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Endocrine substrates of cognitive and affective changes during pregnancy and postpartum

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Abstract

Pregnancy and motherhood constitute periods of tremendous hormonal variation that orchestrate parturition, lactation, maternal care and aggression, and recognition of offspring, among other functions. Cognitive processing also varies during pregnancy and motherhood and may serve an adaptive function in preparation for parturition and rearing. Additionally, maternal experience may have enduring consequences for the brain, behavior and cognition long after offspring are mature. However, the early postpartum period also renders women vulnerable as approximately 15% of women experience postpartum depression, with estimates of 50 - 80% reporting a milder form of depression termed ‘maternal blues.’ This review will present literature on pregnancy- and parity- related changes in both cognition and affect and how these changes likely involve plastic changes within the hippocampus, a region that is sensitive to reproductive hormones. Further, this review will discuss steroid and peptide hormones that may contribute to affective and cognitive disruptions during pregnancy and postpartum. Research in this area may reveal insight into how pregnancy and motherhood alter the likelihood of developing postpartum depression and related disorders.

Keywords: reproduction, depression, females, learning and memory, hormones

1. Introduction

Pregnancy and motherhood are associated with a suite of new behaviors that develop to ensure the survival of the offspring (Neumann, 2003). A substantial amount of plasticity occurs during both pregnancy and the postpartum period in order to prepare the mother. Endocrine events during pregnancy and postpartum initiate parturition, maternal behavior, lactation, aggression, and recognition of offspring, among other functions (Numan & Woodside, 2010). It is perhaps not surprising that substantial brain plasticity accompanies maternal behavioral plasticity. Given that pregnancy and postpartum represent energetically costly phases in the lifespan of females, the reproductive period may have necessitated trade-offs in brain plasticity (which also represents an energetically expensive process) that manifest as changes in cognition and affect. For example, compromised maternal brain plasticity (and in turn cognition) across species may be an adaptive process to conserve energy for functions that promote offspring survival. Furthermore it is also possible that in some women altered maternal brain plasticity underlies cognitive impairments and depression. Although a complete discussion of the evolutionary development of parity-related trade-offs is beyond the scope of this review, similarities across species in changes in cognitive and affective processes during pregnancy and postpartum may represent conserved traits. Such conservation allows for a more mechanistic investigation of hormonal events that contribute to changes in cognitive and affective processes. In this review we will present literature outlining the effects of both pregnancy and motherhood on cognition and postpartum depression and suggest future directions for this area of research.

2. Pregnancy, Motherhood and Cognition

Pregnancy and motherhood are associated with dramatic alterations in the physiology and biology of the mother. During this time drastic fluctuations in steroid and peptide hormone levels occur and are related to alterations in the morphology, physiology, and function of many different brain structures that are involved in the induction of maternal behavior (Numan, 1988; Rosenblatt, Mayer, & Giordano, 1988). Alterations also occur in brain regions that are not typically directly associated with the maternal circuit, but are involved in mediating learning and memory, and include regions such the hippocampus and the cortex (Hamilton, Diamond, Johnson, & Ingham, 1977; Kinsley, 2008; Leuner & Gould, 2010; Macbeth & Luine, 2010; Pawluski, Brummelte, Barha, Crozier, & Galea, 2009). Reproductive experience (pregnancy and motherhood) dramatically alters the morphology and structure of the hippocampus (Kinsley & Lambert, 2008; Pawluski, Brummelte, *et al.*, 2009), which may in turn have behavioral implications for pregnant females. This may be in part related to the high concentration of steroid and peptide hormone receptors in the hippocampus, particularly glucocorticoid receptors (Sapolsky, Krey, & McEwen, 1984; Sapolsky, McEwen, & Rainbow, 1983), and to a lesser extent estrogen (Shughrue & Merchenthaler, 2000), progesterone (Guerra-Araiza, Coyoy-Salgado, & Camacho-Arroyo, 2002; Guerra-Araiza, Villamar-Cruz, Gonzalez-Arenas, Chavira, & Camacho-Arroyo, 2003), oxytocin (Muhlethaler, Sawyer, Manning, & Dreifuss, 1983) and prolactin (Torner et al., 2009) receptors. The presence of these receptors renders the hippocampus directly sensitive to fluctuations in hormones across pregnancy and the postpartum period. This review will primarily concentrate on the effects of reproductive experience and hippocampal function and offer future directions for investigating prefrontal cortical-dependent functions.

The hippocampus has an important role in mediating numerous types of learning and memory, including contextual memory (Maren, 2001) and spatial learning and memory (Burgess, 2008; Morris, 1984). Many tasks have been developed to assess the function of this region. One of the more popular tasks in the literature is the Morris water maze (Morris, 1984). This involves a rat escaping from a large circular pool filled with water by finding and learning the location of submerged platform using distal spatial cues arranged around the room. Through successive training days, rats are able to apply their spatial knowledge of the environment to find the hidden platform, with shorter latencies and path lengths to reach the platform indicative of better spatial learning and memory. Alterations in this basic protocol can be used to access and assess different types of memory, including spatial reference memory and spatial working memory. Reference memory is long-term stable memory (Olton & Papas, 1979), and working memory can be defined as the manipulation and retrieval of trial-unique information to guide prospective behavior (Baddeley, 2003). The majority of studies show that late pregnancy is associated with impairment in hippocampus-dependent spatial memory, whereas motherhood, particularly post-weaning, is associated with an enhancement in hippocampus-dependent spatial memory (Figure 1). In the next few sections we will review the literature on cognition during pregnancy and motherhood.

2.1 Early and late pregnancy are associated with differential effects on cognition in rodents

Late pregnancy is associated with impairments of hippocampus-dependent learning and memory, whereas early pregnancy is associated with enhancements of hippocampus-dependent learning in rodents. In pregnant rodents, steroid hormones fluctuate dramatically across the 23-day gestational period. This hormonal profile includes a progressive shift from low levels of

estradiol (approximately 15 pg/ml) during the first two weeks to high levels of estradiol (approximately 40 pg/ml) during the third and final week of pregnancy (Anderson *et al.*, 1996; Paris & Frye, 2008; Rosenblatt *et al.*, 1988). High levels of progesterone are maintained for the duration of gestation but then drastically drop 3 days prior to parturition (Bridges, 1984). This pattern of estradiol and progesterone ratio during gestation is necessary for induction of maternal behavior in females (Bridges, 1984) and may contribute to the differential cognitive abilities in early versus late pregnancy. Corticosterone also varies across gestation and may play a role in modulating cognition at this time. Corticosterone remains stable during the first two weeks of gestation before increasing during the last week (Waddell & Atkinson, 1994) and levels range from 50ng/ml to 150ng/ml, with higher levels seen near the time of parturition (Takahashi, Turner, & Kalin, 1998).

During the first two weeks of pregnancy, pregnant female rats have enhanced spatial working memory in the Morris water maze compared with virgin control rats (Galea *et al.*, 2000; Figure 2). Spatial working memory was impaired in pregnant rats compared with virgin controls during the third week of pregnancy (Galea *et al.*, 2000), when estradiol levels are high and progesterone levels are very low. Furthermore Galea *et al.* (2000) found slightly smaller hippocampal volumes in pregnant female rats compared with virgin female rats. Bodensteiner and colleagues (2006) have also found enhanced spatial working memory throughout pregnancy compared with virgin rats, using a very similar testing protocol as Galea *et al.* (2000). Interestingly, this enhancement did not extend into the early postpartum period. Pregnant female rats also show enhanced spatial memory on gestational day 7 and 16 in the hippocampus-dependent object placement task in which memory for a spatial location is tested two hours after initial learning (Macbeth, Gautreaux, & Luine, 2008). Together these studies indicate that

hippocampus-dependent learning and memory is enhanced during early pregnancy and impaired during late pregnancy. However, it is important to note that the effects of pregnancy on cognition likely depend on the memory system being investigated and the gestational day subjects are tested, as hormonal profiles in the rodent can change quite dramatically as a function of gestational day.

Hormonal profiles during and after pregnancy are also altered by previous reproductive experience. For example primiparous rats (1 previous reproductive experience) have reduced circulating levels of estradiol and prolactin during the proestrous stage of the estrous cycle compared with nulliparous rats (Bridges & Byrnes, 2006). Furthermore multiple previous reproductive experiences lead to higher levels of estradiol and lower levels of prolactin across gestation during subsequent pregnancy compared with primiparous pregnant females (Bridges, Felicio, Pellerin, Stuer, & Mann, 1993; Paris & Frye, 2008). These differences in hormone levels during pregnancy in multigravid females and primigravid rats may also impact spatial memory. For example, multigravid rats (with 3 previous pregnancies) outperformed primigravid (first time pregnant) rats on the object placement task on gestational days 2 through 17 (Paris & Frye, 2008). Together these studies indicate that different types of memory may be differentially influenced by pregnancy and effects may be dependent on gestational day, fluctuating hormone levels and reproductive experience.

2.2 Motherhood is associated with enhanced cognition

The specific hormonal profile across pregnancy and parturition elicits the maternal care repertoire seen in female rats towards their offspring (Rosenblatt et al., 1988), whereas exposure to the offspring maintains maternal behavior. Once a rat becomes maternal, the memory for

maternal behavior extends past the actual reproductive experience and is known as the maternal memory (Bridges, 1975). Thus maternal behavior is quicker to elicit after subsequent pregnancies (Bridges, 1975; Orpen & Fleming, 1987). In addition to this maternal memory, it is perhaps not surprising that other permanent alterations in the mother's behavior exist. Recently studies have shown that motherhood itself is associated with permanent enhancements in specific cognitive processes that are evident in middle-age and even older aged rodents (Kinsley, Franssen, & Meyer, 2011). It is likely that the hormonal profile characteristic of pregnancy and parturition that is necessary for the induction of maternal behavior, also mediates many of the cognitive effects seen with reproductive experience.

The impairment seen in spatial memory during late pregnancy in rodents (Galea et al., 2000) continues after parturition, and the early postpartum period is associated with deficits in hippocampus-dependent learning. Specifically, primiparous mothers show impaired spatial learning of a stable platform location in the Morris water maze on postpartum days 1 to 4 compared with nulliparous rats (Darnaudery et al., 2007). Interestingly despite impaired learning, primiparous mothers have better long-term retention of the platform location on postpartum day 14, indicating enhanced spatial reference memory compared with nulliparous rats. The initial impairment in spatial learning seen in the primiparous mothers may be related to hormonal fluctuations at parturition. Specifically, primiparous rats have lower levels of estradiol and higher levels of corticosterone than multiparous rats that vary by postpartum day (Atkinson & Waddell, 1995; Darnaudery *et al.*, 2007; Paris & Frye, 2008; Pawluski, Charlier, Lieblich, Hammond, & Galea, 2009).

The effects of motherhood on hippocampus-dependent learning and memory extend beyond the early postpartum period and can be seen throughout lactation and after weaning

(the removal of offspring from the mother). Both the late postpartum period and the post-weaning period are associated with enhanced spatial memory. Kinsley and colleagues (1999) were the first to show that motherhood enhances hippocampus-dependent learning and memory. Primiparous and multiparous rats had enhanced spatial reference memory compared with nulliparous rats approximately 2 weeks postpartum. Furthermore during postnatal days 20 – 24 primiparous females show enhanced medial prefrontal cortex-dependent cognitive performance on a task assessing attentional shifting and behavioral flexibility compared with nulliparous female rats, which coincided with increased dendritic spine density on pyramidal neurons located in layer 2/3 of the medial prefrontal cortex (Leuner & Gould, 2010).

Primiparous rats, and to a lesser extent multiparous rats, have enhanced spatial working and reference memory on the radial arm maze compared with nulliparous rats when testing began either immediately after weaning (25 – 55 days postpartum; Figure 3) or 1 month after weaning (55 – 85 days postpartum) (Pawluski, Vanderbyl, Ragan, & Galea, 2006; Pawluski, Walker, & Galea, 2006). Consistent with these previous studies, Lemaire et al. (2006) also found enhanced spatial reference memory in the Morris water maze in primiparous rats shortly after weaning compared with nulliparous rats.

Motherhood consists of many different experiences, including pregnancy, parturition, and mothering. Thus the improvements in spatial learning and memory with reproductive experience could be occurring via pregnancy, mothering (pup exposure), or both. Studies show that improvements in spatial memory with reproductive experience are not due to the effects of pregnancy alone, as females who had their pups removed within 24 h could not complete the radial arm maze (Pawluski, Vanderbyl, *et al.*, 2006). However, pup exposure itself does have some effects on spatial memory. Repeated exposure of nulliparous rats to pups enhances spatial

reference memory in the dry-land version of the Morris water maze compared with nulliparous rats without pup-exposure when tested shortly after weaning (Kinsley et al., 1999; Lambert et al., 2005). However, Pawluski et al. (2006) found that sensitized rats (nulliparous rats exposed to pups until they became maternal) did not show enhanced spatial memory when tested weeks after pups were removed, indicating that any enhancements in spatial memory after sensitization, pup-exposure, or pup-directed maternal behaviors alone are transitory. Together these studies indicate that the entire reproductive experience, including pregnancy, parturition, and mothering, is required to produce long-lasting alterations in hippocampus-dependent learning and memory.

2.2.1 Role of steroid and peptide hormones during the postpartum period

The hormonal profile of a parturient female rat is dramatically altered following birth. For example, estradiol levels that are elevated during late pregnancy (Garland, Atherton, Baylis, Morgan, & Milne, 1987; Siegel & Rosenblatt, 1978; Yoshinaga, Hawkins, & Stocker, 1969), drop drastically at parturition and then remain low during lactation (Hapon, Simoncini, Via, & Jahn, 2003) whereas progesterone is elevated during pregnancy, decreases prior to parturition, and is elevated during mid-lactation in lactating dams (Gala & Westphal, 1965; Hapon *et al.*, 2003; Nicholas & Hartmann, 1981). Plasma corticosterone levels increase at the time of parturition (Atkinson & Waddell, 1995; Gala & Westphal, 1965), and are elevated during the postpartum period in the early part of the light cycle in lactating dams (Fischer, Patchev, Hellbach, Hassan, & Almeida, 1995; Pawluski, Charlier, *et al.*, 2009; Stern, Goldman, & Levine, 1973). During the early postpartum period the circadian rhythm of corticosterone is blunted compared with the nulliparous and pregnant rats, with a 50% decrease in mean corticosterone level from late pregnancy to early lactation (Atkinson & Waddell, 1995). Additionally

reproductive experience can also alter corticosterone levels after parturition, as primiparous female rats had significantly elevated levels of plasma corticosterone on postpartum day 1 compared with multiparous and nulliparous female rats (Pawluski, Charlier, *et al.*, 2009).

Lactating primiparous and multiparous mothers also showed decreased levels of corticosteroid binding globulin (CBG), which alters the bioavailability of corticosteroids (Hammond, 2002), on postpartum days 14 and 21 compared with nulliparous females, with primiparous females having the lowest CBG levels (Pawluski, Charlier, *et al.*, 2009). The significant changes in steroid hormone levels during the postpartum period may coincide with some of the alterations in hippocampal function. Further research is required to determine whether these hormonal fluctuations mediate the changes in memory.

In addition to steroid hormones, changes in the levels of peptide hormones prolactin and oxytocin also occur during the postpartum period. Prolactin, a hormone with many diverse functions is produced in the pituitary in rodents and humans as well as in extrapituitary tissue in humans. Estrogens regulate prolactin release in rats and to a lesser degree in humans (Ben-Jonathan, LaPensee, & LaPensee, 2008). The antepartum prolactin surge aids in the final maturation of the mammary gland for lactation and is involved in the onset of maternal behavior (Mann & Bridges, 2001). Prolactin is also involved in the maintenance of the corpus luteum and thus the production of progesterone during pregnancy and the maintenance of gestation in rats. In both humans and rats prolactin is involved in lactation. Although no studies have looked at the effects of prolactin on learning and memory across pregnancy, rats with elevated levels of prolactin have enhanced acquisition of avoidance behaviors (Drago, Bohus, & Mattheij, 1982) but impaired motor activity and latency to explore (Alvarez & Banzan, 1994; Gonzalez-Mora, Guadalupe, & Mas, 1990).

Another hormone involved during the postpartum period is oxytocin. In addition to the role oxytocin plays in parturition and milk ejection, it is involved in social bonding, sexual behavior, aggressive behavior and spatial memory. Recent work has begun to investigate the role of oxytocin in mediating changes in spatial learning and memory with motherhood (Tomizawa et al., 2003). Specifically oxytocin is involved in the enhancements seen in reference memory, but not working memory, with motherhood. Oxytocin administered to nulliparous mice enhanced spatial reference, but not working memory in the radial arm maze, compared with nulliparous control mice (Tomizawa et al., 2003). Treatment with an oxytocin antagonist impaired spatial reference memory in multiparous mice compared with nontreated multiparous mice (Tomizawa et al., 2003). Although this work points to a possible role for oxytocin on enhanced spatial reference memory in mothers, it did not compare parous dams with nulliparous females and did not account for full maternal behavior as all multiparous mice were tested 3 days after parturition.

2.3 Effects of motherhood on cognition throughout the lifespan

Reproductive experience may permanently alter hippocampus-dependent learning and memory, as the enhancement in cognition with motherhood during the postpartum period continues to manifest throughout the lifespan (Figure 1). Using a dry land version of the Morris water maze, Gatewood et al. (2005) tested multiparous female rats (2 previous reproductive experiences), primiparous female rats and nulliparous female rats at 6, 12, 18, and 24 months of age. Spatial reference memory was enhanced in multiparous compared with primiparous and nulliparous females at all age points, suggesting that the beneficial effect of reproductive experience on memory is additive. Primiparity was sufficient in enhancing reference memory

compared with nulliparity. Furthermore this additive enhancement in memory with previous reproductive experiences was also seen with reversal learning (Gatewood et al., 2005). Love et al. (2005) also found that primiparous and multiparous rats had enhanced spatial reference memory compared with nulliparous rats when repeatedly tested on the same task at 5 and 13, but not 9, months of age. The enhancement in spatial reference memory in primiparous female rats, as tested in the Morris water maze, also persists into old age (16 months) (Lemaire et al., 2006). Interestingly this beneficial effect of reproductive experience on reference memory is completely abolished by a stressful experience during gestation (Lemaire et al., 2006). Similarly, exposure to stress during gestation prevents the increased long-term potentiation seen in primiparous females in the CA1 region of the hippocampus relative to nulliparous females (Lemaire et al., 2006).

In addition to life-long enhancements of spatial reference memory, previous reproductive experience also benefits object placement memory. Multiparous female rats (in this case defined as 5 to 6 previous reproductive experiences) had stronger spatial memory as tested in the object placement task at 12 months old compared with nulliparous females (Macbeth, Scharfman, Maclusky, Gautreaux, & Luine, 2008). There are equivocal findings for non-hippocampus dependent object recognition as one study found that middle-aged multiparous females had better performance on object recognition task compared with nulliparous females (Macbeth, Scharfman, *et al.*, 2008), although another study did not find a significant difference in object recognition between primiparous and nulliparous female rats (Lemaire et al., 2006), indicating that effects of reproductive experience on cognition are dependent on factors such as the number of pregnancies, the particular memory system under investigation, other environmental experiences, and the age of the mother at the time of testing.

Perhaps not surprisingly there are differences in protein expression in older reproductively experienced female rats. Multiparous, and to a lesser extent primiparous, females have fewer amyloid precursor protein (APP) immunoreactive cells in the dentate gyrus and the CA1 regions of the hippocampus at 24 months of age compared with nulliparous rats. APP is a marker of neurodegeneration and of age-related cognitive decline (Chapman *et al.*, 1999). Thus, reproductive experience may be a natural model akin to hormone replacement therapy later in life in terms HRTs putative effects on neuroprotection (Henderson, 2010; Loucks & Berga, 2009; Struble, Cady, Nathan, & McAsey, 2008). In addition, increased levels of brain-derived neurotrophic factor (BDNF), which is involved in neuronal plasticity and hippocampus-dependent spatial memory (Allen & Dawbarn, 2006), are seen in the CA1 and septum of multiparous female rats compared with nulliparous rats (Macbeth, Scharfman, *et al.*, 2008). Interestingly an increased risk for developing neurodegenerative disorders like Alzheimer's disease is seen with parity (Beeri *et al.*, 2009; Colucci *et al.*, 2006; Corbo *et al.*, 2007; Sobow & Kloszewska, 2004). This may be related to alterations in the ability of the brain to respond to steroid hormones later in life in parous females. Previous reproductive experience (pregnancy and motherhood) altered the capacity of the hippocampus to respond to estrogens later in middle age (Barha & Galea, 2009). Specifically, we found that estrogens (17α -estradiol, 17β -estradiol, estrone) increased cell proliferation in the dentate gyrus of middle-aged multiparous rats but none of the estrogens altered cell proliferation in nulliparous rats (Figure 4). Collectively these findings suggest that effects of reproductive experience on hippocampus structure and function extends well beyond the postpartum period and may permanently alter the brain of mothers.

2.4 Steroid hormones integral to pregnancy and the postpartum period regulate hippocampus structure and function in rodents

As stated previously, estradiol and progesterone levels are altered during pregnancy and these fluctuations may contribute to the alterations seen in hippocampus-dependent memory in rodents. There is an abundance of evidence that both estradiol and progesterone influence hippocampus function and structure in virgin female rats (Barha & Galea, 2010; Daniel, 2006; Foy, Baudry, Akopian, & Thompson, 2010; Frick, Fernandez, & Harburger, 2010). For example high levels of estradiol can impair spatial reference and working memory (Daniel, Roberts, & Dohanich, 1999; Frye, 1995; Galea, Wide, Paine, *et al.*, 2001; Holmes, Wide, & Galea, 2002; Warren & Juraska, 1997; Wilson, Puolivali, Heikkinen, & Riekkinen, 1999), whereas low levels of estradiol facilitate spatial working memory (Fader, Johnson, & Dohanich, 1999; Holmes *et al.*, 2002; Luine, Richards, Wu, & Beck, 1998) but do not influence spatial reference memory (Berry, McMahan, & Gallagher, 1997; El-Bakri *et al.*, 2004; Holmes *et al.*, 2002) in young virgin female rats (Barha & Galea, 2010; Frick *et al.*, 2010). Contextual fear conditioning, memory that relies on the integrity of the hippocampus and the amygdala, is impaired by high levels of estradiol (Barha, Dalton, & Galea, 2010; Gupta, Sen, Diepenhorst, Rudick, & Maren, 2001), and is enhanced with low levels of estradiol (Barha *et al.*, 2010). Treatment with progesterone can facilitate object recognition memory and spatial reference memory (Frye & Walf, 2008a, 2008b; Harburger, Pechenino, Saadi, & Frick, 2008; Lewis, Orr, & Frick, 2008; Orr, Lewis, & Frick, 2009). Importantly progesterone, when given in combination with estradiol, can reverse the beneficial effects of estradiol (Bimonte-Nelson, Francis, Umphlet, & Granholm, 2006; Bimonte-Nelson, Nelson, & Granholm, 2004; Harburger, Bennett, & Frick, 2007; Rosario, Ramsden, & Pike, 2006), although this is not consistently found (Gibbs, 2000;

Harburger, Saadi, & Frick, 2009; Markham, Pych, & Juraska, 2002). Therefore the characteristic alterations in estradiol and progesterone levels during pregnancy may potentially mediate many of the cognitive effects seen with reproductive experience as fluctuations in these hormones at other time points in the lifespan are known to affect cognition.

As well as effecting cognition, endogenous and exogenous exposure to estradiol and progesterone also alters dendritic spine density, synaptic protein levels and adult neurogenesis in the hippocampus. Dendritic spine density in the CA1 region of the hippocampus is increased with high levels of estradiol (Gould, Woolley, Frankfurt, & McEwen, 1990; Miranda, Williams, & Einstein, 1999; Woolley, 1998; Woolley, Gould, Frankfurt, & McEwen, 1990; Woolley & McEwen, 1994), and subsequent progesterone treatment reduces CA1 spine density back to baseline in adult virgin females (Woolley *et al.*, 1990; Woolley & McEwen, 1993). Furthermore different types of estrogens including estradiol and estrone can increase expression of the synaptic protein synaptophysin in the hippocampus of female rats, and these levels could be related to impairments in memory (Barha *et al.*, 2010). Acute treatment with high (proestrous) or low (diestrous) levels of estradiol also increases cell proliferation in the dentate gyrus of the hippocampus (Barha & Galea, 2009; Barha, Lieblich, & Galea, 2009; Ormerod, Lee, & Galea, 2003; Tanapat, Hastings, & Gould, 2005). Progesterone treatment in combination with estradiol decreases cell proliferation (Tanapat *et al.*, 2005) in virgin female rats, whereas progesterone treatment alone increases cell proliferation and survival in the dentate gyrus of adult male rats (Barha, Ishrat, Epp, Galea, & Stein, *in press*; Liu *et al.*, 2009; Zhang *et al.*, 2010). Thus, there is ample evidence to indicate that estradiol and progesterone can influence hippocampus structure in virgin female rats.

2.5 Hormonal profiles across pregnancy and the postpartum period in humans and rodents

The fluctuating hormonal profile seen in rodents across pregnancy and the postpartum period is also seen in humans albeit with some important differences. Specifically estrogens are elevated throughout pregnancy in humans, whereas estradiol is only elevated during the final few days of gestation in the rodent. Both rodents and humans have increased levels of progesterone during pregnancy and progesterone falls prior to parturition in the rodent and after expulsion of the placenta in humans. Similar to the increase in corticosterone levels during pregnancy in rodents, cortisol levels steadily rise during pregnancy in women, peaking during the third trimester with levels 2 to 3 times nonpregnant levels (Abou-Samra *et al.*, 1984; Magiakou, Mastorakos, Webster, & Chrousos, 1997). However the diurnal rhythm of cortisol secretion is maintained during pregnancy (Abou-Samra *et al.*, 1984; Lindholm & Schultz-Moller, 1973). Immediately after parturition the HPA axis is slightly suppressed until about 12 weeks (Magiakou *et al.*, 1997); although cortisol levels are within the normal range and slowly return to prepregnant levels (Chrousos, Torpy, & Gold, 1998), which is unlike the blunting of the circadian rhythm of corticosterone release seen in postpartum female rats (Fischer *et al.*, 1995; Stern *et al.*, 1973). Furthermore it is important to note that in terms of fetal development the third trimester of pregnancy in humans occurs outside of the womb in rodents, making it hard to determine analogous time points in fetal development between the two species.

2.6 Cognition in humans across pregnancy and the postpartum period

Subjective reports indicate dramatic impairments in cognitive functioning across pregnancy and the postpartum period, with 50 to 80% of women perceiving deficits in memory functioning (Brett & Baxendale, 2001). However findings from objective measures are

equivocal, with some studies finding memory is adversely affected during pregnancy with impairments lasting 2 months or longer postpartum (Cuttler, Graf, Pawluski, & Galea, 2011; de Groot, Vuurman, Hornstra, & Jolles, 2006; Eidelman, Hoffmann, & Kaitz, 1993), whereas others do not find any impairments (Casey, Huntsdale, Angus, & Janes, 1999; McDowall & Moriarty, 2000). A recent meta-analysis found relatively subtle impairments in executive functioning with deficits in tasks that only assessed effortful processing and measured free recall and executive processing of working memory across pregnancy and persisting into the postpartum period (Henry & Rendell, 2007). Cuttler et al. (2011) recently showed pregnant women consistently reported subjective impairments in memory but that objective laboratory measures of prospective memory, which requires high degree of effortful processing, were not affected by pregnancy status. However prospective memory was impaired by pregnancy when assessed with field tasks that are completed in the context of the person's everyday life (Cuttler et al., 2011). Intriguingly Vanston and Watson (2005) found that fetal sex played a role in cognitive impairments: women pregnant with a male fetus were more likely to perform better on tests of working memory and spatial ability than women pregnant with a female fetus. This could be related to different levels of circulating hormones influenced by the sex of the unborn fetus, as human chorionic gonadotropin concentrations are elevated in mothers carrying female fetuses and this may play a role in the impairment seen in working memory and spatial ability in these mothers (Vanston & Watson, 2005). Other studies have found more specific deficits in cognitive domains such as working memory, verbal memory or attention in pregnant women that may also be related to maternal hormone levels (Buckwalter *et al.*, 1999; Glynn, 2010; Vanston & Watson, 2005). For instance poorer performance on verbal recall memory is seen in pregnant women compared with nonpregnant women during the third trimester (Glynn, 2010). This impairment is related to

maternal levels of steroid hormones, as cortisol levels were lower and estradiol levels were higher in pregnant women with poorer performance (Glynn, 2010). Cortisol levels are also associated with detriments in verbal recall memory and spatial ability during pregnancy and the postpartum period whereas prolactin levels during pregnancy are associated poorer executive functioning and verbal recall memory (see Henry and Sherwin, submitted to *Behavioral Neuroscience*, this issue). Consistent with potential impairments in memory performance during pregnancy Oatridge et al. (2002) have shown that total brain size decreases during pregnancy and returns to preconception size during the postpartum period similarly to female rodents (Galea et al., 2000).

Few studies have examined whether motherhood itself is associated with enhanced cognition as is seen in rodents. Buckwalter et al. (2001) found an improvement in cognitive abilities at 2 years postpartum compared with late pregnancy and the early postpartum period, suggesting possible enhancing effects of motherhood on memory in women. Vanston and Watson (2005) also found that working memory was still enhanced after resumption of menses in previously pregnant women (between 5 and 18 months postpartum). Conversely impairments in verbal recall memory during pregnancy persist at 3 months postpartum (Glynn, 2010). Furthermore the memory of primigravidae women (experiencing their first pregnancy) may be more negatively affected by pregnancy than multigravidae women (experiencing subsequent pregnancy) (Brindle, Brown, Brown, Griffith, & Turner, 1991). However this has not been consistently found (McDowall & Moriarty, 2000). Together these studies indicate that although deficits in specific cognitive domains may exist during pregnancy and the postpartum period, the effects are subtle and may depend on many factors including the trimester of pregnancy, the type

of memory system being examined, the sex of the fetus, how and where the memory is tested, and the gravidae status of the women.

3. Depression during pregnancy

3.1 Overview

Women are significantly more likely than men to develop major depressive disorder, as well as its subtypes (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). Overall, women have a lifetime prevalence of depression approximately 1.5 – 3 times higher than that of men, which is attributable at least in part to a greater incidence during the childbearing years (Gutierrez-Lobos, Scherer, Anderer, & Katschnig, 2002; Kessler *et al.*, 1993; Sloan & Kornstein, 2003). Although psychosocial factors likely contribute to this sex difference, it is also possible that elevated and fluctuating (or aberrant physiological responses to) reproductive hormones after the onset of puberty predispose women to mood disturbances (Soares & Zitek, 2008). Specifically, varying concentrations of steroid and peptide hormones associated with the menstrual cycle, pregnancy, and parturition may underlie coincident depressive disorders (Young & Korszun, 1998). Depressive disorders during pregnancy and parturition reduce the quality of life for women, strains marital relationships, and may reduce the physical and psychological wellbeing of developing fetuses and offspring (Grace, Evindar, & Stewart, 2003). Thus, a solid understanding of neuroendocrine processes, especially using well-designed animal models with special attention to brain plasticity, will lead to discoveries of treatments safe for fetuses and developing offspring, inform clinical practices, and improve outcomes for all involved.

Although considered a joyous period in a woman's life, pregnancy represents neither a risk factor nor a protective period for depression. Rather, pregnancy may confer vulnerability

upon women already at risk for developing depression. Approximately 7-12% of women experience depression during this time (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; O'Hara, Neunaber, & Zekoski, 1984). Maternal depression and anxiety may induce obstetric complications including preeclampsia, preterm labor and physiological changes in fetuses and neonates (Alder, Fink, Bitzer, Hosli, & Holzgreve, 2007). Self reported depression during pregnancy also predicts low birth weight (Steer, Scholl, Hediger, & Fischer, 1992) and negative affective responses in infants (Huot, Brennan, Stowe, Plotsky, & Walker, 2004).

Antidepressants, however, may pose further risk for the fetus. For instance, pregnant women taking fluoxetine, a selective serotonin reuptake inhibitor (SSRI), during their third trimester may have a higher rate of early delivery and their offspring are at risk for low birth weight and respiratory complications (Chambers, Johnson, Dick, Felix, & Jones, 1996). These findings, however, are not without controversy (Cohen & Rosenbaum, 1997; Goldstein, Sundell, & Corbin, 1997) as others have reported that fluoxetine is relatively safe for use in pregnant women (Goldstein, 1995). However it should be noted that fetal exposure to antidepressants, independently of maternal mood, alters levels or expression of plasticity-related proteins such as $\text{s100}\beta$ (Pawluski, Galea, Brain, Papsdorf, & Oberlander, 2009) and reelin (Brummelte, Oberlander, Devlin, & Galea, 2010) in infants. Thus, clinicians must weigh risks of untreated depression against the benefits of not exposing fetuses to pharmaceuticals (Udechuku, Nguyen, Hill, & Szego, 2010). The remainder of this review will focus on the neuroendocrine correlates of depression and cognitive changes during pregnancy and postpartum and summarize relevant animal models. Our goal is to inform and stimulate future research in animal models of depression in females because, although depression afflicts significantly more women than men,

animal research in this area has been biased toward males (Beery & Zucker, 2011; Zucker & Beery, 2010).

3.2 Potential neuroendocrine mechanisms of depression during pregnancy

3.2.1 Ovarian hormone correlates

Concentrations of progesterone and estradiol increase substantially throughout pregnancy (Soldin et al., 2005), which coincide with increasing prevalence rates of a depressive episode (i.e., 7.4%, 12.8%, and 12.0% during the first, second, and third trimesters, respectively) (Bennett et al., 2004). In pregnant women, progesterone (but not estradiol) concentrations were associated with mood disturbances, including depression (Buckwalter et al., 1999). In another study, the progesterone metabolite 5 α -dihydroprogesterone was significantly higher in pregnant women with depression compared with pregnant nondepressed controls during their second and third trimesters (Pearson Murphy, Steinberg, Hu, & Allison, 2001). Others have proposed that sharp changes in circulating estrogens and progestins (rather than high, stable concentrations) may precipitate affective disturbances. In a study of pregnant Chinese women, both progesterone and estradiol (but not cortisol) were significantly correlated with depression scores in all three trimesters (Zou et al., 2009). In euthymic women with a history of depression, 50% relapsed during the first trimester, and 90% relapsed by the end of the second trimester (Cohen et al., 2006). Together, this suggests that women who are vulnerable to depression may be differentially sensitive to increases in estrogens and progestins.

3.2.2 Stress-related hormones and depression during pregnancy

Given the relationship between stress and depression (reviewed elsewhere: McEwen, 2008; Pittenger & Duman, 2008), excessive stress and glucocorticoids could also contribute to mood disturbances in pregnancy. Women with normal pregnancies have increased cortisol concentrations (Allolio *et al.*, 1990; Yim *et al.*, 2009) and reduced day-night variation in cortisol at 34 – 38 weeks of pregnancy (Burke & Roulet, 1970). Significant stressors leading to further elevated cortisol during pregnancy may contribute to depression. Pregnant women who are depressed perceive life as more stressful and have higher resting cortisol concentrations compared with pregnant women who are not depressed (Parcells, 2010). In contrast, other studies have reported no relationship between cortisol and depressive symptoms during pregnancy (Figueiredo & Costa, 2009; King *et al.*, 2010; Pluess, Bolten, Pirke, & Hellhammer, 2010). These studies, however, included participants who did not meet the diagnostic criteria for clinical depression and differed in the source of cortisol (urinary, saliva), gestational day and time of day of sampling, all factors that may play a role in the relationship between cortisol and depressive symptoms. It is important to note that during pregnancy the placenta releases increasing concentrations of corticotrophin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) which contribute to the elevated levels of cortisol during the course of pregnancy (Thomson, 2008). The relationship between placental CRH (pCRH) and depression, however, is equivocal as some, but not others, demonstrate a relationship between pCRH and prenatal depression (Meltzer-Brody *et al.*, 2011; Rich-Edwards *et al.*, 2008).

In summary, no consistent picture emerges in regard to the relationship between hormone concentrations and depression during pregnancy. Simply investigating circulating concentrations of hormones provides a rather limited picture. As such, many researchers have suggested that mood disruptions that co-occur with steroid hormone fluctuations may reflect a heightened

vulnerability or sensitivity to reproductive hormones (Bloch *et al.*, 2005; Soares & Zitek, 2008). Thus, animal research will be important in determining how other endocrine factors (e.g., receptors, binding proteins, enzymes, metabolites, and coactivators) regulate hormone action and in turn, the behavioral phenotype.

4. Postpartum depression

4.1 Overview

Postpartum depression (PPD) is a devastating illness that afflicts ~15% of new mothers (McCoy, Beal, & Watson, 2003; Seyfried & Marcus, 2003). Two primary risk factors are a history of depression (family or personal) and depression during pregnancy (O'Hara & Swain, 1996). To complicate matters, women are reluctant to take antidepressants during pregnancy or the postpartum period with only 18% of depressed mothers seeking treatment (Dennis & Chung-Lee, 2006). Women with untreated PPD have impaired cognitive ability, increased marital difficulties, and are more likely to commit infanticide or abuse their children (Grace *et al.*, 2003; Seyfried & Marcus, 2003). As mentioned in the previous section, substantial fluctuations in hormones such as estrogens, progesterone and cortisol associated with pregnancy and parturition may precipitate a depressive episode. However, a complete understanding of the causes of PPD has yet to be established. Many women with PPD experience high levels of stress associated with the demands of pregnancy and giving birth and high levels of stress hormones may be a factor in the development of PPD (Seyfried & Marcus, 2003). PPD reduces quality of life for women, strains family life, and has grave developmental consequences for infants. Understanding the mechanisms of PPD may lead to novel therapeutic insights and will lead to better quality of life for women with PPD and improved developmental and behavioural

outcomes for their children. In the next several sections, we review the literature on steroid and peptide hormones and postpartum depression, particularly the impact of ovarian steroid withdrawal, and elevated corticosterone in animal models relevant to postpartum depression.

4.2 Estrogen Withdrawal

Due to the significant drop in concentrations of reproductive hormones after parturition, depressive symptoms may be induced by withdrawal from estrogens, which has led to the “estrogen withdrawal hypothesis” of PPD. Women with PPD have lower levels of estradiol at week 36 of gestation and day 2 postpartum (O'Hara, Schlechte, Lewis, & Varner, 1991), but others have reported no relationship between estradiol or progesterone and PPD (Buckwalter *et al.*, 1999; Heidrich *et al.*, 1994; Klier *et al.*, 2007). However, estradiol treatment alleviates depression symptoms in postpartum women (Ahokas, Kaukoranta, Wahlbeck, & Aito, 2001; Gregoire, Kumar, Everitt, Henderson, & Studd, 1996) either as adjunct treatment or on its own. Additionally, exogenous estradiol and progesterone followed by hormone withdrawal precipitates a depressive episode in women with (but not in those without) a history of PPD (Bloch *et al.*, 2000). Collectively, these data suggest that PPD may arise from heightened vulnerability to changes in gonadal hormone concentrations, rather than absolute concentrations. Although it has been used as a treatment of PPD in clinical studies, estradiol may not be an optimal treatment itself, because it can be transferred to the infant through breastmilk and may have developmental consequences for infants (Ball & Morrison, 1999; Nilsson, Nygren, & Johansson, 1978). However, some of the actions of estradiol can be mimicked with the use of an estrogen receptor beta (ER β) agonist called diarylpropionitrile (DPN), which alleviates depressive-like behavior in rodents (as described below).

4.3 HPA axis-related hormones

As in major depression, the HPA axis becomes dysregulated in women suffering from PPD (Taylor, Glover, Marks, & Kammerer, 2009). At the end of pregnancy, cortisol peaks resulting from high levels of pCRH. The postpartum period is accompanied by significant physical and psychological stressors (Groer, Davis, & Hemphill, 2002). Postpartum blues have been associated with elevated ACTH (O'Keane *et al.*, 2011) but in general, there is a paucity of support for cortisol as a causative factor in PPD (Hendrick, Altshuler, & Suri, 1998). Some researchers have proposed, however, that PPD encompasses different subtypes (similarly to major depression) and thus may involve differential regulation of the HPA axis in each subtype (Kammerer, Taylor, & Glover, 2006). Indeed, exposure to a hormone-simulated pregnancy resulted in elevated cortisol responses in women with, but not in women without, a history of PPD in response to CRH (Bloch *et al.*, 2005). In women, the HPA axis response to external stressors is diminished during the postpartum period after acute suckling (Heinrichs *et al.*, 2001). It may be the case that women with PPD fail to show this normal suppression of the HPA axis as they are less likely to breastfeed.

4.4 Peptide hormones

Oxytocin and prolactin are integral for breastfeeding and both may be important for mood regulation as oxytocin assists with mother-infant bonding. Disruption in either hormone system may underlie some aspects of PPD, especially when it involves disordered maternal care (Neumann, 2003). Women with PPD are less likely to breastfeed early in the postpartum period (Hatton *et al.*, 2005). One study found that women with PPD have reduced prolactin levels,

which correlated with depressive symptoms (Harris *et al.*, 1989); but see also (O'Hara *et al.*, 1991). Additionally, acute breastfeeding improved mood scores and reduced cortisol concentrations after an acute stressor (Heinrichs *et al.*, 2001). In a recent study, low plasma oxytocin during the third trimester of pregnancy also predicted symptoms of PPD (Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011). Additional research should replicate and extend this finding.

4.5 PPD and parity

PPD may vary with parity as depression and anxiety are more prevalent in primigravid compared with multigravid mothers (Fleming, Steiner, & Corter, 1997). Furthermore parity itself modulates the expression of maternal depression as stress reactivity in multigravid mothers is not as severe as in primigravid mothers (Tu, Lupien, & Walker, 2005) and depressed primigravid mothers do not touch their infants as much as depressed multigravid mothers (Ferber, 2004; Fleming *et al.*, 1997). Parity itself also affects hormone fluctuations during the estrous cycle and subsequent pregnancies and during the postpartum period (Bridges & Byrnes, 2006; Pawluski, Charlier, *et al.*, 2009). Collectively, these data indicate that PPD may arise in vulnerable women from a number of hormonal factors that coalesce after parturition. In particular, withdrawal from estrogens, and perhaps dysregulated HPA axis that may be further complicated by reduced breastfeeding during the postpartum period may contribute to PPD in vulnerable women. Animal research will prove integral in understanding how these hormonal factors individually contribute to changes in the brain and a depressive-like phenotype.

5. Animal Models

Although it is not possible to model all symptoms of depression in animals, animal models can examine some of the more prominent symptoms of depression such as anhedonia, body weight changes and cognitive disturbances, allowing researchers to examine alterations in limbic structures such as reduced hippocampal volume, dendritic complexity and hippocampal neurogenesis. Depressed individuals have smaller hippocampi, which is related to the duration of the disease and antidepressant treatment protects against hippocampal volume loss (Sheline, Gado, & Kraemer, 2003; Sheline, Sanghavi, Mintun, & Gado, 1999). A recent meta-analysis determined that smaller hippocampal volume in depressed patients was only evident after 2 years with depression and only in children and middle-aged and older adults (McKinnon, Yucel, Nazarov, & MacQueen, 2009). Reduced hippocampal volume may be due to a combination of a number of factors including: reduced neurogenesis, reduced neuropil, and reduced cell body size.

Several animal models of depression, including our estradiol-withdrawal model of PPD and CORT-induced model of PPD, are associated with reduced hippocampal neurogenesis (Brummelte & Galea, 2010a; Brummelte, Pawluski, & Galea, 2006; Green & Galea, 2008). Treatment with pharmacological antidepressants restores hippocampal neurogenesis to normal levels in these models (R. S. Duman, Nakagawa, & Malberg, 2001; Malberg, Eisch, Nestler, & Duman, 2000). Importantly, chronic, but not acute, pharmacological antidepressant treatment increases neurogenesis in the hippocampus (Malberg *et al.*, 2000) in a timeline which mirrors the alleviation of depressive symptoms in humans (Schule, 2007), and non-pharmacological antidepressants (such as exercise) increase neurogenesis in the hippocampus of rodents (Ernst, Olson, Pinel, Lam, & Christie, 2006; Malberg *et al.*, 2000). The link between hippocampal neurogenesis and depression is compelling but the findings are not without controversy (Bessa *et al.*, 2009; Radley *et al.*, 2004; Sapolsky, 2004). Two studies showed that antidepressant

treatment enhances neurogenesis in both humans and nonhuman primates (Boldrini *et al.*, 2009; Perera *et al.*, 2007), one study did not, however (Reif *et al.*, 2006). The authors of the latter study did not control for sex, age or duration of illness. These factors may have played an important role, given the differences in neurogenesis between the sexes (Galea, 2008), and the association with age (Kuhn, Dickinson-Anson, & Gage, 1996) and the duration of illness with hippocampus volume (McKinnon *et al.*, 2009). It is imperative that these factors must be taken into consideration in future studies. In short, although it is not possible to model all the symptoms of depression in rodents, it is possible to model some of the symptoms and neurobiological correlates of depression (see Table 1 for diagnostic criteria that can be modeled in rodents).

One common behavioral test used in the study of depressive-like behavior is the forced swim test. The forced swim test (FST), first designed as a screen for antidepressant effectiveness (Porsolt, Anton, Blavet, & Jalfre, 1978; Porsolt, Le Pichon, & Jalfre, 1977), is also commonly used to assess depressive-like behavior and immobility in many experimental paradigms is widely interpreted as a ‘depressive-like behavior’ (e.g., C. H. Duman, Schlesinger, Russell, & Duman, 2008; Marks, Fournier, & Kalynchuk, 2009; Pyter & Nelson, 2006). Rodents are placed in an inescapable cylinder of water on two consecutive days and on the second day, immobility (often described as ‘behavioral despair’) is assessed as a depressive-like behavior. A cogent discussion of the limitations to the FST as a measure of depressive-like behavior (as opposed to an antidepressant screen) is provided elsewhere (Cryan, Valentino, & Lucki, 2005). Behavior in the FST, however, is associated with environmental and neural correlates of depression in humans such as chronic stress, serotonergic neurotransmission, and hippocampal atrophy, which further confer validity. Anhedonia, loss of pleasure or interest (a common symptom of

depression), may also be modeled in rodents using the sucrose preference test (Papp, Willner, & Muscat, 1991; Willner, Muscat, & Papp, 1992a, 1992b). Rats are given a choice between either a weakly sweet sucrose solution or water. Chronic stressors significantly reduce preference for sucrose (Koo & Duman, 2008; Papp *et al.*, 1991; Willner *et al.*, 1992b). Thus, although there may be limitations to the conclusions that can be drawn from these tests, they provide useful tools for investigating the effects of hormones on behaviors that may represent depressive-like phenotypes.

5.1 Ovarian hormone effects on depressive-like behaviors in rodents

In contrast to correlational data from human pregnancy studies, animal research has suggested that progesterone has antidepressant properties in the forced swim test (FST; Frye, Walf, Rhodes, & Harney, 2004; Molina-Hernandez & Tellez-Alcantara, 2001) and tail suspension test (TST; Frye, 2011), two behavioral measures used to screen pharmaceutical antidepressants. The antidepressant effects of progesterone do not seem to occur through the progesterone receptor, but rather, 5α -reduced metabolites (Frye, 2011; Frye *et al.*, 2004). Given that pregnancy yields extremely high progesterone concentrations, further research should determine if progesterone metabolites modulate depressive-like behavior in a nonlinear (U-shaped) pattern. Estradiol also consistently reduces depressive-like behaviors (Walf & Frye, 2007, 2010), and withdrawal from estrogens may precipitate PPD as we discuss below.

5.1.1 An animal model of postpartum depression: Ovarian hormone withdrawal after a hormone simulated pregnancy (HSP)

As previously mentioned, estradiol, the most potent estrogen, has an antidepressant effect in both humans and rodents (Walf & Frye, 2007; Walf, Rhodes, & Frye, 2004). Cessation of a hormone simulated pregnancy (HSP), using chronic estradiol and progesterone increases depressive-like behavior (increased immobility in the forced swim test (Galea, Wide, & Barr, 2001; Suda, Segi-Nishida, Newton, & Duman, 2008), reduced sucrose preference, (Green, Barr, & Galea, 2009), increased learned helplessness (Suda *et al.*, 2008) and reduces cell proliferation in the hippocampus (Green & Galea, 2008). Depressive-like behavior and reduced cell proliferation induced by HSP were reversed by treatment with estradiol (Galea, Wide, & Barr, 2001) or DPN (Green & Galea, 2008). Ovarian steroid withdrawal also alters mRNA expression of several candidate genes (SERT, BDNF, among others) thought to be involved in depression (Suda *et al.*, 2008). DPN may also have minimal effects on lactation as ER β is expressed in relatively low levels in the mammary glands of rats (Varas & Jahn, 2005). Mice lacking ER β do not respond to the antidepressant effects of estradiol (Rocha, Fleischer, Schaeffer, Rohrer, & Hickey, 2005) suggesting that some of the antidepressant actions of estradiol occur through ER β . Additionally, estradiol withdrawal may dysregulate postpartum mood by altering serotonergic (Joffe & Cohen, 1998), GABAergic (Maguire & Mody, 2008), and opioid neurotransmission (Bridges & Ronsheim, 1987).

5.2 Animal models of postpartum depression: High corticosterone

In rodents, chronic treatment with high CORT administered to both adult male and nonpuerperal female rats increases depressive-like behaviors (Kalynchuk, Gregus, Boudreau, & Perrot-Sinal, 2004) and reduces cell proliferation in the dentate gyrus (Brummelte & Galea, 2010b). High CORT (40mg/kg) given to dams during the postpartum period also increases

depressive-like behavior (Brummelte & Galea, 2010a; Brummelte *et al.*, 2006) in the FST (increased immobility and decreased struggling), reduces maternal care (i.e., less time spent on the nest; Brummelte & Galea, 2010a; Brummelte *et al.*, 2006) and reduces cell proliferation in the hippocampus (Brummelte & Galea, 2010a) which has been associated with depression. Only high CORT given during the postpartum period, and not during gestation, resulted in a depressive phenotype in the dam (Brummelte & Galea, 2010a). The levels of serum CORT achieved by using this high dose of CORT are akin to those seen after ether stress during the postpartum period (Yeh, 1984). A primary strength of this animal model of postpartum depression is that it allows for investigation of consequences on the development of the offspring. Chronic corticosterone during the postpartum period reduced cell proliferation in male pre-adolescent offspring. Furthermore offspring, regardless of sex, were more resistant to capture and displayed more anxiety-like behavior (Brummelte *et al.*, 2006). Furthermore recent research has shown that offspring exposed to low maternal CORT, but not high maternal CORT, during the postpartum period had higher basal levels of CORT as young adults. Further, male and female offspring of dams exposed to high maternal CORT *in utero* showed more depressive-like behavior in the forced swim test, whereas males of dams exposed to high maternal CORT postpartum exhibited more anxiety-like behavior in the elevated plus maze (Brummelte, Lieblich and Galea., submitted). Moreover, these animal models of postpartum depression also share some of the common characteristics of the human condition (Table 2).

5.3 Peptide hormones

As mentioned, the postpartum period comprises substantial fluctuations of oxytocin and prolactin. Prolactin does not demonstrate antidepressant properties on its own but potentiates the

antidepressant effect of desipramine, a tricyclic antidepressant, in male rats (Drago, Pulvirenti, Spadaro, & Pennisi, 1990). Also, prolactin may act as a buffer to stress, as ovine prolactin reduces ACTH responses after exposure to an anxiety-like behavioral task (Torner, Toschi, Pohlner, Landgraf, & Neumann, 2001). Finally, prolactin protects the hippocampus from stress-induced reductions in neurogenesis in male mice (Torner *et al.*, 2009). Oxytocin may also offer a protective effect. For instance, social isolation increases immobility in the FST, but this is reversed by oxytocin treatment (Grippe, Trahanas, Zimmerman, Porges, & Carter, 2009).

5.4 Reproductive experience and brain plasticity

As noted earlier, structural modifications within the hippocampus can result from exposure to estrogens (Woolley, 1998), progestins, glucocorticoids (McEwen, 2001), peptide hormones (Torner *et al.*, 2009) and natural fluctuations such as the estrous cycle (Woolley *et al.*, 1990), pregnancy and parturition (Pawluski, Brummelte, *et al.*, 2009; Pawluski & Galea, 2006). Furthermore reproductive experience alters hippocampus structure and plasticity. For instance, the first reproductive experience significantly reduces dendritic length and branch points in both the CA1 and CA3 hippocampal subfields (Pawluski & Galea, 2006) and reduces cell survival (Pawluski & Galea, 2007). Further, multiparous rats have increased spine density on CA1 basal dendrites (Pawluski & Galea, 2006), although this may have been due to the higher male sex ratio of the pregnancies. It is also important to note that hormonal events in pregnancy and parturition may interact with experience, such as offspring exposure, to induce plastic changes beyond the effects of merely hormones alone. For example, late pregnancy-related steroids and pup exposure interact to induce astrocytic remodeling in the cingulate cortex of rats (Salmaso, Nadeau, & Woodside, 2009). Hormonal events during pregnancy, parturition and the postpartum

period are altered with previous reproductive experience (Bridges & Byrnes, 2006) and with exposure to stress during gestation (Smith, Seckl, Evans, Costall, & Smythe, 2004). Thus reproductive experiences or stressors can further induce changes with pregnancy and the postpartum period.

6. Overall Conclusions and Future Directions

Together the studies reviewed here suggest that it is important to investigate changes in neural and cognitive processes that occur with parity and mothering in order to understand long-lasting influences in physiology of the mother. As stated in this review hormone fluctuations during pregnancy and the postpartum period may contribute to the pregnancy- and motherhood-associated cognitive disturbances and vulnerability to neuropsychiatric diseases such as PPD. The literature also suggest that the effects of pregnancy and motherhood on cognition and PPD may vary with parity. Furthermore, the effects of reproductive experience are long lasting and alter responses to hormones later in life. Although more attention has been given to the role of the hippocampus in this area, a few studies have investigated cortical changes in structure and function. Dendritic spine changes in the postpartum period seem to be linked with attentional set shifting (Leuner & Gould, 2010) and it is important to determine the degree to which such changes are stable across the lifespan. Further, reproductive experience induces structural changes in glia in the cortex (Salmaso *et al.*, 2009; Salmaso, Quinlan, Brake, & Woodside, 2011), but the functional implications of these changes are currently unknown. Both areas represent exciting new developments in the study of reproductive experience and brain structure and function. Further, the role of cortical areas in mood disorders are becoming increasingly apparent. Thus, it is important to continue to advance our understanding of how parity and

Cognition and depression in pregnancy and postpartum

mothering affects neurological, behavioral and hormonal measures and may provide insight for the development of treatment for postpartum disorders.

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Figure captions:

Figure 1. Spatial cognitive performance in primiparous female rats relative to control nulliparous female rats across the reproductive lifespan. Enhanced spatial cognitive performance is seen initially during pregnancy compared with nulliparous female rats. However performance is impaired in late pregnancy and during the early postpartum period. Performance increases during lactation and the post-weaning period compared with nulliparous females, and enhancements are seen throughout the remainder of the lifespan.

Figure 2. Mean ($\pm$ SEM) latency (A) and distance (B) required for pregnant and non-pregnant female rats to reach the hidden platform in the Morris water maze on week 1, 2 and 3 of pregnancy. Pregnant rats in their first and second week of pregnancy outperformed non-pregnant rats. During week 3 of pregnancy, performance was impaired in pregnant rats. Group differences in performance were not related to changes in swim speed. *Significantly different. Reprinted with permission from Galea et al., 2000.

Figure 3. Mean ($\pm$ SEM) total number of spatial reference and working memory errors committed by primiparous, multiparous and nulliparous rats on the spatial reference/working memory version of the radial arm maze when testing commenced immediately following weaning. Primiparous rats made significantly fewer errors, regardless of error type, than nulliparous rats ($P \leq 0.04$), with a trend for multiparous rats to make fewer errors, regardless of error type, than nulliparous rats ($P \leq 0.07$) and no significant difference between primiparous and multiparous rats in total number of errors ($P \leq 0.48$). *Significantly different from nulliparous rats. Reprinted with permission from Pawluski, Walker and Galea, 2006.

Figure 4. Increased cell proliferation in the dentate gyrus after estrogen replacement in multiparous females but not in nulliparous females. An acute, high dose of 17β -estradiol, estrone, and 17α -estradiol significantly increased cell proliferation in multiparous middle-aged reproductively senescent female rats but not in age-matched nulliparous females. (a) Denotes significantly different from multiparous control group, (b) denotes significantly different from nulliparous group given the same hormone treatment. Reprinted with permission from Barha and Galea, in press.

Figure 1

Figure 2

A

B

Figure 3

Figure 4

Table 1. DSMIV criteria for Major Depressive Episode and those symptoms that are possible to model in rodents

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning;

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

***#(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)**

*#(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

*(4) insomnia or hypersomnia nearly every day

*#(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

*(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

*#(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Bolded (1) and (2) – at least one of these two must be present.

* indicates symptoms that are possible to model in rodents

indicates symptoms that will be examined in this proposal

Table 2: Similarities between PPD and animal models of PPD

Subject	Measure	Human PPD	Animal model	References
Mothers	Depressed mood	✓	✓**	Brummelte & Galea, 2010a; Brummelte et al., 2006; Craft et al., 2010; Galea et al., 2001; Green et al., 2009; Suda et al., 2008
	Reduced Infant contact/vocalizations	✓	✓/?	Brummelte & Galea, 2010a; Brummelte et al., 2006
	Reduced breastfeeding	✓	✓	Brummelte & Galea, 2010a; Brummelte et al., 2006
	Reduced hippocampal plasticity	?	✓	Brummelte & Galea, 2010a; Brummelte et al., 2006; Green & Galea, 2008
Offspring	Depressed mood	✓	~✓	Brummelte et al., 2011 (submitted)
	Antisocial behaviour	✓	?	
	Anxiety	✓	✓	Brummelte et al., 2006; Brummelte et al., 2011 (submitted; stress induced)
	Elevated glucocorticoids	✓	✓	Brummelte et al., 2011 (submitted; stress induced)
	Reduced hippocampal plasticity	?	✓	Brummelte et al., 2006

✓ indicates present in either human condition or animal model

** assessed in the forced swim, sucrose preference, or learned helplessness tests

~ indicates only when CORT is administered during pregnancy