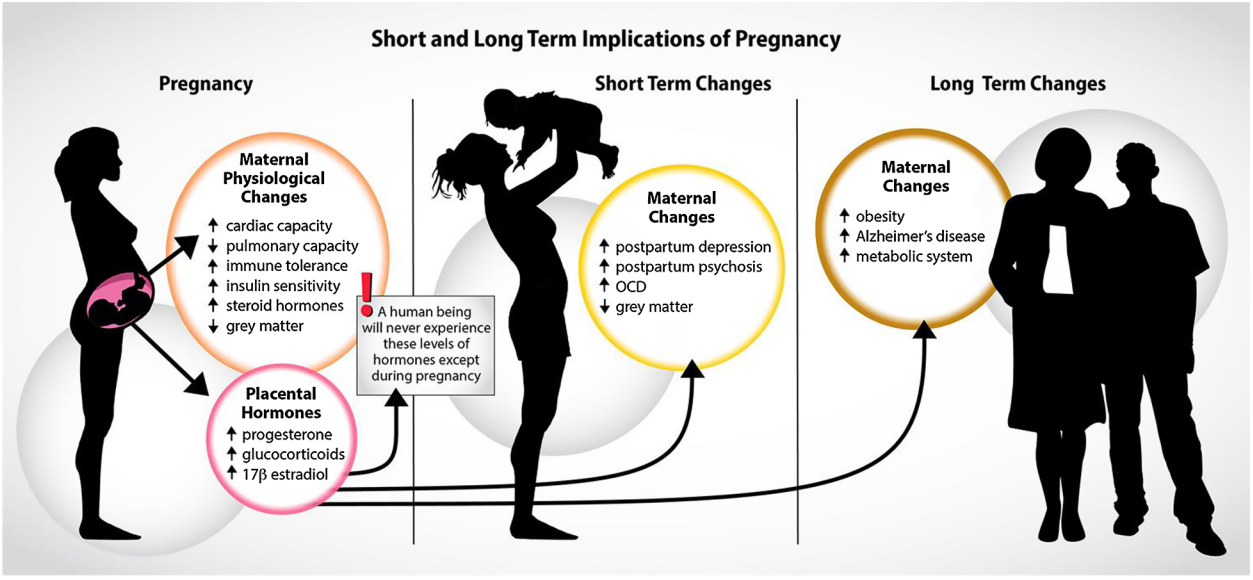

Fig. 1. Physiological and brain changes associated with pregnancy, the postpartum (short-term) and beyond (long-term). Other pregnancy hormones are prolactin and placental lactogens which have been implicated in the regulation of maternal and anxiety related behaviors (Bridges, 2016; Brunton and Russell, 2010; Larsen and Grattan, 2012). Figure reprinted with permission from (Galea et al., 2018a Current Opinion in Physiology).

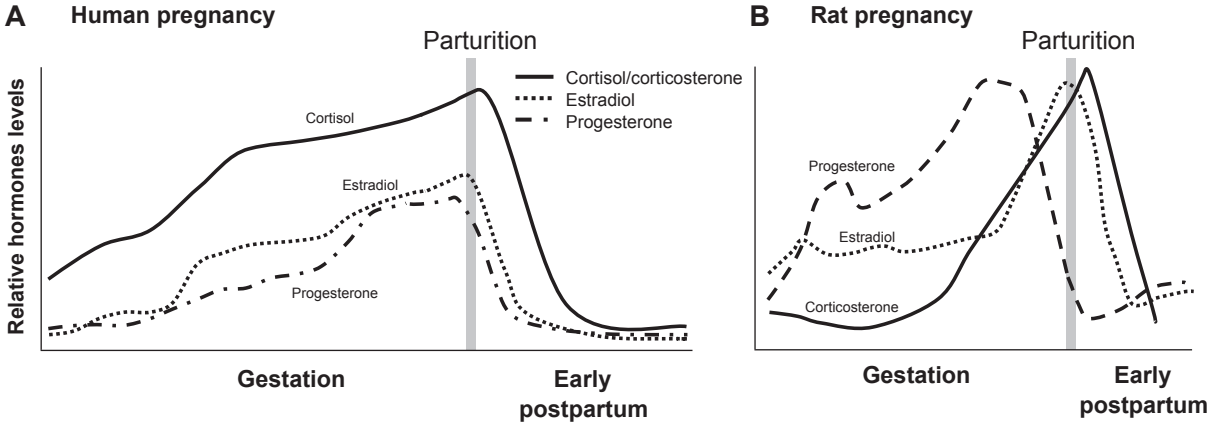

Fig. 2. Hormone profiles during human (A) and rat (B) pregnancy and early postpartum. Based on data from (Brett and Baxendale, 2001; Brunton and Russell, 2010; Pawluski et al., 2009a).

disproportionally affect women (e.g., depression and Alzheimer's disease; Angst et al., 2002; Irvine et al., 2012) and the susceptibility to these disorders either increases during pregnancy/postpartum or with previous parity, respectively. In this review we first summarize, the cognitive and neuroplasticity changes that occur in the short-term (i.e., during pregnancy and postpartum) and then in the long-term (detectable months and years after pregnancy and parturition) in both humans and rodents. Finally we discuss implications of past reproductive experience on neurodegenerative diseases and considerations for future research.

2. The effects of pregnancy and the postpartum on cognition and neuroplasticity

2.1. Human cognition during pregnancy and the postpartum

In humans, there are now three meta-analyses indicating impairments in certain forms of memory during pregnancy and the early postpartum (Anderson and Rutherford, 2012; Davies et al., 2018; Henry and Rendell, 2007). In the meta-analysis of 14 studies, by Henry and Rendell (2007), the authors found impairments in verbal free recall and working memory and these deficits were correlated with hormone levels such as glucocorticoids and estrogens (Glynn, 2010; Henry and Sherwin, 2012). However, in a prospective and large cohort study, no significant differences in cognitive speed, working memory, and immediate and delayed recall were found during pregnancy and postpartum (Christensen et al., 2010). Over the last few years, this topic has attracted more attention and updated meta-analyses have confirmed that pregnant women have small, but significant, deficits in free recall, delayed free recall, working memory, and executive function (Anderson and Rutherford, 2012; Davies et al., 2018). In contrast, recognition memory shows a small improvement during pregnancy (Anderson and Rutherford, 2012). In the postpartum, research is more limited but suggests that cognitive deficits during the early postpartum may be similar to the ones during pregnancy (Anderson and Rutherford, 2012; Henry and Rendell, 2007). However, recent evidence suggests that in the postpartum (2–6 months postpartum), executive function (i.e. mental processes involving goal-directed behaviours such as inhibitory function, working memory, and cognitive flexibility (Diamond, 2013)) is enhanced in mothers versus non-mothers (Almanza-Sepulveda et al., 2018) and this is affected by age at pregnancy with older mothers performing better than teenage mothers (Chico et al., 2014). In terms of

spatial navigation, pregnant women have lower performance compared to non-pregnant controls and these deficits are associated with reductions in striatal volume which in turn are correlated with levels of estradiol (Lisofsky et al., 2016). Davies et al. (2018) also found differences between trimesters, with deficits in cognitive function (including verbal memory, attention, executive functioning, processing speed, and verbal and visuospatial abilities) declining between the first and second trimesters. In addition, fetal sex (Vanston and Watson, 2005) and amount of parity (Glynn, 2012) can have modifying roles on the effects of pregnancy and postpartum on cognition and may explain the differing outcomes between studies (see Section 5). Mothers pregnant with a male fetus outperformed those pregnant with a female fetus on tests of working memory and spatial ability (Vanston and Watson, 2005). Furthermore, parity showed a stepwise reduction in verbal recall memory with multigravid women exhibiting the lowest scores on verbal recall memory followed by bigravid and then primigravid women (Glynn, 2012). A systemic review of 38 studies, by Ouellette and Hampson (2018) also found a modest reduction in memory function (verbal recall, working memory, and prospective memory) in pregnant women, but the authors suggest that this may not be observed in all pregnant women but more in women who are experiencing depression or anxiety. Pregnant women with depressive symptoms, but not in those without symptoms, showed deficits in working memory compared to non-pregnant controls (Hampson et al., 2015). In addition, pregnant women with depression and anxiety have deficits in working memory compared to mothers with no psychiatric symptoms (Kataja et al., 2017). Together this suggests that the effects of pregnancy and motherhood on cognition may be subtle but can be more pronounced in women experiencing depression and anxiety, multiparous women, and pregnant women with a female fetus. Intriguingly, the risk for depression increases in the perinatal period and may also partially explain the somewhat mixed findings in the literature (see Section 4.1).

2.2. Rodents and cognition (spatial, executive function, and social) during pregnancy and into the postpartum

In laboratory rodents, cognitive performance, using spatial hippocampus-dependent tasks, fluctuates during pregnancy and the postpartum period (reviewed in Roes and Galea, 2016; Workman et al., 2012). During early and mid-pregnancy, primiparous female rats display enhanced spatial performance compared to nulliparous females (Bodensteiner et al., 2006; Galea et al., 2000). In contrast, pregnant females late in gestation or primiparous females early in the postpartum display an impaired spatial performance compared to nulliparous females (Darnaudéry et al., 2007; Galea et al., 2000). Intriguingly, after weaning, there is another shift in performance ability with primiparous rats displaying better working and reference memory than nulliparous rats (Kinsley et al., 1999; Pawluski et al., 2006a, 2006b). Pawluski et al. (2006a) demonstrated that these enhancements were seen after weaning and were persistent even when training began 30 days after weaning with improved performance only seen in females that had undergone both pregnancy and mothering but not in foster mothers (pup-induced maternal nulliparous females) or in females that had undergone pregnancy only. Biparous rats also show some enhancements when training was initiated 2–4 days (Pawluski et al., 2006b) and 2 weeks after weaning (Kinsley et al., 1999) but not 30 days after weaning (Pawluski et al., 2006a). One possible mechanism regulating cognitive performance across pregnancy and the postpartum is the fluctuation of steroid and peptide hormone levels during these times (Fig. 2). During early and mid-pregnancy in rodents, estradiol levels are lower than in controls, and lower estradiol is associated with enhanced performance in female rats (Holmes et al., 2002). Late in gestation, estradiol levels are high in both humans and rodents, and high estradiol is associated with poorer spatial performance in female rats (Holmes et al., 2002). In the postpartum, estradiol levels are low but adrenal steroids, oxytocin, and prolactin are high (Bridges, 2016; Darnaudéry et al., 2007; Leuner et al., 2007). Oxytocin improves spatial learning in nulliparous female mice, while blocking oxytocin in multiparous females, early in the postpartum period, inhibits spatial memory (Tomizawa et al., 2003). Surprisingly, the effects of prolactin, a hormone involved in lactation and maternal behaviours (reviewed in Bridges, 2016; Larsen and Grattan, 2012), and adrenal hormones on hippocampal-dependent memory during the postpartum have not yet been investigated. Together, this work provides indirect evidence that fluctuations of estradiol and oxytocin during pregnancy and postpartum could be involved in regulating hippocampal learning and memory.

Compared to spatial tasks, executive function (such as attention and cognitive flexibility) in animal models during pregnancy and motherhood, has received much less attention. During mid- (PD10-11) and late postpartum (PD20-24), cognitive flexibility (a prefrontal cortex-dependent task) is enhanced in mothers (Leuner and Gould, 2010) and requires oxytocin signalling in the prefrontal cortex and the presence of pups (Albin-Brooks et al., 2017). Indeed, blocking the oxytocin receptor with an antagonist in the prefrontal cortex and the removal of the pups eliminates the beneficial effect of motherhood on cognitive flexibility (Albin-Brooks et al., 2017). However, after weaning, there is no beneficial effect of motherhood on performance on a set-shifting task either in primiparous or biparous rats after weaning (Workman et al., 2013). Performance was however affected by the interaction of parity and estrous cycle. The ability to disengage from a previously learned strategy was impaired (increase in perseverative errors) in biparous rats during behavioral estrus (high gonadal hormones) only but once the animals learned the new strategy, they made fewer errors (decrease in regressive errors; Workman et al., 2013). In sum, unlike hippocampus-dependent memory, executive function is enhanced in late pregnancy and the early postpartum period, but this effect does not persist after weaning.

The hippocampus and other regions of the limbic system are implicated in regulating social learning (Choleris et al., 2009), the stress response (Sapolsky et al., 1985), and anxiety (Bannerman et al., 2004), which are also affected during pregnancy and the postpartum. For example, social learning is enhanced in female rats shortly after parturition compared to nulliparous controls (Fleming et al., 1994). In late pregnancy and early postpartum, rats have reduced anxiety and stress responsiveness (Wartella et al., 2003). Young primiparous rats (2–8 weeks after weaning) show reduced anxiety-like behaviour (Byrnes and Bridges, 2006; Love et al., 2005) but this is not always the case (Ladyman et al., 2018; Lemaire et al., 2006; Wartella et al., 2003), which may be due to time since lactation (Tu et al., 2005). In general, pregnancy and lactation are associated with a reduction in anxiety-like behaviour (reviewed in Agrati and Lonstein, 2016) and reduced responses to stress in rodents (Neumann, 2001) and humans (Heinrichs et al., 2001). Taken collectively, pregnancy and motherhood can enhance social learning, reduce anxiety, and stress responsiveness at least during the early postpartum. However, one important aspect to consider in future studies is the challenge of behaviour testing of postpartum female rats as this will result in the separation from her pups. The postpartum is a very sensitive period when the pups depend on their mother for maintaining body temperature and nursing. Separation of the dam from her pups during the first postpartum week alters the pattern of maternal and anxiety-related behaviours and glucocorticoid receptor expression in the hippocampus (Orso et al., 2018). Maternal separation shortly after birth can also have negative effects on maternal attachment in humans (Moore et al., 2012). Future research should carefully consider the effects of maternal separation and take into account measurements of maternal behaviour.

2.3. Neuroplasticity during pregnancy and early postpartum

In women, total brain volume is reduced during pregnancy reaching a nadir at parturition and recovering by 6 months postpartum (Oatridge et al., 2002). It has been suggested that the decrease in brain size with

pregnancy is associated with altered brain metabolism and an increase in intracellular pH after delivery (Holdcroft et al., 2005). Intriguingly, there are notable differences in grey matter volume depending on the brain structure imaged. P. Kim et al. (2010) observed grey matter volume increases during the first 3–4 months postpartum compared to 2–4 weeks postpartum in areas involved in maternal behaviours and motivation, such as the amygdala, hypothalamus, and prefrontal cortex. Similarly Kim et al. (2018) found associations between postpartum months and cortical thickness in the prefrontal cortex during the first 6 months postpartum. However, Hoekzema et al. (2017) saw reductions in grey matter volumes in multiple areas, including the hippocampus, at 2 months postpartum compared to pre-conception levels. Indeed, most grey matter reductions were still observed 2 years after birth (Hoekzema et al., 2017). It is clear that dynamic changes do occur between parturition to 4–6 weeks postpartum. Luders et al. (2018) used the BrainAGE index that estimates the age of the brain with neuroimaging data and compares it to its chronological age (reviewed in Cole and Franke, 2017). They found lower brain ages (i.e., negative BrainAGE index) 6 weeks postpartum compared to 1–2 days postpartum indicating that the brain at 6 weeks postpartum is younger compared to 1–2 days postpartum and therefore the brain seems to recover in the postpartum period from the parturition period. In this latter study, and in the studies by P. Kim et al. (2010), Kim et al. (2018), changes were only investigated during the early postpartum period and so it is not known to what extent the volume and brain age change from preconception, during pregnancy, parturition, or later. As indicated, only one study (Hoekzema et al., 2017) has investigated the long-term effects (2 years) of motherhood compared to preconception on specific brain areas in women. The short and long term effects of pregnancy and motherhood on brain matter volume remain an understudied field, but clearly the effects are time and region-dependent. Further research measuring individual structures with greater anatomical precision (e.g., measuring individual nuclei) at multiple time points (before conception and long after birth) is needed, along with considerations of amount of parity and fetal sex which can affect cognition in pregnancy and postpartum (see Section 5).

Two studies have also investigated functional correlations with changes in brain plasticity during pregnancy and postpartum. Hoekzema et al. (2017) found grey matter reductions in multiple regions involved in social cognition (the superior temporal sulcus, medial and inferior frontal cortex, the fusiform areas and the hippocampus) which were associated with positive maternal attachment. In response to own baby, the strongest neural activity was observed in regions that saw reductions in grey matter volume across pregnancy (Hoekzema et al., 2017) suggesting that the maternal social brain restructures during pregnancy and the postpartum and that reduced volume is associated with enhanced maternal attachment. Furthermore, Zheng et al. (2018) found that postpartum women have decreased neural activity in the cingulate and prefrontal cortex compared to nulliparous controls and this is correlated with impaired cognitive function (visuospatial constructional ability, visual memory, and executive function). These studies are beginning to shed light on the consequences of neuroplasticity and neural activity changes on maternal cognition.

Animal studies have also found brain plasticity changes during pregnancy and the postpartum period. Pregnant rats have slightly smaller hippocampi (Galea et al., 2000) but greater cortical thickness (Hamilton et al., 1977) compared to non-pregnant rats. In the mid-postpartum, primiparous female rats have lower brain weight and hippocampal volume compared to nulliparous females (Hillerer et al., 2014). Studies have also examined changes in neuroplasticity markers during pregnancy and postpartum in the hippocampus (Banasr et al., 2001; Eid et al., 2019; S.K. Kim et al., 2010; Leuner et al., 2010; Leuner and Sabihi, 2016; Pawluski et al., 2010; Pawluski and Galea, 2007; Rolls et al., 2008; Table 1), the dorsal raphe nucleus (Holschbach and Lonstein, 2017), and subventricular zone (SVZ; Furuta and Bridges, 2005; Shingo et al., 2003). In the hippocampus during gestation (GD13) and postpartum (PD8 and PD30), the number of immature neurons (doublecortin (DCX) expression) is lower in primiparous compared to nulliparous female rats and there is a parallel reduction in cell proliferation during gestation and early postpartum (Eid et al., 2019). Similarly in mice and rats, cell proliferation (Ki67) is reduced in the dentate gyrus at GD13 and GD16.5 (Eid et al., 2019; S.K. Kim et al., 2010; respectively) and the survival of new neurons born mid-gestation is reduced (Rolls et al., 2008). In contrast, cell proliferation (through BrdU labeling) is not affected in the hippocampus during early (GD1 and GD7; Furuta and Bridges, 2005; Pawluski et al., 2010) and late pregnancy (GD18 and GD21; Banasr et al., 2001; Furuta and Bridges, 2005; Table 1), although it is increased during gestation in the SVZ (GD21, Furuta and Bridges, 2005; GD7, Shingo et al., 2003). Interestingly, later in gestation (GD18), Banasr et al. (2001) found increased expression of a cell adhesion molecule (the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) involved in cell migration and synaptic reorganization) in the rat dentate gyrus suggesting changes in other forms of structural plasticity may be evident. It is important for studies examining neuroplasticity to take into account timing differences. During pregnancy, hormones show dramatic increases and fluctuations (Figs. 1 and 2), some such as prolactin fluctuate daily during early gestation (reviewed in Brunton and Russell, 2010). Therefore, small variations in timing during early, mid, or late pregnancy/postpartum could reflect hormonal effects on neuroplasticity.

In the early postpartum period, cell proliferation is reduced in the hippocampus (Darnaudéry et al., 2007; Eid et al., 2019; Hillerer et al., 2014; Leuner et al., 2007; Pawluski and Galea, 2007; Table 1). Primiparous dams have decreased cell proliferation on PD2 and PD8, but not on PD28 or PD30 (Darnaudéry et al., 2007; Eid et al., 2019; Leuner et al., 2007; Pawluski and Galea, 2007), compared to nulliparous females. Interestingly, in sheep, cell proliferation is also down-regulated at parturition and early postpartum period in the dentate gyrus (Brus et al., 2010). These findings, along with decreases in brain volume/plasticity in women suggest a conserved mechanism of reduced neuroplasticity in the early postpartum. Not only is cell proliferation reduced but studies show that the survival of new neurons born during early postpartum (PD2-5) is reduced at PD21 (Hillerer et al., 2014; Pawluski and Galea, 2007). Indeed, there is also a reduction in the number of immature neurons at PD21 (Workman et al., 2016, 2015) and PD30 (Eid et al., 2019) compared to age-matched nulliparous females. Together these studies suggest that cell proliferation and survival are reduced during pregnancy and postpartum but only cell proliferation returns to nulliparous levels after the pups have been weaned.

These changes in neurogenesis may be regulated by steroid hormone changes during these time periods. In female rats, a hormone-simulated pregnancy followed by a cessation of estradiol and progesterone (to simulate the postpartum period) replicated the decrease in cell proliferation seen early in the postpartum (Green and Galea, 2008). Adrenalectomy and the subsequent decrease in corticosterone levels eliminated the decrease in cell proliferation at PD8 in postpartum rats (Leuner et al., 2007). Interestingly, exposure to pups in nulliparous females increased neurogenesis in the SVZ (Furuta and Bridges, 2009) and dentate gyrus (Pawluski and Galea, 2007). Exposure to pups for 16 days (Kinsley et al., 1999), but not after 21 days (and tested 1 month later; Pawluski et al., 2006a), enhanced spatial ability in nulliparous rats suggesting that stimuli from pups alone (possibly because of an enriched environment) independently of pregnancy can influence neuroplasticity and spatial behaviour in a time-dependent manner. Conversely, the removal of pups decreased basal corticosterone in the early postpartum and eliminated the subsequent suppression of cell proliferation (Leuner et al., 2007) but not the suppression of new neuron survival (Pawluski and Galea, 2007). In addition to sex steroids, other pregnancy hormones might be involved in regulating hippocampal neurogenesis during pregnancy and postpartum. For example, work in the subventricular zone has demonstrated that high prolactin during early pregnancy in mice induces neurogenesis and is associated

Table 1
Fluctuations in hippocampal neurogenesis during pregnancy and the postpartum period in rats and mice.

	Gestation days							Postpartum days					
	1	7	11–12	13	16.5	18	21	1–2	8	13	21	28	30
Cell proliferation (Ki67 or BrdU)	– [1]	– [2]		↓ [4]	↓ [5]	– [6]	– [2]	↓ [7,8]	↓ [4,8,10]	↓ [9]		– [8]	– [4]
New neuron survival (BrdU)	– Survival of neurons born GD0 [1]		↓ survival of neurons born GD 11–12 [3]					↓ survival of neurons born PD1 [7] and between PD2-5 [9]			– survival of neurons born PD21 [3]		
Neurogenesis (DCX)				↓ [4]					↓ [4]		↓ [11]		↓ [4]
Cell death (pyknotic cells)	↓ [1]						– [1]						

References: [1] Sprague-Dawley rat; Pawluski et al., 2010; [2] Sprague-Dawley rat; Furuta and Bridges, 2005; [3] C57BL/6 mouse; Rolls et al., 2008; [4] Sprague-Dawley rat; Eid et al., 2019; [5] C57BL/6N mouse; S.K. Kim et al., 2010; [6] Wistar rat: Banasr et al., 2001; [7] Sprague-Dawley rat; Pawluski and Galea, 2007; [8] Sprague-Dawley rat; Leuner et al., 2007; [9] Wistar rat; Hillerer et al., 2014 [10] Sprague-Dawley rat; Haim et al., 2017; [11] Sprague-Dawley rat; Workman et al., 2016, 2015.

with anxiety and maternal behaviours in the postpartum (Larsen and Grattan, 2010). Together, this work suggests that reductions in cell proliferation early in the postpartum period are due to pregnancy but not pup exposure without pregnancy, while the reduction in survival of new neurons is due to pregnancy and parturition alone.

In addition to neurogenesis, dendritic spine density in the CA1 region of the hippocampus is higher in late pregnancy and early postpartum compared to nulliparous females (Kinsley et al., 2006). However, dendritic morphology in the CA1 and CA3 regions is reduced in primiparous, but not biparous, rats with no change in spines after weaning (Pawluski and Galea, 2006). In line with this work, using non-invasive proton magnetic resonance spectroscopy, Zhou et al. (2013) found that at GD17, pregnant primiparous rats have higher N-acetylaspartate levels in the hippocampus and thalamus which are associated with increased neuronal metabolism, dendritic sprouting, neurogenesis, or synaptogenesis (Zhou et al., 2013) but also decreased cell proliferation (Cameron et al., 1995). More recently, Chan et al. (2015), using diffusion tensor imaging, found that there are whole brain structural changes at GD17 that facilitate water molecular movement compared to preconception. In addition, in the dorsal hippocampus there is an increase in functional connectivity (measured using resting-state functional MRI) at GD17 suggesting a remodelling of the brain during pregnancy in rats (Chan et al., 2015). Collectively, these studies suggest that in addition to changes in neurogenesis, the hippocampus also undergoes further structural and functional changes during gestation and the postpartum.

There are few studies examining both changes to learning and neuroplasticity during pregnancy and the postpartum period. In the early postpartum, impaired spatial ability is associated with a reduction in cell proliferation in the hippocampus (Darnaudéry et al., 2007). Indirect evidence also suggests that suppression of cell proliferation (Leuner et al., 2007; Pawluski and Galea, 2007) and differentiation (Eid et al., 2019) in the early postpartum coincides with impaired spatial memory (Darnaudéry et al., 2007). Later in the postpartum (PD15), spatial memory is improved relative to nulliparous rats (Darnaudéry et al., 2007) at a time that is coincident with decreased in levels of cell proliferation (PD13; Hillerer et al., 2014). At the point of weaning, primiparous rats have a decreased number of immature neurons (Eid et al., 2019; Workman et al., 2016, 2015), fewer basal branch points, and shorter basal dendritic processes in the CA1 and CA3 regions (Pawluski and Galea, 2006), and this coincides with improved spatial memory when training begins in the late postpartum (Pawluski et al., 2006b). Interestingly, this same atrophy of the CA3 pyramidal neurons (Galea et al., 1997) is coupled with enhanced spatial learning in nulliparous rats after chronic restraint stress (Bowman et al., 2001). At a similar time point (2 weeks after weaning), when spatial memory is still enhanced, hippocampal synaptic potentiation and LTP is increased in primiparous females compared to nulliparous controls (Lemaire et al., 2006) suggesting that enhanced learning and memory is due to combination of neuroplasticity changes (dendritic morphology, neurogenesis, LTP) that occur in the postpartum and after weaning. While hippocampal dendritic spine density increases (Kinsley et al., 2006), neurogenesis decreases during pregnancy (Eid et al., 2019; S.K. Kim et al., 2010; Rolls et al., 2008; Table 1). Previous research has shown that more neurogenesis is not always correlated with better memory (discussed in Duarte-Guterman et al., 2015) and new neurons enhance forgetting (Akers et al., 2014) but also may contribute to impairments in learning given improper integration (Cho et al., 2015; Jessberger et al., 2007). During late pregnancy and the early postpartum, spatial working and reference learning is impaired which is coincident with a decrease in hippocampal neurogenesis. Spatial memory improves after the pups have been weaned which is still evident into middle and older ages (see Section 3.1). In late postpartum, hippocampal neurogenesis is still reduced compared to age-matched nulliparous females, but there is reversal in middle age, with primiparous and multiparous rats exhibiting greater levels of hippocampal neurogenesis compared to nulliparous rats (see Section 3.2; Eid et al., 2019; Barha et al., 2015; Galea et al., 2018b). Thus, while changes in neurogenesis in the hippocampus may be coincident with changes in learning and memory, it is unlikely that these changes contribute completely to cognitive ability, as neurogenesis has been linked to some, but not all forms of memory (reviewed in Cameron and Glover, 2015; Epp et al., 2013). Certainly, increase in the number of new neurons is not sufficient to promote memory, as these new neurons must also make appropriate and advantageous connections into the existing circuitry (e.g., see Akers et al., 2014; Cho et al., 2015; Jessberger et al., 2007). Other modifications such as changes in dendritic structure, synaptic proteins, neurotrophic factors, and neuroimmune signals all likely play a role in altering cognitive ability and have been shown to be affected by parity (Fig. 3). Further research is needed to understand the functional implications of alterations in neuroplasticity in the hippocampus and other brain regions during pregnancy and late postpartum.

At the molecular level, only two studies have investigated changes in gene transcription in the hippocampus during pregnancy and postpartum (Kinsley et al., 2008; Ray et al., 2015). Kinsley et al. (2008) did a microarray analysis of gene expression in the CA1 region of primiparous females at PD5 compared to age-matched nulliparous females. They demonstrated that 12 genes were up-regulated in lactating mothers compared to nulliparous controls. Three of these genes were insulin-like growth factor and insulin-like growth factor binding proteins (Kinsley et al., 2008). Other genes included, synuclein (involved in neurodegenerative disorders), synaptojanin (synaptic vesicle

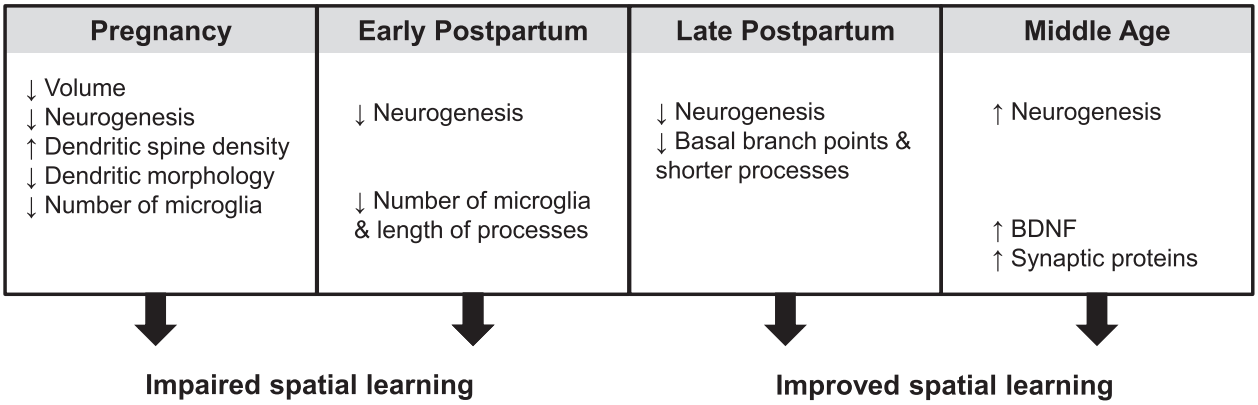

Fig. 3. Summary figure of the effects of reproductive experience on neuroplasticity and neuroimmune changes in the hippocampus of female rodents in the short term (pregnancy and postpartum) and into middle age. See text for details.

recycling), and proenkephalin (an endogenous opioid; Kinsley et al., 2008). Ray et al. (2015) measured expression patterns (using RNA sequencing) in several brain regions during gestation and early postpartum. In the hippocampus, genes with the most significant change were related to hormone and peptide binding, chloride binding, glutathione peroxidase activity, and antioxidant activity, among other gene ontology terms (Ray et al., 2015). The greatest differences in gene expression were observed between nulliparous and GD16 females (788 differentially expressed genes) and between nulliparous and PD10 mothers (867 differentially expressed genes; Ray et al., 2015). Together this work suggests that the hippocampal transcriptome is modified during gestation and the early postpartum period, and although the research is still limited, this supports the many neuroplasticity and cognitive changes that take place during this period.

2.4. Neuroimmune alterations during the peripartum period

Along with changes in hormones, neuroplasticity, and cognitive behavior, there are dramatic changes in the maternal peripheral immune system during the peripartum period (Aagaard-Tillery et al., 2006; Luppi, 2003; Mor and Cardenas, 2010; Schumacher et al., 2014; Sherer et al., 2018). During pregnancy, a hormonally-driven shift from a pro-inflammatory to an anti-inflammatory signaling milieu occurs in order to protect the semi-allogenic fetus from rejection (Robinson and Klein, 2012). Parturition also depends upon peripheral immune changes, with a burst in pro-inflammatory signaling serving as a major trigger to induce uterine contractions and begin labor (Vannuccini et al., 2016). Afterwards, during the postpartum period, the immune response continues when healing and involution take place through the influence of both pro- and anti-inflammatory mediators ultimately normalizing in the days to weeks after birth (Groer et al., 2015). Reproductive experience can also affect the immune system via a neuroendocrine mechanism in the postpartum. In rats, reproductive experience decreases prolactin levels and oxidative burst activity in peritoneal macrophages (Carvalho-Freitas et al., 2011, 2007). Blocking dopamine receptors increases prolactin secretion, oxidative bursts and phagocytosis in peritoneal macrophages in female rats. This work suggest that reproductive experience affects neuroendocrine signalling (hypothalamic dopamine leading to prolactin release) which then affects immune signalling in rats (Carvalho-Freitas et al., 2013, 2011, 2007).

The brain is also an immunocompetent organ that is highly populated with immune cells, called microglia. Microglia are brain-resident macrophages that provide immune surveillance, clear debris to maintain homeostasis, and also engage in inflammatory signaling in response to pathogens, injuries, or other perturbations (Kettenmann et al., 2011). In addition, microglia actively contribute to a variety of normal physiological processes in the healthy brain including neurogenesis, apoptosis, spinogenesis, synaptic refinement and synaptic pruning via the secretion of cytokines, chemokines, and neurotrophic growth factors (Werneburg et al., 2017; Wu et al., 2015). Emerging evidence further points to an essential role for microglial function in behavior, including learning and memory (Parkhurst et al., 2013; Rogers et al., 2011). Importantly, microglia and their signaling are influenced by various pregnancy-related hormones, including estrogens, progesterone, oxytocin, and prolactin (Habib and Beyer, 2015; Karelina et al., 2011; Lei et al., 2014; Sierra et al., 2008; Vegeto et al., 2001; Yuan et al., 2016). Thus, microglia are ideally situated to be hormonally responsive during the transition to motherhood and to regulate peripartum-related neuroplastic changes in brain regions such as the hippocampus as well as their behavioral output.

Although this possibility remains to be investigated, recent studies have begun to explore the neuroimmune environment during pregnancy and the postpartum period in rodents. This work has revealed significant shifts in microglia properties in limbic regions of the rat brain (Haim et al., 2017; Eid et al., 2019). Specifically, in late pregnancy (GD20) and extending into the early-mid postpartum period (PD8), the overall number of microglia in the hippocampus was decreased, an effect driven by a reduction in microglia proliferation and not microglia death (Haim et al., 2017). Other work has found microglia in the hippocampus have shortened processes on PD8 (Eid et al., 2019). The changes in both microglia number and morphology are transitory as the number of microglia and length of microglia processes recover by late postpartum (PD21) and weaning (PD30), respectively (Haim et al., 2017; Eid et al., 2019). Interestingly, the peripartum decrease in microglia number was also found in the prefrontal cortex, amygdala, and nucleus accumbens but was not observed in the motor cortex, suggesting regional specificity, potentially as a result of differential sensitivity of limbic and non-limbic brain regions to hormones. Accompanying the microglial changes, brain levels of the anti-inflammatory cytokine, interleukin (IL-) 10 and the pleiotropic cytokine, IL-6 were increased postpartum (Haim et al., 2017). Other work has reported similar pregnancy-related changes in neuroimmune parameters, including decreased microglia staining in the hippocampus (Posillico and Schwarz, 2016) as well as blunted inflammatory gene expression in the brain following an immune challenge (Sherer et al., 2017). Together, the available evidence thus indicates the peripartum neuroimmune environment is significantly modified. Moreover, the changes that have been observed suggest that the maternal brain may be assuming a protective inflammatory resistant state beginning during late pregnancy and persisting for some time postpartum. These data provide a foundation to further explore the peripartum neuroimmune system and its potential role in regulating different aspects of neuroplasticity and cognitive function during this time. It is also important to consider that the transition to new motherhood is a vulnerable time for mental health (O'Hara and Wisner, 2014). While a number of studies

have implicated neuroimmune dysregulation in anxiety and depression (Hodes et al., 2015; Wohleb et al., 2016), to date only peripheral immune markers have been examined in postpartum depression and these studies have yielded mixed results (Boufidou et al., 2009; Corwin et al., 2015; Maes et al., 2000; Osborne and Monk, 2013; Segman et al., 2010). Because peripheral immune changes may not necessarily reflect immune changes occurring in the brain (Setiawan et al., 2015), future work addressing neuroimmune disruption as a contributor to postpartum mood disorders is needed.

3. Beyond the postpartum: long-term effects of parity on cognition and neuroplasticity

3.1. Cognition

In both humans and rodents, reproductive experience alters cognitive function well past the postpartum and into middle age. In older age women, nulliparity or lower parity is associated with better cognitive function in later adulthood in some studies (Jang et al., 2018; McLay et al., 2003; Rasgon et al., 2005; Smith et al., 1999) but not in others (Geerlings et al., 2001; Henderson et al., 2003; Low et al., 2005; Ryan et al., 2009). Other factors related to reproductive history and endogenous estrogens affect cognition such as the length of reproductive period, age at first pregnancy, and duration of breastfeeding. Giving birth at a younger age is associated with worse cognitive performance (measured with the Mini–Mental State Examination (MMSE)) and verbal fluency (Ryan et al., 2009). Comparatively, later age at last pregnancy is associated with better verbal and cognitive performance later in life (Karim et al., 2016). In addition, measures of higher endogenous estrogens (i.e., lower parity, longer reproductive period, shorter breastfeeding period) are associated with better cognition (Heys et al., 2011; Smith et al., 1999). Indeed, parity can have long term effects on the endocrine system, although this is not observed in all studies (Endogenous Hormones and Breast Cancer Collaborative Group et al., 2011). Young parous women have shorter menstrual cycles, lower levels of estradiol, androgens, and prolactin compared to nulliparous women (Bernstein et al., 1985; Dorgan et al., 1995; Musey et al., 1987b, 1987a). In postmenopausal women, higher parity is associated with higher levels of sex-hormone binding globulin (Chavez-MacGregor et al., 2008) which decreases the levels of free sex hormones including estradiol. It will be important for future studies to take all these reproductive factors into account and to measure hormone levels to better understand the effects and mechanisms of parity on cognition.

In rats and mice, parity has also long term consequences on cognition and is generally associated with better spatial learning and memory in middle age or older (Barha et al., 2015; Cui et al., 2014; Galea et al., 2018b; Gatewood et al., 2005; Kinsley et al., 2008; Lemaire et al., 2006; Love et al., 2005; Macbeth et al., 2008). Studies have found that primiparous and biparous females have better re-acquisition of spatial performance and an attenuated age-dependent cognitive decline compared to nulliparous females (Gatewood et al., 2005). Improvements in spatial reference memory were observed with repeated testing in adult biparous females (6 months of age) while primiparous females had shorter latencies than nulliparae beginning at middle age (12 months of age; Gatewood et al., 2005). Lemaire et al. (2006) found that improvements in spatial memory with parity that lasted the entire lifespan in 22 month old female rats with repeated testing (at 6 and 12 months of age). In middle age, multiparity slightly enhances spatial working memory performance but impairs spatial reference memory (Barha et al., 2015), while primiparity slightly improves spatial reference memory (Galea et al., 2018b) but has no significant effect on spatial working memory at middle age (Zimberknopf et al., 2011). In non-spatial tasks, the evidence is limited. At middle age, multiparous female rats perform better in non-spatial tasks such as object recognition than nulliparous females (Macbeth et al., 2008) although this is not observed in younger primiparous rats (Lemaire et al., 2006). Together this suggests that the effects on hippocampal-dependent cognition depend on age, types of memory, and the amount of parity (see Section 5).

Finally, there is mixed evidence that parity can have effects on anxiety-related behaviours into middle age. At middle age, some studies have found that parity increases (Byrnes and Bridges, 2006), decreases (Love et al., 2005) or has no significant effect (Macbeth et al., 2008) on anxiety-like behaviour. It is possible that differences in ages (time since weaning of the pups), level of parity (primiparous, biparous or multiparous; see Section 5), and gonadal hormones (cycling vs non-cycling) may account for some of the discrepancies between studies.

3.2. Neuroplasticity and other mechanisms

In women, to our knowledge no studies have investigated the long-term effects of parity on neuroplasticity. In animal studies, hippocampal function is indeed altered with motherhood well into middle age. Adult hippocampal neurogenesis declines with age but the decline is steeper in nulliparous compared to primiparous females (Eid et al., 2019). Similarly, at middle age, multiparous and primiparous females showed an increase in the number of immature neurons (Barha et al., 2015; Eid et al., 2019), but not in cell proliferation (Barha and Galea, 2011), in the hippocampus compared to nulliparous females, and as noted above (Section 3.1) slightly enhanced spatial working and reference memory acquisition (Barha et al., 2015; Galea et al., 2018b). This suggests that past reproductive experience mitigates age-dependent declines in neurogenesis and this is associated with improvement in spatial learning and memory. In addition, LTP, synaptic proteins and neurotrophic factors are increased by reproductive experience. In 22 month old primiparous rats, LTP and spatial memory are enhanced compared to nulliparous controls (Lemaire et al., 2006). In multiparous rodents, synaptic proteins, synaptophysin, and spinophilin are upregulated compared to nulliparous female mice (Cui et al., 2014) and rats (Rossetti et al., 2016). At middle age, multiparous females have higher levels of BDNF in the hippocampus compared to nulliparous females (Macbeth et al., 2008; Rossetti et al., 2016). BDNF is an important neurotrophic factor for learning and memory (Bekinschtein et al., 2008) and an increase in levels along with synaptic proteins may be an underlying mechanism of the better performance in spatial memory tasks. Together these studies have shown that reproductive experience attenuates the effects of aging on several hippocampal endpoints (adult neurogenesis, BDNF, and synaptic and neurotrophic genes).

Neuropathology of Alzheimer's disease (AD) is characterized by deposition of β-amyloid peptide (Aβ), which is generated from amyloid precursor protein (APP; Perl, 2010; West et al., 1994). Lower levels of APP in the CA1 and dentate gyrus of the hippocampus were found in multiparous compared to nulliparous and primiparous females which were correlated with better spatial performance (Gatewood et al., 2005). Intriguingly, genotype interacts with parity to influence brain health, as in an AD mouse model (APP23), reproductive experience *decreases* spatial memory performance and *increases* Aβ plaques in the hippocampus compared to wildtype mice at middle age (Cui et al., 2014). Importantly, parity is detrimental in APP23 but not in wildtype females. The APP23 genotype also decreased synaptophysin and CREB in multiparous transgenic females (Cui et al., 2014) suggesting that parity may affect cognition by increasing brain hippocampal APP and synaptic proteins.

As discussed above (Section 2.4), there are neural and neuroimmune changes during pregnancy and postpartum. To date, only two studies has investigated the long-term effects of parity on hippocampal microglia and circulating cytokine levels (Eid et al., 2019; Galea et al., 2018b; see Section 4.2). With aging, the number of microglial cell processes increases in nulliparous but not primiparous rats (Eid et al., 2019). Primiparity also reduced microglia soma size during aging which could have an effect on microglial activation and altered serum cytokine levels during aging (Eid et al., 2019). Levels of serum cytokines show age-related changes that are dependent on parity. For

example, serum IFNγ and IL-10 increase during aging in nulliparous but not primiparous rats, and nulliparous have higher levels of IFNγ, IL-10, and IL-4 than primiparous females at 13 months of age (Eid et al., 2019). In addition, circulating levels of IFNγ, IL-10, and IL-4 are negatively correlated with the length of hippocampal microglia processes in primiparous but not nulliparous females (Eid et al., 2019), suggesting that circulating inflammatory markers may be associated with changes in neuroinflammation depending on reproductive experience. Interactions between the peripheral immune system, hormones, microglia, and neurons may be important during healthy aging and disease and how they may be affected by parity warrants further investigation.

4. Reproductive experience and health

4.1. Parity influences risk of brain disorders and stroke outcomes

After pregnancy and motherhood, women show increased and decreased susceptibility to a variety of diseases although the mechanisms remain largely unknown (except for certain types of cancers; Nandy et al., 2014; Rotunno et al., 2014). The perinatal period is a time of great risk for women to develop affective disorders such as depression and anxiety-related disorders. After giving birth, approximately 15% of women will experience postpartum depression, 8% will experience anxiety disorders and a wide range (26–84%) will experience the postpartum blues (Goodman et al., 2016; O'Hara and Wisner, 2014; Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium, 2015). In addition, amount of parity is positively associated with an increased risk to develop AD, increased levels of AD neuropathology, and an earlier age of AD onset (Beeri et al., 2009; Colucci et al., 2006; Geerlings et al., 2001; Jang et al., 2018; McLay et al., 2003; Prince et al., 2018; Ptok et al., 2002; Sobow and Kloszewska, 2004). In women, grand multiparity (having more than three or five children, but not one or two children) is associated with an increased risk of developing AD (Colucci et al., 2006; Jang et al., 2018). More than five complete pregnancies increases the risk of AD, while having one incomplete pregnancy reduces the risk of AD (Jang et al., 2018). In addition in women without dementia, incomplete pregnancies increase memory (MMSE scores) relative to women without incomplete pregnancies (Jang et al., 2018) suggesting that incomplete pregnancies are also associated with a reduction in cognitive impairment with aging. Higher parity is also associated with an increased AD neuropathology (Beeri et al., 2009). However, to date, not all studies have found associations between parity and increase risk of AD (e.g., Fox et al., 2018) and this could be due to differences in genotype (Corbo et al., 2009, 2007) as suggested by the findings in a mouse AD model by Cui et al. (2014) discussed above (Section 3.2). For example, apolipoprotein E (APOE) ε4 allele is a major genetic risk factor for AD, it reduces the age of AD onset, and interacts with parity to influence age of AD onset (Corbo et al., 2007). In women parity is associated with lower AD onset in ε3/ε3 genotype, but not in ε4 carriers (Corbo et al., 2007), suggesting that nulliparity is protective against developing AD in non-ε4 carriers. Taken together, factors such as genotype and amount of parity can interact to affect health later in life and should be taken into account in future studies.

In the long-term, higher parity is also associated with reduced survival more so in women than in men (Penn and Smith, 2007). Later maternal age is associated with increased longevity in women, however higher parity (3 or more children) diminishes longevity relative to women with 1–2 children (Sun et al., 2015). One potential mechanism is that reproductive history is associated with shorter telomere length in leukocytes (Gray et al., 2014; Pollack et al., 2018) suggesting an accelerated cellular aging. Telomere attrition and a decrease in telomerase activity are in fact associated with poor immune function and a variety of diseases such as cancer, inflammation, type 2 diabetes, and AD (Blackburn et al., 2015). Interestingly, greater endogenous estrogens, also observed with lower parity and a longer reproductive period, is associated with longer telomeres (Lin et al., 2011) and therefore slower cellular aging.

AD has been linked to obesity (Alford et al., 2018) and increasing parity is associated with obesity and excessive weight gain (Harris et al., 1997; Hollis et al., 2017; We et al., 2016). In addition, higher risk of cardiovascular disease and stroke with parity is detected particularly in women that had pregnancy complications such as pre-eclampsia or gestational diabetes (Hauspurg et al., 2018; Hinkula et al., 2006; Humphries et al., 2001; Skilton et al., 2009). However, parity is associated with lower cardiovascular disease mortality in a meta-analysis that did not take pregnancy complications into account (Lv et al., 2015). In mice, parity improves stroke outcome in middle age (3–4 months postpartum) but also increases body weight, reduces activity levels (Ritzel et al., 2017), and impairs energy homeostasis 4–8 weeks after weaning of the pups (Ladyman et al., 2018). Parity reduces estradiol levels across estrous cycles (Byrnes and Bridges, 2006) and estradiol treatment increases stroke damage in middle-aged retired breeder mice (Selvamani and Sohrabji, 2010) suggesting that parity's protective effect on stroke brain injury may be related to the low estradiol levels compared to nulliparous females. Because dementia has been previously linked to diabetes, obesity, stroke, and cardiovascular disease (Alford et al., 2018; Kuźma et al., 2018; Moran et al., 2015; Santos et al., 2017; Schilling, 2016), it is not surprising to also observe effects of parity on these diseases. Even though the research is only beginning to understand the risks associated with previous parity, it is becoming clear that it is an important factor to take into account. In the future, tailored treatment based on sex, genetics, and possibly reproductive history may need to be developed to best treat individuals.

4.2. Parity influences the effects of antidepressants and hormone treatments

In this review we focused on the effects of parity on cognition and related changes in brain plasticity and inflammation. It is important to acknowledge that parity can also affect how an individual responds to a variety of challenges and insults in the postpartum and in middle age. In younger animals, parity can facilitate behavioural recovery from a neural insult at least in the short term. After a hippocampal neurotoxic insult (with kainic acid), multiparous female rats (20 days after weaning) have an enhanced memory compared to nulliparous female rats (Franssen et al., 2012). In response to a high fat diet, parity can have effects on energy balance 8 weeks post-weaning by reducing activity levels, increasing body weight, and impairing glucose tolerance (Ladyman et al., 2018). Parity can affect the endocrine response to stress and antidepressant treatment (Workman et al., 2016) as primiparity reduces corticosterone concentrations following acute swim stress. In addition, chronic corticosterone increases estradiol levels in primiparous but not nulliparous rats (Workman et al., 2016). In a postpartum depression model, fluoxetine (a selective serotonin reuptake inhibitor, SSRI) reduces corticosterone levels in nulliparous but not postpartum females (Workman et al., 2016). In addition, SSRIs are not efficacious during the late postpartum, depending on the depression model used and the dependent variable measured. For example, fluoxetine and paroxetine do not restore levels of passive coping and hippocampal neurogenesis late in the postpartum but they do restore maternal behaviour deficits early in the postpartum (Gobinath et al., 2018; Overgaard et al., 2018; Workman et al., 2016). One possible mechanism for this lack of effect is the fact that postpartum females have very low levels of circulating estradiol. In nulliparous females, the efficacy of fluoxetine depends on the levels of estradiol (Mahmoud et al., 2016a) so it is possible that postpartum females do not respond to SSRI treatment because of their unique endocrine physiology.

Finally, we and others have shown that in rats, parity influences how hormone treatments affect cognition in young (1 week, Hussain et al., 2013) and middle age females (12–15 months old; Barha et al., 2015; Galea et al., 2018b). Previous parity also influences how estrogens affect neuroplasticity and inflammation in middle age (Barha

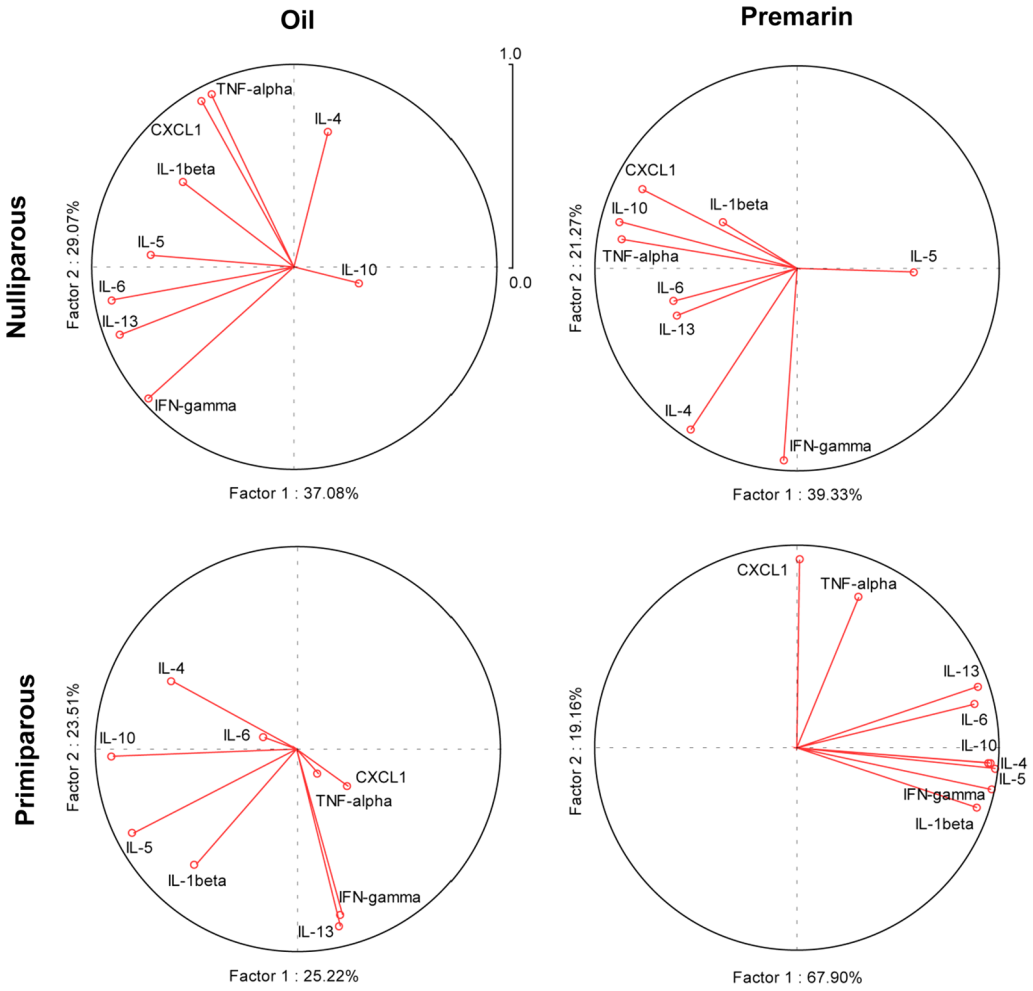

Fig. 4. Biplots of serum cytokines principal component analysis in primiparous and nulliparous middle-aged female rats treated with oil or Premarin. The vectors indicate that serum cytokines have different profiles (loads) depending on reproductive history and Premarin treatment. Alone among the four treatments, the primiparous females treated with Premarin exhibit a high degree of correlation among the components of the cytokine response (Factor 1: 67.9% vs < 39.3%). Data analyzed from (Galea et al., 2018b Neurobiol Aging).

et al., 2015; Barha and Galea, 2011; Galea et al., 2018b). For example, Premarin (an estrone-based hormone therapy) improves early spatial acquisition and increases cytokine (TNFα and CXCL1) levels in nulliparous but has the opposite effects in primiparous middle-aged rats (Galea et al., 2018b). There is also a shift in the relationship between how nine serum cytokines load on principle component factors depending on reproductive history and Premarin treatment (Fig. 4) indicating that parity and Premarin interact to affect circulating cytokine levels. Going forward, it will be important to consider reproductive experience not only in aging research and take into account that retired breeders (multiparous rats), commonly used in aging studies, can have a different physiology and respond differently to stressors, hormones, and challenges than their nulliparous counterparts and may influence findings in aging studies using females.

5. Considerations for future research

We need to acknowledge and consider that a unique female experience, pregnancy and motherhood, can have short and long term implications for physiology and disease risk (Galea et al., 2018a). Past reproductive experience affects brain, behaviour, and disease risk, but many factors can play modifying roles: amount of reproductive experience, age of first pregnancy/last pregnancy, biological sex of children, and pregnancy/obstetric complications. As discussed above (Section 4.1), increasing parity is associated with higher AD risk (Beeri et al., 2009; Colucci et al., 2006; Jang et al., 2018; McLay et al., 2003; Prince et al., 2018; Ptok et al., 2002; Sobow and Kloszewska, 2004). In addition, in postmenopausal women, higher parity is associated with higher levels of sex-hormone binding globulin (SHBG; Chavez-MacGregor et al., 2008). SHBG is a transport protein that binds androgens and estrogens with high affinity and while bound restricts their biological activity (Laurent et al., 2016). One possibility is that high levels of SHBG observed with increasing parity result in lower levels of free or biologically active sex steroids due to binding to SHBG, but another possibility is that these high levels of SHBG allow for more mobilization of sex steroids to distant targets. In rodents, the degree of multiparity (primiparous, biparous or multiparous) also affects circulating hormone levels (e.g., corticosterone (Paris and Frye, 2008; Pawluski et al., 2009b), estradiol (Paris and Frye, 2008), and prolactin (reviewed in Bridges, 2016)), as well as hippocampal neurogenesis (Pawluski and Galea, 2007), dendritic morphology (Pawluski and Galea, 2006), and cognition (Barha et al., 2015; Paris and Frye, 2008). Together this suggests that amount of parity can have physiological consequences but how these affect brain health later in life remains to be investigated.

The sex of the fetus or children has effects on maternal cognition and health (immune markers and pregnancy outcomes). Women pregnant with male fetuses have better working memory and spatial ability than women pregnant with female fetuses (Vanston and Watson, 2005) suggesting that the sex of the fetus is an important factor for brain

function and memory. There are associations between sex of the fetus and immune markers during pregnancy. For example, male fetuses are associated with higher levels of pro-inflammatory cytokines (Enninga et al., 2015) while female fetuses are associated with lower levels of certain pro-inflammatory cytokines (IFNγ and IL-12) in the first trimester and higher levels of other cytokines (IL1β, TNFβ, IL-5, and IL-10) in the second trimester (Taylor et al., 2018). Mitchell et al. (2017) did not find differences in serum cytokine levels in relation to fetal sex but found that the stimulated production of cytokines was higher in women carrying female compared to male fetuses suggesting that the maternal immune system responds differently to a challenge depending on fetal sex. It is now recognized that during pregnancy there is a bi-directional flow of cells between the mother and the fetus. One way that the fetus can affect the mother and her health is through fetal microchimerism, a phenomenon when cells from the fetus spread to the mother's body incorporating into many tissues including the brain (Chan et al., 2012; Gammill and Harrington, 2017; Zeng et al., 2010). These fetal cells accumulate during pregnancy (Adams Waldorf et al., 2010) but some persist after birth and have been detected many years later in the mother's blood (Bianchi et al., 1996; Gammill and Harrington, 2017). While the number of fetal microchimeric cells is small, the consequences of this foreign genetic material on women's health may not be. Fetal cells have been proposed to play a role in pre-eclampsia, miscarriage, and premature birth. But microchimerism is also associated with certain cancers, Parkinson's disease in a mouse model, and AD pathology in women (reviewed in Boddy et al., 2015). In the brain, a lower prevalence of male microchimerism (male cells in female brain) is observed in women with AD (Chan et al., 2012). In this latter study, pregnancy history was not known and microchimerism may be due to other factors (e.g., twins and older siblings; Boddy et al., 2015), nevertheless the results would suggest that past pregnancy may affect AD risk through microchimerism. Others have suggested a possible role of microchimerism in maternal emotional and mental health (e.g., see Boddy et al., 2015). This line of research is still evolving but suggests that in addition to studying the mother's physiology we need to start considering the interactions with her fetus and their potential long-term effects on physiology and health.

6. Conclusions

In this review, we summarized the literature addressing the short and long term impact of pregnancy and motherhood on neuroplasticity and cognition. More studies are accumulating examining the long-lasting effects of parity on the health of the mother. Intriguingly, pregnancy and motherhood can also affect how the brain responds to challenges (hormones, diet, and stress) even in midlife long after the reproductive event. These findings have important implications for disease treatments as nulliparous women may not have the same response as previously parous women in response to a particular treatment. In order to make progress in women's health we need to acknowledge that unique female experiences such as pregnancy and motherhood can have long term effects on physiology and disease.

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