Published in final edited form as:

Neurosci Biobehav Rev. 2022 February ; 133: 104475. doi:10.1016/j.neubiorev.2021.11.045.

Less Can Be More: Fine Tuning the Maternal Brain

Jodi L. Pawluski[1,*], **Elseline Hoekzema**[2,3], **Benedetta Leuner**[4], **Joseph S. Lonstein**[5]

[1]Univ Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail), UMR_S 1085, F-35000, Rennes, France.

[2]Brain and Development Laboratory, Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, The Netherlands.

[3]Hoekzema Lab, Amsterdam University Medical Center, Amsterdam, The Netherlands.

[4]The Ohio State University, Department of Psychology & Department of Neuroscience Columbus, OH, USA.

[5]Neuroscience Program & Department of Psychology, Michigan State University, East Lansing, MI 48824, USA.

Abstract

PAWLUSKI, J.L., Hoekzema, E., Leuner, B,. and Lonstein, J.S. Less can be more: Fine tuning the maternal brain. NEUROSCI BIOBEHAV REV (129) XXX-XXX, 2022. Plasticity in the female brain across the lifespan has recently become a growing field of scientific inquiry. This has led to the understanding that the transition to motherhood is marked by some of the most significant changes in brain plasticity in the adult female brain. Perhaps unexpectedly, plasticity occurring in the maternal brain often involves a decrease in brain volume, neurogenesis and glial cell density that presumably optimizes caregiving and other postpartum behaviors. This review summarizes what we know of the 'fine-tuning' of the female brain that accompanies motherhood and highlights the implications of these changes for maternal neurobehavioral health. The first part of the review summarizes structural and functional brain changes in humans during pregnancy and postpartum period with the remainder of the review focusing on neural and glial plasticity during the peripartum period in animal models. The aim of this review is to provide a clear understanding of when 'less is more' in maternal brain plasticity and where future research can focus to improve our understanding of the unique brain plasticity occurring during matrescence.

Keywords

brain imaging; cortex; hippocampus; neurogenesis; neuroimmunology; neuroplasticity; maternal behavior; maternal brain; motherhood; glia; pregnancy; postpartum

[*]Corresponding author: Jodi L. Pawluski, University of Rennes 1, Irset (Institut de Recherche en Santé, Environnement et Travail), UMR_S 1085, F-35000, Rennes, France. j.pawluski@gmail.com.

1. Introduction

The peripartum period represents one of the most neurobehaviorally plastic phases in a female's life, on par with other critical hormonal-developmental stages such as adolescence and menopause (Leuner et al., 2010; Lonstein, 2018; Pawluski et al., 2009a; Rehbein et al., 2021). Consequently, this dynamic developmental phase, often referred to as matrescence, presents a valuable context to gain a better understanding of the mechanisms and functions of plasticity in the adult female brain. Neuroplastic change across motherhood has been quite well-studied in non-human laboratory animals (Hillerer et al., 2014a; Levy et al., 2011; Medina and Workman, 2018; Pawluski et al., 2009a) but only recently has work been conducted to understanding the structural and functional brain changes that occur in women as they transition through pregnancy and the postpartum period. This research provides some exciting parallels that suggest conservation across species in how motherhood sculpts the female brain.

When we think about the emergence of new neurobehavioral competencies across the lifespan, it is common to assume that they are supported by significant proliferative events in the nervous system. Therefore, it may be surprising to know that there are reports of a decrease across pregnancy in various measures of brain plasticity – from structural changes to changes in neurogenesis and glial plasticity (Haim et al., 2017; Hoekzema et al., 2017; Pawluski et al., 2016). These decreases in aspects of brain plasticity are not linked to deficits in behavioral outcomes, similar to those often associated with aging but, in fact, may be a 'fine tuning' of the maternal brain where *less can be more* for female behavioral function. This idea is in line with numerous events occurring during other developmental stages such as early childhood or adolescence where decreases in neurogenesis and synaptic pruning are well-known to be necessary for healthy behavioral outcomes (Lambert et al., 2019). It should be noted that changes in the maternal brain are not always specific to birthing parents. For reviews of brain changes with fatherhood and alloparenting see (Feldman et al., 2019; Glasper et al., 2019; Kim et al., 2014). The present review will highlight the 'fine tuning' of the maternal brain as it relates to changes in brain plasticity in humans and laboratory rodent models. We will first focus on the structural and functional changes in the maternal brain in women and non-human animals, then discuss changes in neurogenesis, neuron structure and spine density in areas of the maternal brain studied to date. Finally, we will consider what we know of changes in glial cell structure and function in the maternal brain. The mechanisms behind these normative changes, and how this brain plasticity is critical for mothering, will also be discussed. Highlighting the widespread and significant changes in brain plasticity with motherhood will provide a basis for understanding and optimizing brain health during this critical period in a female's life.

2. Brain changes accompanying motherhood in humans

2.1. Structural neuroimaging

Although the first observations of changes related to brain anatomy in pregnant women date from the 19th century (Comte, 1898), research on the impact of pregnancy and motherhood on the human brain is relatively scarce. The first observations came from the enlargements of the pituitary gland observed in autopsies (Comte, 1898), which were confirmed *in vivo* a

century later by magnetic resonance imaging (MRI) and were found to reflect an increase in the size and number of prolactin-synthesizing cells within this structure (Dinc et al., 1998; Elster et al., 1991; Gonzalez et al., 1988). Insights into the effects of pregnancy on brain anatomy were obtained over 100 years later in a clinical study by Oatridge and colleagues that outlined the borders of the brain in five pregnant women with preeclampsia and nine without preeclampsia, observing transient reductions in overall brain size in pregnant women compared to non-pregnant women (Oatridge et al., 2002).

Fifteen years after the study by Oatridge et al., a pre-conception prospective cohort MRI study resulting in complete “pre-post pregnancy” datasets of 25 first-time mothers, 20 nulliparous control women, 19 first-time fathers and 17 nulliparous control men who were all scanned before and after their (partner’s) pregnancy, or at a comparable time interval, showed that primiparous women undergo extensive and highly consistent reductions in regional grey matter volumes across pregnancy in comparison to all three control groups. The very large effect sizes and fact that all women could be classified as having been pregnant or not based only on the changes in their brain structure point to very robust and consistent neural changes. These changes in grey matter volume were mirrored by reductions in surface area and cortical thickness and the reductions remained for at least two years after delivery (Hoekzema et al., 2017). Further analyses showed that the affected areas, which comprised many brain regions but primarily centered on the medial frontal cortex, precuneus, posterior cingulate cortex, inferior frontal gyri and superior temporal sulci, showed the greatest quantitative overlap with the neural network regulating “theory of mind” (Hoekzema et al., 2017). Theory of mind is the ability to decode mental states in ourselves and others, such as someone else’s intentions and emotions, and is critical for sensitive maternal caregiving (Schaafsma et al., 2015). Furthermore, these motherhood-related reductions in the brain also strongly overlapped with the mothers’ neural reactions to stimuli of their babies when measured in a functional MRI (fMRI) paradigm, and the observed structural changes predicted measures of postpartum maternal attachment. Anatomical delineation of the ventral striatum, a core part of the mesolimbic reward system containing the nucleus accumbens, also demonstrated volumetric reductions that were associated with mothers’ stronger ventro-striatal neural responses to their infants (Hoekzema et al., 2020).

Together, these findings give rise to the notion that pregnancy can generate neural reductions, both transient reductions in overall brain size and regional reductions exceeding and outlasting the global changes (Table 1). It is interesting to note that the anatomical reductions observed during and across pregnancy are reminiscent of those observed in human adolescence, another transitional life stage characterized by increases in plasma and brain concentrations of sex steroid hormones (Peper et al., 2011). In fact, a longitudinal study comparing the changes in brain anatomy between 25 women undergoing pregnancy to those of 25 girls undergoing adolescence using various morphometric measures showed strong similarities between these groups, suggesting that pregnancy and adolescence might entail similar hormone-driven morphological brain adaptations (Carmona et al., 2019). However, rather than a purely hormone-driven process, the observed brain changes likely reflect an interplay among various biological and experiential factors. In addition, osmotic processes could also play a role in the observed brain changes, particularly with regard to the

observed transient global reductions in brain size. Spectroscopic studies in pregnant women have found lower levels of neural choline, creatine and myo-inositol, which correlated with osmolality (Nelander et al., 2018; Rutherford et al., 2003), although differences in these neural metabolites have not been observed in all studies (Holdcroft et al., 2005). Future studies monitoring various biological and environmental factors could potentially further unravel the mechanisms driving the brain size changes associated with pregnancy.

Consistent with the longitudinal findings described above, cross-sectional studies examining brain structure in mothers compared to non-mothers have shown smaller regional volumes or cortical thickness in various stages of the postpartum period Luo and colleagues observed a thinner cortex in various regions, including the frontal lobe and cingulate gyrus, in nine mothers scanned within 24 hours after delivery compared to a control group of eight non-pregnant women (Luo et al., 2020). These regions corresponded to areas of cerebral blood flow increases and changes in electroencephalography (EEG) measured during the third trimester of pregnancy (Luo et al., 2020). Smaller volumes were also observed in the left striatum of 30 primiparous mothers scanned within the first two months after delivery when compared to 30 nulliparous women (Lisofsky et al., 2016). A recent study comparing 35 primiparous and 26 nulliparous women around 8 months after delivery found widespread clusters of smaller grey matter volume and cortical thickness, as well as increases in white matter volume and gyrification (Zhang et al., 2020). Future cross-sectional studies may find even longer-lasting differences, as predicted by longitudinal studies that found reductions in grey matter volume still present two years (Hoekzema et al., 2017) and even six years after delivery (Martinez-Garcia et al., 2021).

While these studies paint a coherent picture of grey matter reductions in pregnancy that persist well into the late postpartum period, longitudinal studies examining mothers in the postpartum period reveal that this is also a dynamic period in terms of brain plasticity. Several longitudinal studies have observed increases in grey matter volume in widespread cortical and subcortical areas in mothers in the first weeks and months of the postpartum period, some of which correspond to brain regions affected by pregnancy, although these studies did not include a control group (Kim et al., 2010a; Lisofsky et al., 2019; Luders et al., 2020). Lisofsky et al. also observed volume increases, particularly in frontal and cerebellar areas, across the first postpartum months in 24 first-time mothers in comparison to 24 nulliparous control women scanned at a comparable time interval (Lisofsky et al., 2019). Accordingly, a positive correlation was observed between the number of postpartum months and cortical thickness in various regions primarily centered in the prefrontal cortex and lateral occipital cortex (Kim et al., 2019). Hoekzema et al. also observed volume increases across the first two years after delivery, although these were restricted to the hippocampal complex (Hoekzema et al., 2017). On the other hand, Zhang et al. observed cortical thinning between around eight months and two years after delivery in 22 mothers in widespread areas across the brain (Zhang et al., 2020). Analyses comparing brain anatomy around two years after delivery to a pre-pregnancy baseline scan showed a pattern of changes nearly identical to that observed when comparing the early postpartum scans to the pre-pregnancy scans (Hoekzema et al., 2017), suggestive of a major shift in brain structure as a result of pregnancy followed by a period of relatively more subtle changes in the postpartum period. The available findings thus seem to point to long-lasting pregnancy-induced brain changes

that undergo a partial reversal across the postpartum period, likely in combination with novel brain changes primarily induced by postpartum experiential factors.

Interestingly, some recent studies have also examined the impact of childbearing on women's brain anatomy much later in life. Orchard and colleagues examined cortical thickness in 235 healthy older women (mean age = 73 years old) and found that mothers have thinner left dorsolateral prefrontal cortex and right pericalcarine sulcus (Orchard et al., 2020). Furthermore, there were associations between reduced cortical thickness in the left pericalcarine sulcus, left cuneus, right precuneus and a higher number of children parented by the women. Studies estimating brain age also consistently show an impact of motherhood in late life, with less signs of brain aging in mothers when compared to non-mothers (de Lange et al., 2020b; De Lange et al., 2019; Ning et al., 2020). These findings are also interesting to consider in relation to the development of Alzheimer's Disease or other age-related neurodegenerative disorders, although it should be noted that studies have actually shown a positive correlation between the number of children and Alzheimer's neuropathology in women (Beeri et al., 2009). Although many factors likely contribute to the observed effects of motherhood on the aging brain, these findings suggest that the neural modifications during pregnancy and early motherhood are detectable decades after giving birth.

2.2 Functional neuroimaging

It can be assumed that the neuroplasticity seen across pregnancy and the postpartum period is not limited to brain anatomy but involves functional changes as well (Table 1). In line with the localization of pregnancy-related structural brain changes (Hoekzema et al., 2017), several studies performed in pregnant women point to potential neural adaptation in social cognition (Anderson and Rutherford, 2012). For instance, pregnant women show electrophysiological alterations in comparison to non-pregnant women while processing emotional face-stimuli (Raz, 2014) as well as an association between prefrontal activation, increased distress, and increased levels of cortisol and testosterone to fearful faces (Roos et al., 2012). Furthermore, pregnant women have improved facial recognition (Anderson and Rutherford, 2011), better ability to encode threat-expressing faces (Pearson et al., 2009), a preference for individuals perceived as healthier (Jones et al., 2005), and increased ethnocentrism (Navarrete et al., 2007). These changes seem to entail enhanced vigilance towards a range of threats, such as those potentially associated with angry or fearful faces, sick-looking or out-group individuals. In addition to changes in threat responsiveness, altered social cognition is likely to facilitate a mother's recognition of her infant's needs and signals and promote mother-infant bonding, which is in accordance with associations between various maternal brain measures and aspects of maternal caregiving (Hoekzema et al., 2017; Hoekzema et al., 2020; Kim et al., 2010b; Laurent and Ablow, 2012; Laurent et al., 2011; Musser et al., 2012). However, pregnancy-related neuro-functional changes are not restricted to social stimuli. For example, Rutherford et al. demonstrated stronger EEG responses to non-social stimuli in 30 women pregnant with their first child compared to 33 multiparous pregnant women (Rutherford et al., 2019). Differences in electrophysiological responses have been observed in pregnant women when compared to non-pregnant women in a number of tasks (Fiterman and Raz, 2019; Luo et al., 2020), including a stop-signal task

in which pregnant women showed improved performance as well as altered amplitudes of P1, N2 and P3 during stop signals (Fiterman and Raz, 2019).

In the postpartum period, a handful of fMRI studies have examined mothers' responses to visual or auditory cues of their infants. Brain areas consistently activated in response to cues of own versus other infants as observed in systematic literature reviews or meta-analyses include the insula, orbitofrontal gyrus, inferior frontal gyrus, precentral gyrus, thalamus, amygdala and striatum (Bjertrup et al., 2019; Paul et al., 2019; Rocchetti et al., 2014). Several networks are strongly engaged in mothers in response to cues from their infants. These include the brain's reward system, which regulates reward processing and the hedonic value of stimuli and is also known to play a crucial role in maternal motivation in various other mammals (Brunton et al., 2008; Rincón-Cortés and Grace, 2020). In addition to core structures of the mesolimbic reward pathway, many other subcortical and cortical structures contribute to reward processing including the dorsal striatum, amygdala, hippocampus and various prefrontal areas (Berridge and Kringelbach, 2015; Haber and Knutson, 2010). Viewing or hearing their infants has been found to activate many reward-related brain regions in human mothers in fMRI studies (Bartels and Zeki, 2004; Lorberbaum et al., 2002; Noriuchi et al., 2008). Accordingly, human maternal bonding was found to relate to dopamine responses in the nucleus accumbens and pallidum, and was associated with the strength of intrinsic connectivity within the medial amygdala network (Atzil et al., 2017).

Functional MRI studies also strongly converge on recruitment of the brain's empathy and theory of mind networks in mothers exposed to cues from their infants (Gingnell et al., 2015; Leibenluft et al., 2004; Lenzi et al., 2009). The anterior insula and middle anterior cingulate cortex play crucial roles in empathy (Lamm et al., 2011), while the theory of mind network includes various midline areas such as the precuneus, posterior cingulate and medial frontal cortex, as well as the anterior temporal lobes, temporo-parietal junction, superior temporal sulcus and inferior frontal gyri (Schurz et al., 2014). A meta-analysis of fMRI studies in mothers using their own and unfamiliar infant cues indicated strong activations in the bilateral insula extending to the inferior frontal gyrus, basal ganglia and thalamus (Rocchetti et al., 2014).

Finally, converging evidence points to roles for the salience network and emotion regulation network in a mother's neural reactivity to her infant's cues (Seeley et al., 2007). The salience network, which is built around paralimbic structures such as the dorsal anterior cingulate and orbital fronto-insular cortices, is activated in response to highly salient and relevant stimuli resulting in a state of alertness. The emotion regulation network, which is a key system for regulating mothers' emotional responses to their infants, comprises prefrontal and cingulate control systems that modulate activity in emotion systems (Rutherford et al., 2015a; Rutherford et al., 2015b; Zaki and Ochsner, 2012). These networks are activated by one's own versus unfamiliar infant stimuli (Leibenluft et al., 2004), especially if the stimulus comprises a negative emotional cue signaling infant distress (Lorberbaum et al., 2002; Noriuchi et al., 2008; Swain, 2008).

Interestingly, studies have revealed links between a mother's neural response to her infant and aspects of her maternal caregiving. For example, associations have been

found between a mother's neural response to infant cries in frontal regions and a better quality of attachment (Laurent and Ablow, 2012), more sensitive behaviors to their infants (Musser et al., 2012), and between reduced activation in the anterior cingulate cortex and medial prefrontal cortex with greater cortisol reactivity to stress (Laurent et al., 2011). A connectome-based predictive modeling approach applied to fMRI data involving infant face and cry stimuli in 55 mothers showed that greater segregation between cerebellar and fronto-parietal networks and within the motor-sensory-auditory networks was associated with more maternal anxiety toward the infant, while changes in network connectivity were associated with changes in maternal anxiety toward bonding with her infant (Rutherford et al., 2020). Furthermore, several longitudinal fMRI studies have observed alterations in brain activity in key emotion processing regions such as the insula and amygdala across the postpartum period or associations with the duration of maternal experience (Gingnell et al., 2015; Parsons et al., 2017), possibly reflecting adaptations to the continuous development of the infant.

Resting state fMRI studies further support the implication of the neural networks identified in task-based fMRI and a link to maternal caregiving. For example, Dufford et al. revealed an association between postpartum months and resting state functional connectivity in regions involved in the salience network and the maternal motivation system in 47 primiparous women (Dufford et al., 2019), and functional connectivity between the left amygdala and left nucleus accumbens was positively correlated with maternal structuring during a mother –child interaction (Dufford et al., 2019). Postpartum women were also found to show differences from non-mothers in resting state activity, including reduced functional connectivity between the posterior cingulate cortex and left medial prefrontal cortex (Zheng et al., 2020) and in the amplitude of low-frequency fluctuations and regional homogeneity values in the posterior cingulate and prefrontal cortex (Zheng et al., 2018). A recent study investigating resting state fMRI data in 220 aged women indicated associations between the number of children parented and measures of functional connectivity—involving increased segregation between networks, decreased connectivity between hemispheres, and decreased connectivity between anterior and posterior regions—which were considered an indication of neuroprotective effects of parenthood (Orchard et al., 2020).

Taken together, a considerable amount of converging evidence points to the existence of a dynamic neural plasticity associated with motherhood in humans, which seems to serve an adaptive purpose for maternal caregiving and is evident throughout the lifespan.

3. Neuroplasticity accompanying motherhood in non-humans

Structural and functional changes in the maternal brain aren't unique to humans (Table 2). Over 40 years of research in animal models documents a wide range of differences between the maternal and non-maternal brain (Numan, 2020). Regarding neuroplasticity, recent research is showing that alterations in neurogenesis and neuron morphology occur with motherhood and may be important for maternal caregiving of offspring, as well as other aspects of motherhood such as stress regulation (Leuner et al., 2010; Leuner and Sabihi, 2016; Pawluski et al., 2016). The majority of this research on neuroplasticity in the maternal

brain has been carried out in rodent models but research in sheep, birds, and even recently in insects suggests conserved aspects of neuroplasticity in addition to species-specific brain modifications. The following sections summarize changes in neuroplasticity in specific brain regions during motherhood in non-human animals.

3.1 Structural brain changes in non-human mothers

Due to the ability to use more invasive neuroscience techniques, research in animal models has allowed for a greater understanding of the structural and functional changes in the maternal brain. When looking at whole brain changes it has been documented in rat mothers that there is a reduction of overall brain size in early postpartum females compared to cycling females (Hillerer et al., 2014b) similar to what was reported in human mothers mentioned above (Oatridge et al., 2002).

When looking at changes in grey matter volumes, similar to what is measures brain imaging studies in humans, a recent study in mice using MRI techniques documented the dynamic changes in the brain with motherhood (Barriere et al., 2021). Barrière et al. showed that, as in humans, there were significant changes in gray matter concentration in many brain areas of female mice with the transition to motherhood. What's interesting about this work is that there was an increase, and not a decrease, in grey matter concentration in mouse mothers compared to virgin female mice particularly in mPOA, BNST, amygdala, and hippocampus in the early postpartum period. Furthermore, they showed that the degree of maternal caregiving behaviors, either high or low amounts of pup-directed care, was further associated with these brain changes such that highly maternal female mice had greater hypertropohies in a number of brain regions compared to female mice that were less maternal (Barriere et al., 2021). These changes in grey matter concentration were reversible shortly after weaning. Thus, species specific changes in grey matter concentrations exist between humans and mice. This is likely due to differences in the hormonal milieu of the peripartum period (including a postpartum estrus in mice but not in humans) and different demands on the mother (singleton births in humans, multiple offspring in mice), to name a few. Regardless, it is clear that pregnancy and motherhood significantly impact grey matter concentrations in the maternal brain.

It should be mentioned that structural changes in the brain with female reproduction are not unique to mammals as there have been reports of changes in brain size in advance of the breeding seasons in songbirds and other vertebrates (usually males) (Tramontin and Brenowitz, 2000). Recent research also shows that gamergates, reproductively totipotent worker ants (*Harpegnathos saltator),* exhibit a decrease in brain size (i.e., 24% decrease in optic lobes size) compared to non-reproductive workers (Penick et al., 2021). This decrease in brain size in ants prior to reproduction is thought to divert additional metabolic resources to egg production and not the metabolically expensive brain tissue and is associated with changes in reproductive hormone levels (Niven and Laughlin, 2008). Interestingly, once gamergate ants no longer have reproductive status their brain re-expands to match the brain size of non-gamergates, or in this case, foragers (Penick et al., 2021).

Given the widespread effect of reproduction on the female brain, understanding the molecular, cellular, and behavioral implications of these findings is important to further

delineate the impact of reproduction. The sections below will highlight what we know about neuroplasticity in specific brain areas studied in non-human mammals.

3.2 The Hippocampus

The hippocampus has not traditionally been documented as an area critically important for maternal offspring-directed behaviors (Lonstein et al., 2014), although some of the first studies on the hippocampus and motherhood revealed the important role that it plays. In 1967, Kimble et al. showed that bilateral dorsal hippocampal lesions in laboratory rats result in marked alterations in maternal caregiving behaviors, particularly less time spent nursing, poorer nest building, poorer retrieval of pups, and increased maternal cannibalism (Kimble et al., 1967). Severing the main fiber tract projecting to the CA1 and CA3 regions of the hippocampus (i.e., the fimbria), results in abnormal nest building and pup retrieval in rat mothers (Terlecki and Sainsbury, 1978). These mothers built multiple nest sites and retrieved pups to more than one location (Terlecki and Sainsbury, 1978). While this early work pointed to a role for the hippocampus in aspects of maternal caregiving behavior, it was not until the late 1990s that the possible relationship between the hippocampus and motherhood was revisited. More recent research on the hippocampus and motherhood has often focused on this brain area because of its importance in memory, stress regulation and mental health (Dickens and Pawluski, 2018; Leuner and Gould, 2010; Lucassen et al., 2010; Pawluski et al., 2016).

During each phase of female reproduction (i.e., pregnancy, parturition, postpartum, and post-lactation) there is a significant effect of motherhood on plasticity in the hippocampus that likely plays a role in cognitive flexibility, stress regulation, and affective behaviors in the mother. Below is a summary of recent work on hippocampal plasticity during pregnancy (3.2.1) and the postpartum period (3.2.2) with a focus on rodent models.

3.2.1 Pregnancy—In a study showing that late pregnant female rats (day 21) have poorer working memory compared to their non-pregnant counterparts, Galea et al. reported a strong trend toward reduced hippocampal volume in late-pregnant rats (Galea et al., 2000). This work predated the research in women showing that hippocampal volume is reduced across pregnancy (Hoekzema et al., 2017) and points to an effect of pregnancy on the hippocampus that is conserved across mammals.

The hippocampus is often associated with adult neurogenesis as it is one of two areas in the adult brain (the other being the subventricular zone of the lateral ventricles; SVZ) where there is a high degree of neuron birth, although a number of other brain areas show neurogenesis as well (Jurkowski et al., 2020). Neurogenesis in the hippocampus occurs in the dentate gyrus where the primary neuron type is the granule neuron and these new neurons play a role in cognition, stress regulation and emotional regulation (Snyder and Drew, 2020). Often research on neurogenesis examines aspects of neuron birth including rates of cell proliferation, analysis of immature neurons, and implications of new neuron survival. Each stage of neurogenesis is of interest in understanding how motherhood may affect the hippocampus and its functions (Levy et al., 2011; Pawluski et al., 2009a).

Cell proliferation in the dentate gyrus was first shown to be affected by pregnancy in wild meadow voles. Galea and McEwen (1999) reported that wild pregnant meadow voles captured during the breeding season had decreased levels of hippocampal cell proliferation compared to non-pregnant female meadow voles captured during the non-breeding season (Galea and McEwen, 1999). In addition, late pregnancy in the rat (day 21) and mouse (day16.5) also decreased cell proliferation when measured using an endogenous marker, Ki67, compared to non-pregnant females (Kim et al., 2010c; Pawluski et al., 2015; Pawluski et al., 2020). However, early pregnancy (day 1 or 7) in the rat has not been associated with any changes in cell proliferation in the hippocampus (Pawluski et al., 2010; Pawluski et al., 2011; Shingo et al., 2003) suggesting an effect of pregnancy on hippocampal plasticity. When looking at the production of immature neurons in the dentate gyrus during pregnancy in rats, recent research shows that during late pregnancy (day 20) there is a significant decrease in the number of new neurons, as measured by the endogenous marker, doublecortin (DCX), as compared to non-pregnant females (Pawluski et al., 2020). Interestingly, survival of new neurons across pregnancy in the rat does not differ from that seen in non-pregnant females (Furuta and Bridges, 2005; Pawluski et al., 2010; Pawluski et al., 2015; Pawluski et al., 2011; Shingo et al., 2003), although it may differ at other periods of reproduction. In contrast, a reduction in new cell survival has been reported during the second week of pregnancy in mice, with a return to pre-pregnancy levels during the postpartum period (Rolls et al., 2008) while recent research in guinea pigs found increased neurogenesis in the dentate gyrus of the dorsal hippocampus from early pregnancy to the postpartum period (Wan et al., 2019). Taken together, the available evidence suggests a species-specific effect of reproduction on cell birth within the dentate gyrus (Wan et al., 2019).

In addition to neurogenesis, other work has examined hippocampal dendritic and synaptic remodeling during pregnancy. Looking at dendritic remodeling of pyramidal neurons in the dorsal hippocampus during late pregnancy in the rat (day 21), Pawluski et al. (2012) reported that in the CA3, but not CA1, pyramidal cells have significantly decreased dendritic complexity, as measured by Sholl analysis, compared to non-pregnant females (Pawluski et al., 2012). Late pregnancy (day 21) was also accompanied by increased spine density in the apical CA1 region of the hippocampus as compared to virgin females. Similarly, recent work has shown that late pregnancy in rats increases synaptophysin density in both the dorsal CA3 and the dentate gyrus compared to non-pregnant females (Pawluski et al., 2020). Along with structural plasticity, others have shown that epileptiform network excitability in the CA1 region of the hippocampus is decreased in pregnant mice (day 18) and this decrease is associated with changes in expression of the delta subunit of the GABA(A)R (Maguire et al., 2009).

Several studies have attempted to link pregnancy-related hippocampal changes to hormones. The initial work investigating hippocampal cell proliferation during pregnancy in wild-caught meadow voles showed that the reductions in hippocampal cell proliferation was associated with increased circulating levels of estradiol and corticosterone, suggesting that the hormonal changes of pregnancy may be responsible for changes in hippocampal cell proliferation (Galea and McEwen, 1999). However, subsequent work in rats has not found an association between hippocampal cell proliferation or neurogenesis and circulating levels

of either estradiol or corticosterone (Banasr et al., 2001; Pawluski et al., 2010; Pawluski et al., 2011). It is perhaps surprising that the hormones of pregnancy have no association with hippocampal neurogenesis in the female rat given the significant effects of estradiol on other aspects of plasticity in the female hippocampus (Galea et al., 2013; McEwen, 2002; Pawluski et al., 2009a). For example, steroid hormones influence dendritic spine density in the maternal hippocampus, particularly in the CA1 region. Indeed, Kinsley et al. showed that the increase in hippocampal CA1 spine density during late pregnancy was due to increased estradiol and progesterone levels at this time (Kinsley et al., 2006). Taken together, this work in laboratory rodents shows that there is decreased production of new neurons and reduced neuron complexity, but an increase in synaptic plasticity, in the hippocampus during late pregnancy. This may point to the brain preparing for the complex learning involved in offspring-directed care that mothers display postpartum (Feldman, 2015; Lomanowska et al., 2015). Further work is needed to determine why these changes in the hippocampus occur during pregnancy and how they are related to maternal pup-directed care, affective behaviors and changing physiology.

3.2.2. Postpartum—Compared to pregnancy, a greater number of studies in laboratory rodents have investigated how plasticity in the hippocampus is altered in the postpartum period. Tomizawa et al. were the first to show that electrophysiological responses of the hippocampus are altered with motherhood. Specifically, they found that multiparous mice exhibit increased long-lasting long-term potentiation (LTP) along the Schaffer collaterals during the early-postpartum period (day 3) compared to nulliparous mice (Tomizawa et al., 2003). It has also been consistently demonstrated in maternal rats and sheep that cell proliferation in the hippocampus during the early postpartum period is lower than in age-matched virgin females (Brus et al., 2010b; Darnaudery et al., 2007; Hillerer et al., 2014b; Leuner et al., 2007; Pawluski and Galea, 2007). There are also fewer immature neurons at weaning in the dorsal and ventral hippocampus of rat dams compared to virgin females (Workman et al., 2016) and fewer new neurons in the entire hippocampus at weaning in first, but not second-time rat dams suggesting an influence of reproductive experience (Pawluski and Galea, 2007).

Decreased hippocampal cell proliferation during the postpartum period appears to be related, in part, to increased levels of adrenal steroids, as removal of the adrenal glands prevents the postpartum reduction in cell proliferation in rats (Leuner et al., 2007). Moreover, postpartum neurogenesis is associated with improved learning and memory in the mother (Darnaudery et al., 2007; Hillerer et al., 2014b; Leuner et al., 2007; Pawluski and Galea, 2007). For example, at the time of weaning when hippocampal neurogenesis is suppressed in rat dams (Pawluski and Galea, 2007), there is an improvement in spatial learning and memory (Pawluski et al., 2006a; Pawluski et al., 2005). This may seem counterintuitive, but in the adult virgin female rat there are reports of increased glucocorticoids and decreased hippocampal plasticity being associated with improved memory performance (Pawluski and Galea, 2008).

Reproductive experience also influences new neuron survival in the postpartum hippocampus (Pawluski and Galea, 2007). Pawluski and Galea (2007) showed that primiparous rats (birthed and mothered once) had significantly fewer new surviving cells

during the late postpartum period (day 21) than either nulliparous or multiparous rats (birthed and mothered twice). Interestingly, they found that age-matched multiparous females had a greater number of surviving new neurons compared to nulliparous and primiparous females across the postpartum period. These changes in hippocampal neurogenesis accompanying motherhood are thought to be related to changes in hippocampal-dependent memory performance at the time of weaning, with primiparous females showing the best memory performance compared to nulliparous females (Pawluski et al., 2006a; Pawluski et al., 2006b).

A growing body of research is beginning to reveal that lactation may be driving the effects on hippocampus neurogenesis given that the effects of pregnancy and birth on hippocampal neurogenesis do not persist in the weeks after weaning (Leuner et al., 2007; Medina and Workman, 2018; Rolls et al., 2008). De Guzman et al. recently showed that increasing nursing demand in rats by providing food deprived litters to the dam every 12 hours decreased hippocampal neurogenesis, as indicated fewer immature neurons and less cell proliferation at the time of weaning. The reduction in neurogenesis with increased nursing demand was associated with higher circulating corticosterone levels and more active coping as indicated by lower immobility in the forced swim test (De Guzman et al., 2018). Notably, dams in this study exposed to pups but unable to nurse due to removal of the nipples (i.e., thelectomy) did not show the same reductions in hippocampal neurogenesis and associated increase in corticosterone and decrease in immobility in the forced swim test. This suggests that lactation itself modulates aspects of hippocampal neurogenesis and the HPA axis in rat dams. This is perhaps not a surprise as lactation's influence on the maternal HPA axis is well known (Almanza-Sepulveda et al., 2020; Hillerer et al., 2014b; Pawluski et al., 2008; Walker et al., 2004). However, it is important to note that in biparental California mice, both mothers and fathers have decreased survival of new hippocampal neurons during the mother's postpartum period (Glasper et al., 2011). Thus, lactation's impact on hippocampal neurogenesis may be species-specific and other factors, such as interaction with the offspring are also important.

In the De Guzman et al. study, the non-lactating thelectomized rat dams allowed to interact to pups had more immature hippocampal neurons, fewer proliferative and intermediate immature neurons, and more postmitotic immature neurons compared to lactating rat dams which points to a role for pup interactions in influencing neurogenic processes. Consistent with this, an increase in hippocampal neurogenesis after pup exposure in virgin rodents has been reported. Nulliparous female rats exposed to pups in order to induce maternal caregiving toward them (a process termed *sensitization*; (Rosenblatt, 1969)) have more neurogenesis in the hippocampus, via both cell proliferation and new cell survival, compared to either lactating rats (primiparous and multiparous) or nulliparous female rats not exposed to pups (Pawluski and Galea, 2007). In virgin prairie voles, both males and females that were exposed to pups, regardless of whether or not they acted parentally towards them, had more hippocampal cell proliferation compared to unexposed controls (Ruscio et al., 2008). The virgin prairie voles that did not act parentally towards the pups had greater cell proliferation compared to virgin prairie voles that were parental (Ruscio et al., 2008) suggesting an impact of degree of care-giving on hippocampal neurogenesis. These findings

indicate that exposure to pups and parenting alone may be an additional modulator of hippocampal neurogenesis postpartum, particularly in some species.

Although the evidence above suggests that interactions with pups can influence neurogenesis, the impact of offspring removal on hippocampal neurogenesis in the rat dam has received little attention. One study showed that removing the pups 24 h after birth did not impact new neuron survival 3 weeks later (Pawluski and Galea, 2007). However, dams that had offspring removed within a day of giving birth have increased depressive-like behavior and impaired memory weeks later (Pawluski et al., 2009b; Pawluski et al., 2006a), suggesting a disconnect between postpartum cell survival and maternal affective behaviors. Dams with complete pup removal also show alterations in the HPA axis (Demarchi et al., 2021). Understanding the link between hippocampal neurogenesis, glucocorticoid levels, maternal behavior and affective state is important to determine how these new neurons act to facilitate normative mothering.

Dendrite spine remodeling is also evident in the maternal hippocampus during lactation. Kinsley et al. (2006) reported that rat dams (day 5-6) have increased spine density in the CA1 apical region of the hippocampus during early lactation (Kinsley et al., 2006) and others have shown that this effect persists into the late-postpartum period (Leuner and Gould, 2010) but not after weaning (Pawluski and Galea, 2006). Primiparous rats, at weaning, exhibit decreased dendritic complexity in both the CA1 and CA3 pyramidal neurons compared to nulliparous as well as multiparous rats (Pawluski and Galea, 2006). In this same study, multiparous rats had enhanced spine density in the CA1 region of the hippocampus, which correlated with number of male pups in a litter (Pawluski and Galea, 2006) suggesting a role of experience on spine plasticity at weaning.

With aging changes in the morphology of CA1 pyramidal neurons with parity are not evident in rats (at two years of age), showing that some changes with motherhood can be reversible (Love et al., 2005). Other work indicates that some functional consequences of motherhood on the hippocampus persist. For example, Lemaire et al. showed that there is increased hippocampal LTP in mother rats two weeks after weaning and well into aging at 22 months old (Lemaire et al., 2006). Furthermore, Gatewood et al (2005) showed that aged (24 months old) reproductively experienced females have lower levels of amyloid precursor protein (APP), a marker of neurodegeneration in the hippocampus along with attenuated memory decline (Gatewood et al., 2005). Eid et al. have also shown that during middle age (10 months old) there is an increase in hippocampal neurogenesis in primiparous rats but a continued decrease in neurogenesis in nulliparous female rats (Eid et al., 2019) further pointing to an enduring effect of motherhood on the hippocampus. Motherhood also has lasting effects on the response of hippocampal progenitor cells to estrogens, with different estrogens significantly upregulating cell proliferation in the hippocampus in middle-aged multiparous female rats but not of middle-aged virgin rats (Barha and Galea, 2011).

In summary, these studies demonstrate numerous types of plastic changes in the hippocampus accompanying motherhood that often endure in the mother’s brain. The exact role of these changes in neuroplasticity on cognition, stress regulation, or affective behaviors remain to be determined but future work using methods that inhibit hippocampal plasticity,

as seen in some studies investigating other brain sites and described below, would be valuable (Medina and Workman, 2018; Pawluski et al., 2016; Slattery and Hillerer, 2016).

3.3 SVZ and Olfactory Bulb

While the hippocampus has been the major focus for studying motherhood-induced neuroplasticity, newborn cells also exist in the adult SVZ and the number of new cells is affected by motherhood. In the first study of its kind, Shingo et al. (2003) found that the number of proliferating cells in the female mouse SVZ was briefly elevated at early pregnancy (day 7), and again at day 7 postpartum, with a return to low pre-mating levels within a week in both cases (Shingo et al., 2003). This effect could not be reproduced with exogenous estradiol with or without progesterone, suggesting that other aspects of reproduction and later caregiving experience are required. A pregnancy-associated increase in proliferating cells has also been found in the SVZ of laboratory rats, but at the end of pregnancy rather than in early pregnancy (Furuta and Bridges, 2005). This increase in newborn cells in the SVZ of rats does not require that females reproduce, however, because nulliparous female rats repeatedly exposed to pups until the point of displaying maternal care show more proliferating cells compared to nulliparous rats that were never exposed to pups or nulliparous rats that were exposed to pups but never showed maternal caregiving behaviors (Furuta and Bridges, 2009).

Many newborn cells in the adult SVZ are known to migrate to the olfactory bulbs (Brann and Firestein, 2014) and this appears to also be true in mothers. Shingo et al. (2003) reported that early and late in the postpartum period mouse dams have more new interneurons in the granule and periglomerular layers of their olfactory bulbs. A more recent study found only a small, non-significant rise in the number of newborn neurons in the female mouse olfactory bulb postpartum (Belnoue et al., 2016), but differences between that studies in the mouse strain (CD1 vs. C57BL/6J), stage of neurogenesis investigated, and cell genesis marker used (CldU vs. BrdU) may be partly responsible. Belnoue et al. (2016) did find, though, that new neurons two weeks postpartum had longer apical (but not basal) dendrites in the granular cell layer of the SVZ when compared to virgins. Adult-born cells in the granule layer of early postpartum mother mice also show more stable dendritic spines consistent with greater maturity and, although they have lower spine density, are better integrated into the bulbar network when compared to the newborn cells in the olfactory of nulliparous females (Kopel et al., 2012).

The pituitary peptide, prolactin, is an important regulator of neurogenesis in the maternal olfactory bulbs. Exogenous prolactin can increase the number of proliferating cells in the female mouse (Shingo et al., 2003), which is somewhat surprising given that estradiol is a strong stimulator of pituitary prolactin release (Chen and Meites, 1970) but is unable to stimulate neurogenesis in the SVZ (Shingo et al., 2003). Yet others have found that exogenous estradiol instead decreases newborn cells in the female mouse olfactory bulb (Veyrac et al., 2011). In any case, further support for a prolactin-mediated process is that mutation of the prolactin receptor gene prevents the effects of reproduction to increase SVZ neurogenesis (Shingo et al., 2003). In addition, other methods that increase circulating prolactin can also stimulate neurogenesis in the female mouse SVZ and olfactory

bulb. Nulliparous mice exposed to the pheromones of conspecific males have chronically high circulating prolactin, along with more newborn cells in their SVZ and olfactory bulbs (Larsen and Grattan, 2010). These effects of male pheromones were prevented by ovariectomizing females or pharmacologically inhibiting their pituitary prolactin release, and conversely, mimicked in pheromone-unexposed females by injecting exogenous prolactin (Larsen and Grattan, 2010; Larsen et al., 2008).

The functional significance of greater numbers of newborn cells in the maternal SVZ or olfactory bulb has been demonstrated either directly or indirectly. In transgenic mice that allow experimenters to temporally destroy newborn cells in the SVZ and elsewhere in the brain when they begin differentiating into neurons, parturient females show a severe impairment in pup caregiving (Sakamoto et al., 2011). Pregnancy stress, which often but not always impairs postpartum maternal caregiving, also reduces newborn neurons and their dendrite length in the maternal olfactory bulb (Belnoue et al., 2016). Prolactin manipulations that alter neurogenesis in mice also hasten or impair maternal responsiveness (Larsen and Grattan, 2010; Larsen et al., 2008), as does early-pregnancy injections of a mitotic inhibitor (Larsen and Grattan, 2010). On the other hand, focal irradiation of the SVZ that lead to a large reduction in newborn cells in the olfactory bulb did not impair mothering in parturient mice, but instead increased the time that dams spent in the nest with pups (Feierstein et al., 2010).

The studies above in laboratory rodents can be contrasted to those involving maternal sheep. Adult female sheep also have many proliferating cells in their SVZ and olfactory bulbs, but the numbers of these cells are reduced in parturient females that interact with their lambs compared to estrus ewes housed with a ram or anestrous ewes housed alone (Brus et al., 2010a; Brus et al., 2014). Despite having fewer newborn olfactory cells, neuroblast dendrite length is longer in parturient ewes compared to virgin ewes, but not if the lamb is removed immediately after birth (Brus et al., 2010a). Because nulliparous ewes primed with progesterone and estradiol before given acute ICV oxytocin infusions show reduced cell survival in the olfactory bulb compared to CSF-infused control ewes (Levy et al., 2019), the tremendous release of oxytocin that occurs at the birth of the lamb and necessary for the onset of maternal behavior (Levy et al., 1992) is likely responsible for the downregulation of newborn cells seen in naturally parturient ewes. Despite mothers having fewer newborn cells in the olfactory bulb, the cells that do remain are critical for normal motherhood. Chronic ICV infusion of an anti-mitotic drug (Ara-C) for one month during early pregnancy reduces ewes' maternal vocalizations at and soon after parturition, as well as led the ewes unable to discriminate between their own lamb and an unfamiliar lamb (Corona et al., 2018). Thus, whether new mothers have more (mice, rats) or fewer (sheep) newborn cells in their SVZ and olfactory bulb, these cells can be critical for the olfactory regulation of maternal caregiving.

3.4 Medial Preoptic Area

The medial preoptic area (mPOA) anterior to the hypothalamus is the most-studied brain site for the hormonal initiation and later pup-induced maintenance of maternal caregiving in numerous species (Lonstein et al., 2014). It undergoes significant neuroplasticity in

mothers, involving a host of plasticity-related genes (Udvari et al., 2019). Neurogenesis is known to exist in the adult rodent mPOA (e.g., (Huang and Bittman, 2002; Kostin et al., 2021), but only one study has examined this in maternal females. Akbari and Fleming (2007) found that female rats permitted to interact with pups on the day after parturition had non-significantly fewer new surviving cells in the mPOA compared to dams that never interacted with pups after giving birth (Akbari et al., 2007).

Other types of plasticity have been shown to occur in the maternal mPOA. Late-pregnant rats have larger mPOA somata and more basal dendritic branches compared to virgins and these measures shrink back to premating levels by the end of the first week postpartum (Keyser-Marcus et al., 2001). Dendrite length was longer in both late-pregnancy and postpartum (Keyser-Marcus et al., 2001). These effects could be induced by treating ovariectomized virgins with exogenous estradiol plus progesterone, suggesting that the steroid hormone milieu of pregnancy is a driving factor (Keyser-Marcus et al., 2001). Similar studies also found evidence of greater mPOA cells primary dendrite branching in female rats one day or one week after parturition (Frankfurt et al., 2011; Shams et al., 2012), but fewer dendritic branches further away from the soma and no differences between mothers and virgins in total dendrite length (Shams et al., 2012).

Of the structural factors regulating neuroplasticity across the brain, perineuronal nets (PNNs) have become of great interest. PNNs are part of the extra-cellular matrix and surround neural somata and proximal dendrites (Sorg et al., 2016). PNNs are thought to act as physical and chemical barriers to neuroplasticity, and thus high numbers of PNNs are associated with relatively consolidated or fixed neuronal function (Sorg et al., 2016). Uriarte et al. (2020) recently found that while no PNNs were found in the mPOA of cycling female rats (or males), they appeared by mid-pregnancy, reached high levels in late pregnancy and the end of the first week postpartum, then declined but not completely disappeared by the end of lactation (Uriarte et al., 2020). Treating ovariectomized virgin females with estradiol plus progesterone (but not estradiol alone) also increased PNNs in the mPOA, but this was mostly prevented if pituitary prolactin release was pharmacologically inhibited (Uriarte et al., 2020). These data indicate that PNNs may be involved in hormone-induced plasticity in the mPOA necessary to establish maternal caregiving and consolidate the experience, and then regulate changes in maternal care as the pups grow and develop over lactation.

3.5 Cerebral Cortex

The primary somatosensory cortex (S1) is essential for processing incoming tactile information from the surface of the body and integrating that information with motoric activity necessary for behavior. It contains a mostly topographic map of the skin and is one of the most use-dependent neuroplastic regions of the brain during early development and in adulthood (Harding-Forrester and Feldman, 2018). One would expect that motherhood, which involves novel use of the ventral and perioral skin to most sensitively detect and respond to pup cues (Stern, 1996), would involve neuroplasticity in S1. Indeed, during the first days postpartum there is an increase in cortical depth in rat dams (Hamilton et al., 1977) and the S1 of lactating rats (but not parturient rats whose pups were removed at parturition)

exhibits >50% greater representation of the ventral skin, along with a tremendous reduction in receptive field size compared to nulliparae (Rosselet et al., 2006; Xerri et al., 1994).

Another change in S1 during the expression of caregiving also involves PNNs. Virgin female mice that were cohoused with late-pregnant females and then given 5 days of alloparental experience with pups had more PNNs in the barrel field (S1 representation of whiskers on the mystacial pad) than inexperienced virgins (Lau et al., 2020). This could be related to the central oxytocin released when even virgins interact with pups (Okabe et al., 2017), as oxytocin receptor activity in the midbrain dorsal raphe (DR) - which contains the most forebrain-projecting serotonin neurons – regulates PNN expression in the barrel field of parturient rats and disrupting oxytocin signaling in the DR derails almost all postpartum behaviors (Grieb et al., 2021).

Auditory perception is less consequential for maternal caregiving compared to somatosensation in mice and rats (D'Amato and Populin, 1987; Herrenkohl and Rosenberg, 1972; Kolunie et al., 1994), but motherhood-induced plasticity still occurs in the primary auditory cortex and facilitates dams' responsiveness to pups' vocal cues. When female mice become mothers, the number of A1 cells selectively responding to pup ultrasonic vocalizations increases, followed by a decrease after weaning the litter (Tasaka et al., 2020). This functional plasticity is not accompanied by morphological plasticity such expansion of the A1 *in toto* (Shepard et al., 2015), or altered dendritic spine density or size (Tasaka et al., 2020). The A1 of virgin mice induced to become maternal via co-housing with a dam and pups also show increased "tuning" to pup vocalizations (Liu et al., 2006; Liu and Schreiner, 2007; Schiavo et al., 2020), but this increased proficiency does not last as long after removal of the pups as it does in mothers, suggesting that not just maternal experience but the physiology of reproduction contributes to sustained auditory plasticity (Lin et al., 2013). This plasticity in virgins (and presumably parturient mothers) relies on oxytocin release from the paraventricular nucleus of the hypothalamus (Marlin et al., 2015; Schiavo et al., 2020) and involves changes in excitatory and inhibitory balance that alters A1 response to sound pitch and rate (Cohen and Mizrahi, 2015).

Mothers also show plasticity in non-sensory region of the cortex. This includes increased dendritic spine number and density in the anterior cingulate and infralimbic regions of the mPFC, which in the latter declines considerably within 2-3 weeks after weaning the litter (Leuner et al., 2010; Opala et al., 2019). Increased spine density in the mPFC has been associated with improved attention and cognitive flexibility, functions which rely on this region of the cortex (Leuner et al., 2010).

3.6 Dorsal Raphe Nucleus

As clearly seen from the discussion above, motherhood-related plasticity extends throughout the forebrain. The midbrain, hindbrain, spinal cord, and periphery have been mostly neglected but may be the next "frontier" for studying where female reproduction and infant caregiving sculpt the nervous system. A recent venture outside mothers' forebrain by the Lonstein lab hypothesized that differences in cell birth or survival could be expected to exist in the maternal midbrain, given that the lining of the midbrain cerebral aqueduct is a proliferative niche from early development through adulthood (Zhao and Janson Lang,

2009). Lonstein and Holschbach (2017) found that the lining of the adult female rat aqueduct has a high degree of cell proliferation (Holschbach and Lonstein, 2017) and that newborn cells exist in the dorsal raphe nucleus (DR) lying just below the aqueduct. Cells of the DR are the source of most forebrain serotonin (Lowry et al., 2008) and maternal care is disrupted by selectively lesioning DR serotonin neurons (Holschbach et al., 2018). While they found that there were no effects of pregnancy and postpartum state on DR cell proliferation, cells that were born during the postpartum period were less likely to survive (12days later) than cells born during pregnancy and surviving into the early postpartum period (12 days later) (Holschbach and Lonstein, 2017). The nearby median raphe also contained newborn cells, but there were few and the number was unaffected by female reproductive state. The early-postpartum rate of new cell survival in the DR was concomitant with higher DR levels of serotonin's precursor, 5-HTP, and its metabolite, 5-HIAA. Many of the newborn cells had a neuronal phenotype. Less cell death was also found during the early postpartum period compared to late postpartum (Holschbach and Lonstein, 2017). The effects of motherhood on these temporal changes in DR new cell survival and cell death were prevented by removing the pups at parturition, indicating that simply giving birth was not alone responsible. The inability of maternal adrenalectomy to influence cell survival indicated that circulating corticosterone was not also not singularly responsible. Whether some the newborn cells eventually become serotonergic neurons, and what role any of them play in DR- and serotonin-dependent postpartum behavior and physiology, remains to be discovered.

4. Glial cell plasticity in the maternal brain

Glia are abundant in the vertebrate brain (Herculano-Houzel, 2014) and provide an ample, additional substrate for how motherhood influences central nervous system structure and function. This is evident in the mPOA, where along with neuronal changes described above, there is an increase in the number of cells containing the glia-activating factor basic fibroblast growth factor (bFGF) in postpartum lactating rats (day 16) compared to cycling or hormone-treated virgins (Salmaso et al., 2005; Salmaso and Woodside, 2006). More cells containing the astrocyte cytoskeleton protein, glial fibrillary acidic protein (GFAP) have also been reported in the mPOA of multiparous, postpartum (day 5) rats (Featherstone et al., 2000). These findings are consistent with a very recent study using MRI in mice to reveal an enlargement of the mPOA from late pregnancy through late lactation (Barriere et al., 2021).

Significantly more glial cells, as indicated by bFGF and GFAP expression, specifically in area 2 of the cingulate cortex are also found in mothers compared to cycling virgins, with cells containing these proteins beginning to appearing in late pregnancy, increase within hours after parturition, and remain at high numbers throughout lactation (Salmaso et al., 2005; Salmaso and Woodside, 2006). This particular region of the rodent anterior cingulate is thought to best correspond to the human anterior cingulate cortex (ACC) (van Heukelum et al., 2020), and as such is involved in numerous functions including higher-order reward-based decision making and affective control (Holroyd and Verguts, 2021; Hunt, 2021). Maternal upregulation of bFGF and GFAP is accompanied by greater number of apical dendritic spines very early postpartum and greater basilar dendritic complexity late postpartum, suggesting increased network integration (Salmaso et al., 2011). Unlike most

neuroplasticity in the maternal brain, this increase in glial cell markers does not require that dams interact with pups or lactate, as removing the litter at parturition has little effect on GFAP expression, and it takes 5-6 weeks after a normal period of lactation for levels to return to those found before mating (Salmaso and Woodside, 2006, 2008). Interestingly, there is no increase in either protein in rats that are remated and allowed to care for pups again, suggesting that remodeling of the Cg2 could be involved in maternal "learning" effects in inexperienced females that are unnecessary in experienced caregivers (Salmaso and Woodside, 2008).

Of the glial changes that occur with female reproduction and motherhood, much recent work has focused on microglia. Microglia, comprising approximately 8–12% of total brain cells, are the resident macrophages of the of the CNS (Kettenmann et al., 2011). Microglia provide immune surveillance, clear debris to maintain homeostasis, and engage in inflammatory signaling in response to pathogens, injuries or other perturbations (Kettenmann et al., 2011). In addition, through phagocytic activity and inflammatory signaling, microglia mediate normal changes in neuronal structure, function, and resulting behavioral output during other periods of dramatic plasticity in the brain such as development (Lenz and Nelson, 2018) and aging (Hong et al., 2016). Whether microglia are involved in the dynamic remodeling of the maternal brain has yet to be determined but recent data have shown that microglia are modified across the peripartum period. Specifically, studies in laboratory rats show that the numbers of microglia are reduced in the days prior to parturition and remain reduced until approximately one week postpartum in numerous brain regions, including the medial prefrontal cortex, nucleus accumbens, amygdala, and hippocampus (Haim et al., 2017; Posillico and Schwarz, 2016). 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 (Eid et al., 2019; Haim et al., 2017).

In addition to the microglial alterations, inflammatory signaling is also modified in the maternal brain with postpartum increases seen in the anti-inflammatory cytokine, interleukin (IL)-10 and the pleiotropic cytokine, IL-6 (Haim et al., 2017). Similarly, IL-4 and brain derived neurotrophic factor (BDNF) are elevated in the brains of maternal rats (Posillico and Schwarz, 2016; Sherer et al., 2017). Other work has examined the neuroimmune response of the maternal brain to immune/inflammatory challenge and found it to be suppressed such that up-regulation in gene expression for the cytokines, IL-1β and IL-6, in response to bacterial endotoxin LPS administration was markedly attenuated in the PFC, mPOA, hypothalamus and hippocampus of late-pregnant rats, compared with non-pregnant females (Sherer et al., 2017). When taken together with the peripartum decrease in microglia levels, these data suggest that the maternal brain may be assuming a protective, inflammatory resistant state. Although there are some differences in time course, these central immune changes mirror immune changes in the periphery that are necessary for sustaining a pregnancy and fetal development (Sherer et al., 2017).

Because changes in central immune function across motherhood is a new area of investigation, there are a number of open questions that require further study. For example,

the mechanisms underlying peripartum neuroimmune changes has yet to determined. Given that some of the changes are evident during late pregnancy, it is likely that they are not primarily driven by parturition or maternal experience but rather some physiological change of pregnancy. Hormones are the most likely candidates, as microglia express receptors for many hormones that are altered across the peripartum period and which exert effects on neuroinflammatory signaling, including glucocorticoids, estrogens, progestins and oxytocin (Bruce-Keller et al., 2000; Dimayuga et al., 2005; Lei et al., 2014; Sierra et al., 2008; Vegeto et al., 2001). Another possibility is that non-hormonal chemical signals that are dynamic during the peripartum period may be responsible for the microglial changes observed. For example, microglia express receptors for GABA, serotonin and dopamine and fluctuations of these neurotransmitters have been shown to influence microglia (Lee, 2013; Pocock and Kettenmann, 2007). In addition to mechanism, the functional significance of peripartum immune changes is an open question. Given their timing, it is possible that peripartum central immune changes may play a role in the motivational, cognitive and mood-related changes found in new mothers. It is also important to consider that the postpartum period is a time of heightened vulnerability for the development of mood disorders. A number of studies have implicated peripheral immune dysregulation in human anxiety and depression (Hodes et al., 2015; Wohleb, 2016), including postpartum depression, although these have yielded mixed results (Boufidou et al., 2009; Corwin et al., 2015; Maes et al., 2000; Osborne and Monk, 2013; Segman et al., 2010). More work in humans and rodent models are needed to further explore the role of central neuroinflammation as a mechanistic pathway that contributes to peripartum depression. For now, however, the available data are largely consistent with the theme of ‘less is more’ and suggest that less inflammation is likely better for maternal affective state and possibly other outcomes.

5. Conclusions and future directions

The female brain goes through many developmental shifts across the lifespan, with the transition to motherhood (i.e., matrescence) being one of the most significant. In this review we summarize many levels of ‘fine-tuning’ of the maternal brain, in both structure and function across this developmental phase, that are important for maternal care-giving behaviors and maternal mental health. This ‘fine-tuning’ of the brain to presumably optimize brain function occurs in a number of species studied to date. Although these brain changes are not always similar between species there is clear evidence that significant modifications occur in the female brain during the transition to motherhood. It is important to point out that it is not necessarily the ‘amount’ of brain plasticity accompanying motherhood that is key but likely the function and connectivity between cells (both neuron and glial) within and among brain areas that need to be investigated in order to fully determine how these changes in ‘amount’ correspond to changes in function within the maternal brain.

Some of these brain modifications with motherhood are reversible, such as the rate of hippocampal neurogenesis, but other modifications, or even new modifications, resulting from pregnancy and motherhood likely exist throughout the maternal brain later in life (de Lange et al., 2020a; Lambert et al., 2019). Knowing this, future research in many realms needs to move beyond the study of sex differences (often comparing nulliparous females with sexually inexperienced males) to more broadly address how reproductive experience

and parenting specifically impact brain health throughout the lifespan. Thus, it is anticipated that future research investigating intricate functional aspects of brain plasticity during pregnancy and the postpartum period will increase our understanding of how reproductively-related modifications in the female brain optimize complex behavioral outcomes with the transition to motherhood. In addition, as mentioned, understanding the impact of pregnancy and parenting on the female brain is of vital importance to the future of neuroscience research, particularly as the majority of females are parturient in many species. One thing that is certain is that matrescence has a significant impact on the adult female brain.

Acknowledgements

JLP was supported by the INCR (Institut des Neurosciences Cliniques de Rennes) and BAA (Bretagne Atlantique Ambition); EH is supported by the Netherlands Organization for Scientific Research, the Brain & Behavior Research Foundation and the European Research Council ERC StGr 948031; JSL is supported by NICHD grant HD097085; BL is supported by NIMH grant MH117482-02.

References

Akbari EM, Chatterjee D, Levy F, Fleming AS, 2007. Experience-dependent cell survival in the maternal rat brain. Behav.Neurosci 121, 1001–1011. [PubMed: 17907831]

Almanza-Sepulveda ML, Fleming AS, Jonas W, 2020. Mothering revisited: A role for cortisol? Horm Behav 121, 104679. [PubMed: 31927022]

Anderson MV, Rutherford MD, 2012. Cognitive reorganization during pregnancy and the postpartum period: an evolutionary perspective. Evolutionary Psychology: An International Journal of Evolutionary Approaches to Psychology and Behavior 10, 659–687. [PubMed: 23052608]

Atzil S, Touroutoglou A, Rudy T, Salcedo S, Feldman R, Hooker JM, Dickerson BC, Catana C, Barrett LF, 2017. Dopamine in the medial amygdala network mediates human bonding. Proceedings of the National Academy of Sciences of the United States of America 114, 2361–2366. [PubMed: 28193868]

Banasr M, Hery M, Brezun JM, Daszuta A, 2001. Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus. Eur.J Neurosci 14, 1417–1424. [PubMed: 11722603]

Barha CK, Galea LA, 2011. Motherhood alters the cellular response to estrogens in the hippocampus later in life. Neurobiol Aging 32, 2091–2095. [PubMed: 20034703]

Barriere DA, Ella A, Szeremeta F, Adriaensen H, Meme W, Chaillou E, Migaud M, Meme S, Levy F, Keller M, 2021. Brain orchestration of pregnancy and maternal behavior in mice: A longitudinal morphometric study. Neuroimage 230, 117776. [PubMed: 33516895]

Bartels A, Zeki S, 2004. The neural correlates of maternal and romantic love. Neuroimage 21, 1155–1166. [PubMed: 15006682]

Beeri MS, Rapp M, Schmeidler J, Reichenberg A, Purohit DP, Perl DP, Grossman HT, Prohovnik I, Haroutunian V, Silverman JM, 2009. Number of children is associated with neuropathology of Alzheimer's diseasein women. Neurobiol Aging 30, 1184–1191. [PubMed: 18079025]

Belnoue L, Malvaut S, Ladeveze E, Abrous DN, Koehl M, 2016. Plasticity in the olfactory bulb of the maternal mouse is prevented by gestational stress. Sci Rep 6, 37615. [PubMed: 27886228]

Berridge KC, Kringelbach ML, 2015. Pleasure systems in the brain. Neuron 86, 646–664. [PubMed: 25950633]

Bjertrup AJ, Friis NK, Miskowiak KW, 2019. The maternal brain: Neural responses to infants in mothers with and without mood disorder. Neurosci Biobehav Rev 107, 196–207. [PubMed: 31518637]

Boufidou F, Lambrinoudaki I, Argeitis J, Zervas IM, Pliatsika P, Leonardou AA, Petropoulos G, Hasiakos D, Papadias K, Nikolaou C, 2009. CSF and plasma cytokines at delivery and postpartum mood disturbances. J Affect.Disord 115, 287–292. [PubMed: 18708264]

Brann JH, Firestein SJ, 2014. A lifetime of neurogenesis in the olfactory system. Front Neurosci 8, 182. [PubMed: 25018692]

Bruce-Keller AJ, Keeling JL, Keller JN, Huang FF, Camondola S, Mattson MP, 2000. Antiinflammatory effects of estrogen on microglial activation. Endocrinology 141, 3646–3656. [PubMed: 11014219]

Brunton PJ, Russell JA, Douglas AJ, 2008. Adaptive responses of the maternal hypothalamic-pituitary-adrenal axis during pregnancy and lactation. J. Neuroendocrinol 20, 764–776. [PubMed: 18601699]

Brus M, Meurisse M, Franceschini I, Keller M, Levy F, 2010a. Evidence for cell proliferation in the sheep brain and its down-regulation by parturition and interactions with the young. Horm Behav 58, 737–746. [PubMed: 20692260]

Brus M, Meurisse M, Franceschini I, Keller M, Levy F, 2010b. Evidence for cell proliferation in the sheep brain and its down-regulation by parturition and interactions with the young. . Hormones and behavior 58, 737–746. [PubMed: 20692260]

Brus M, Meurisse M, Keller M, Levy F, 2014. Interactions with the young down-regulate adult olfactory neurogenesis and enhance the maturation of olfactory neuroblasts in sheep mothers. Front Behav Neurosci 8, 53. [PubMed: 24600367]

Carmona S, Martinez-Garcia M, Paternina-Die M, Barba-Muller E, Wierenga LM, eman-Gomez Y, Pretus C, Marcos-Vidal L, Beumala L, Cortizo R, Pozzobon C, Picado M, Lucco F, Garcia-Garcia D, Soliva JC, Tobena A, Peper JS, Crone EA, Ballesteros A, Vilarroya O, Desco M, Hoekzema E, 2019. Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes. Hum.Brain Mapp 40, 2143–2152. [PubMed: 30663172]

Chen CL, Meites J, 1970. Effects of estrogen and progesterone on serum and pituitary prolactin levels in ovariectomized rats. Endocrinology 86, 503–505. [PubMed: 5410438]

Cohen L, Mizrahi A, 2015. Plasticity during motherhood: changes in excitatory and inhibitory layer 2/3 neurons in auditory cortex. J Neurosci. 35, 1806–1815. [PubMed: 25632153]

Comte L, 1898. Contribution a l'etude de l'hypophyse humaine. Thesis.

Corona R, Meurisse M, Cornilleau F, Moussu C, Keller M, Levy F, 2018. Disruption of adult olfactory neurogenesis induces deficits in maternal behavior in sheep. Behav Brain Res 347, 124–131. [PubMed: 29501505]

Corwin EJ, Pajer K, Paul S, Lowe N, Weber M, McCarthy DO, 2015. Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression. Brain Behav Immun 49, 86–93. [PubMed: 25937051]

D'Amato FR, Populin R, 1987. Mother-offspring interaction and pup development in genetically deaf mice. Behav Genet 17, 465–475. [PubMed: 3426503]

Darnaudery M, Perez-Martin M, Del Favero F, Gomez-Roldan C, Garcia-Segura LM, Maccari S, 2007. Early motherhood in rats is associated with a modification of hippocampal function. Psychoneuroendocrinology 32, 803–812. [PubMed: 17640823]

De Guzman RM, Saulsbery AI, Workman JL, 2018. High nursing demand reduces depression-like behavior despite increasing glucocorticoid concentrations and reducing hippocampal neurogenesis in late postpartum rats. Behav Brain Res 353, 143–153. [PubMed: 30031882]

de Lange AG, Barth C, Kaufmann T, Maximov II, van der Meer D, Agartz I, Westlye LT, 2020a. Women's brain aging: Effects of sex-hormone exposure, pregnancies, and genetic risk for Alzheimer's disease. Human brain mapping 41, 5141–5150. [PubMed: 32856754]

de Lange AMG, Barth C, Kaufmann T, Anatürk M, Suri S, Ebmeier KP, Westlye LT, 2020b. The maternal brain: Region-specific patterns of brain aging are traceable decades after childbirth. Human Brain Mapping 41, 4718–4729. [PubMed: 32767637]

De Lange AMG, Kaufmann T, Van Der Meer D, Maglanoc LA, Alnæ D, Moberget T, Douaud G, Andreassen OA, Westlye LT, 2019. Population-based neuroimaging reveals traces of childbirth in the maternal brain. Proceedings of the National Academy of Sciences of the United States of America 116, 22341–22346. [PubMed: 31615888]

Demarchi L, Pawluski JL, Bosch OJ, 2021. The brain oxytocin and corticotropin-releasing factor systems in grieving mothers: What we know and what we need to learn. Peptides 143, 170593. [PubMed: 34091013]

Dickens MJ, Pawluski JL, 2018. The HPA Axis During the Perinatal Period: Implications for Perinatal Depression. Endocrinology 159, 3737–3746. [PubMed: 30256957]

Dimayuga FO, Reed JL, Carnero GA, Wang C, Dimayuga ER, Dimayuga VM, Perger A, Wilson ME, Keller JN, Bruce-Keller AJ, 2005. Estrogen and brain inflammation: effects on microglial expression of MHC, costimulatory molecules and cytokines. J Neuroimmunol 161, 123–136. [PubMed: 15748951]

Dinc H, Esen F, Demirci A, Sari A, Resit GH, 1998. Pituitary dimensions and volume measurements in pregnancy and post partum. MR assessment. Acta Radiol. 39, 64–69. [PubMed: 9498873]

Dufford AJ, Erhart A, Kim P, 2019. Maternal brain resting-state connectivity in the postpartum period. Journal of Neuroendocrinology 31, 1–22.

Eid RS, Chaiton JA, Lieblich SE, Bodnar TS, Weinberg J, Galea LAM, 2019. Early and late effects of maternal experience on hippocampal neurogenesis, microglia, and the circulating cytokine milieu. Neurobiol Aging 78, 1–17. [PubMed: 30825663]

Elster AD, Sanders TG, Vines FS, Chen MY, 1991. Size and shape of the pituitary gland during pregnancy and post partum: measurement with MR imaging. Radiology 181, 531–535. [PubMed: 1924800]

Featherstone RE, Fleming AS, Ivy GO, 2000. Plasticity in the maternal circuit: effects of experience and partum condition on brain astrocyte number in female rats. Behav.Neurosci 114, 158–172. [PubMed: 10718271]

Feierstein CE, Lazarini F, Wagner S, Gabellec MM, de Chaumont F, Olivo-Marin JC, Boussin FD, Lledo PM, Gheusi G, 2010. Disruption of Adult Neurogenesis in the Olfactory Bulb Affects Social Interaction but not Maternal Behavior. Front Behav Neurosci 4, 176. [PubMed: 21160552]

Feldman R, 2015. The adaptive human parental brain: implications for children's social development. Trends Neurosci 38, 387–399. [PubMed: 25956962]

Feldman R, Braun K, Champagne FA, 2019. The neural mechanisms and consequences of paternal caregiving. Nat Rev Neurosci 20, 205–224. [PubMed: 30760881]

Fiterman O, Raz S, 2019. Cognitive, neural and endocrine functioning during late pregnancy: An Event-Related Potentials study. Hormones and Behavior 116, 104575. [PubMed: 31442429]

Frankfurt M, Salas-Ramirez K, Friedman E, Luine V, 2011. Cocaine alters dendritic spine density in cortical and subcortical brain regions of the postpartum and virgin female rat. Synapse 65, 955–961. [PubMed: 21480383]

Furuta M, Bridges RS, 2005. Gestation-induced cell proliferation in the rat brain. Brain Res Dev Brain Res 156, 61–66. [PubMed: 15862628]

Furuta M, Bridges RS, 2009. Effects of maternal behavior induction and pup exposure on neurogenesis in adult, virgin female rats. Brain Res.Bull

Galea L, Ormerod B, Sampath S, Kostaras X, Wilkie D, Phelps M, 2000. Spatial working memory and hippocampal size across pregnancy in rats. Hormones and Behaviour 37, 86–95.

Galea LA, McEwen BS, 1999. Sex and seasonal differences in the rate of cell proliferation in the dentate gyrus of adult wild meadow voles. Neuroscience 89, 955–964. [PubMed: 10199627]

Galea LA, Wainwright SR, Roes MM, Duarte-Guterman P, Chow C, Hamson DK, 2013. Sex, hormones, and neurogenesis in the hippocampus: Hormonal modulation of neurogenesis and potential functional implications. J Neuroendocrinol.

Gingnell M, Bannbers E, Moes H, Engman J, Sylven S, Skalkidou A, Kask K, Wikstrom J, Sundstrom-Poromaa I, 2015. Emotion Reactivity Is Increased 4-6 Weeks Postpartum in Healthy Women: A Longitudinal fMRI Study. PLoS One 10, e0128964. [PubMed: 26061879]

Glasper ER, Kenkel WM, Bick J, Rilling JK, 2019. More than just mothers: The neurobiological and neuroendocrine underpinnings of allomaternal caregiving. Front Neuroendocrinol 53, 100741. [PubMed: 30822428]

Glasper ER, Kozorovitskiy Y, Pavlic A, Gould E, 2011. Paternal experience suppresses adult neurogenesis without altering hippocampal function in Peromyscus californicus. The Journal of comparative neurology 519, 2271–2281. [PubMed: 21456007]

Gonzalez JG, Elizondo G, Saldivar D, Nanez H, Todd LE, Villarreal JZ, 1988. Pituitary gland growth during normal pregnancy: an in vivo study using magnetic resonance imaging. Am.J.Med 85, 217–220. [PubMed: 3400697]

Grieb ZA, Ford EG, Yagan M, Lau BYB, Manfredsson FP, Krishnan K, Lonstein JS, 2021. Oxytocin receptors in the midbrain dorsal raphe are essential for postpartum maternal social and affective behaviors. Psychoneuroendocrinology 131, 105332. [PubMed: 34182251]

Haber SN, Knutson B, 2010. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology 35, 4–26. [PubMed: 19812543]

Haim A, Julian D, Albin-Brooks C, Brothers HM, Lenz KM, Leuner B, 2017. A survey of neuroimmune changes in pregnant and postpartum female rats. Brain Behav Immun 59, 67–78. [PubMed: 27686844]

Hamilton WL, Diamond MC, Johnson RE, Ingham CA, 1977. Effects of pregnancy and differential environments on rat cerebral cortical depth. Behav Biol 19, 333–340. [PubMed: 856160]

Harding-Forrester S, Feldman DE, 2018. Somatosensory maps. Handb Clin Neurol 151, 73–102. [PubMed: 29519481]

Herculano-Houzel S, 2014. The glia/neuron ratio: how it varies uniformly across brain structures and species and what that means for brain physiology and evolution. Glia 62, 1377–1391. [PubMed: 24807023]

Herrenkohl LR, Rosenberg PA, 1972. Exteroceptive stimulation of maternal behavior in the naive rat. Physiol Behav 8, 595–598. [PubMed: 5038130]

Hillerer KM, Jacobs VR, Fischer T, Aigner L, 2014a. The maternal brain: an organ with peripartal plasticity. Neural Plast 2014, 574159. [PubMed: 24883213]

Hillerer KM, Neumann ID, Couillard-Despres S, Aigner L, Slattery DA, 2014b. Lactation-induced reduction in hippocampal neurogenesis is reversed by repeated stress exposure. Hippocampus 24, 673–683. [PubMed: 24615851]

Hodes GE, Kana V, Menard C, Merad M, Russo SJ, 2015. Neuroimmune mechanisms of depression. Nat.Neurosci 18, 1386–1393. [PubMed: 26404713]

Hoekzema E, Barba-Muller E, Pozzobon C, Picado M, Lucco F, Garcia-Garcia D, Soliva JC, Tobena A, Desco M, Crone EA, Ballesteros A, Carmona S, Vilarroya O, 2017. Pregnancy leads to long-lasting changes in human brain structure. Nat.Neurosci 20, 287–296. [PubMed: 27991897]

Hoekzema E, Tamnes CK, Berns P, Barba-Muller E, Pozzobon C, Picado M, Lucco F, Martinez-Garcia M, Desco M, Ballesteros A, Crone EA, Vilarroya O, Carmona S, 2020. Becoming a mother entails anatomical changes in the ventral striatum of the human brain that facilitate its responsiveness to offspring cues. Psychoneuroendocrinology 112, 104507. [PubMed: 31757430]

Holdcroft A, Hall L, Hamilton G, Counsell SJ, Bydder GM, Bell JD, 2005. Phosphorus-31 brain MR spectroscopy in women during and after pregnancy compared with nonpregnant control subjects. AJNR Am.J.Neuroradiol 26, 352–356. [PubMed: 15709134]

Holroyd CB, Verguts T, 2021. The Best Laid Plans: Computational Principles of Anterior Cingulate Cortex. Trends Cogn Sci 25, 316–329. [PubMed: 33593641]

Holschbach MA, Lonstein JS, 2017. Motherhood and infant contact regulate neuroplasticity in the serotonergic midbrain dorsal raphe. Psychoneuroendocrinology 76, 97–106. [PubMed: 27898359]

Holschbach MA, Vitale EM, Lonstein JS, 2018. Serotonin-specific lesions of the dorsal raphe disrupt maternal aggression and caregiving in postpartum rats. Behav Brain Res 348, 53–64. [PubMed: 29653128]

Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA, Selkoe DJ, Stevens B, 2016. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science 352, 712–716. [PubMed: 27033548]

Huang L, Bittman EL, 2002. Olfactory bulb cells generated in adult male golden hamsters are specifically activated by exposure to estrous females. Horm Behav 41, 343–350. [PubMed: 11971669]

Hunt LT, 2021. Frontal circuit specialisations for decision making. Eur.J Neurosci 53, 3654–3671. [PubMed: 33864305]

Jones BC, Perrett DI, Little AC, Boothroyd L, Cornwell RE, Feinberg DR, Tiddeman BP, Whiten S, Pitman RM, Hillier SG, Burt DM, Stirrat MR, Smith MJL, Moore FR, 2005. Menstrual cycle, pregnancy and oral contraceptive use alter attraction to apparent health in faces. Proceedings of the Royal Society B: Biological Sciences.

Jurkowski MP, Bettio L, E KW, Patten A, Yau SY, Gil-Mohapel J, 2020. Beyond the Hippocampus and the SVZ: Adult Neurogenesis Throughout the Brain. Frontiers in cellular neuroscience 14, 576444. [PubMed: 33132848]

Kettenmann H, Hanisch UK, Noda M, Verkhratsky A, 2011. Physiology of microglia. Physiol Rev. 91, 461–553. [PubMed: 21527731]

Keyser-Marcus L, Stafisso-Sandoz G, Gerecke K, Jasnow A, Nightingale L, Lambert KG, Gatewood J, Kinsley CH, 2001. Alterations of medial preoptic area neurons following pregnancy and pregnancy-like steroidal treatment in the rat. Brain Res.Bull 55, 737–745. [PubMed: 11595357]

Kim P, Dufford AJ, Tribble RC, 2019. Months Postpartum : Associations with Parental Self-Efficacy. 223, 3267–3277.

Kim P, Leckman JF, Mayes LC, Feldman R, Wang X, Swain JE, 2010a. The plasticity of human maternal brain: Longitudinal changes in brain anatomy during the early postpartum period. Behavioral Neuroscience 124, 695–700. [PubMed: 20939669]

Kim P, Leckman JF, Mayes LC, Newman MA, Feldman R, Swain JE, 2010b. Perceived quality of maternal care in childhood and structure and function of mothers' brain. Developmental science 13, 662–673. [PubMed: 20590729]

Kim P, Rigo P, Mayes LC, Feldman R, Leckman JF, Swain JE, 2014. Neural plasticity in fathers of human infants. Social neuroscience 9, 522–535. [PubMed: 24958358]

Kim SK, Hwang IK, Yoo KY, Yoo DY, Bae E, Lee CH, Choi JH, Choi JW, Seong JK, Yoon YS, Won MH, 2010c. Pregnancy inhibits cell proliferation and neuroblast differentiation without neuronal damage in the hippocampal dentate gyrus in C57BL/6N mice. Brain Res. 1315, 25–32. [PubMed: 20026318]

Kimble DP, Rogers L, Hendrickson CW, 1967. Hippocampal lesions disrupt maternal, not sexual, behavior in the albino rat. J Comp Physiol Psychol 63, 401–407. [PubMed: 6064383]

Kinsley CH, Trainer R, Stafisso-Sandoz G, Quadros P, Marcus LK, Hearon C, Meyer EA, Hester N, Morgan M, Kozub FJ, Lambert KG, 2006. Motherhood and the hormones of pregnancy modify concentrations of hippocampal neuronal dendritic spines. Horm Behav 49, 131–142. [PubMed: 16005000]

Kolunie JM, Stern JM, Barfield RJ, 1994. Maternal aggression in rats: effects of visual or auditory deprivation of the mother and dyadic pattern of ultrasonic vocalizations. Behav Neural Biol 62, 41–49. [PubMed: 7945144]

Kopel H, Schechtman E, Groysman M, Mizrahi A, 2012. Enhanced synaptic integration of adult-born neurons in the olfactory bulb of lactating mothers. J Neurosci. 32, 7519–7527. [PubMed: 22649230]

Kostin A, Alam MA, McGinty D, Alam MN, 2021. Adult hypothalamic neurogenesis and sleep-wake dysfunction in aging. Sleep 44.

Lambert K, Eisch AJ, Galea LAM, Kempermann G, Merzenich M, 2019. Optimizing brain performance: Identifying mechanisms of adaptive neurobiological plasticity. Neurosci Biobehav Rev 105, 60–71. [PubMed: 31356835]

Lamm C, Decety J, Singer T, 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. NeuroImage 54, 2492–2502. [PubMed: 20946964]

Larsen CM, Grattan DR, 2010. Prolactin-induced mitogenesis in the subventricular zone of the maternal brain during early pregnancy is essential for normal postpartum behavioral responses in the mother. Endocrinology 151, 3805–3814. [PubMed: 20484459]

Larsen CM, Kokay IC, Grattan DR, 2008. Male pheromones initiate prolactin-induced neurogenesis and advance maternal behavior in female mice. Horm Behav 53, 509–517. [PubMed: 18258236]

Lau BYB, Layo DE, Emery B, Everett M, Kumar A, Stevenson P, Reynolds KG, Cherosky A, Bowyer SH, Roth S, Fisher DG, McCord RP, Krishnan K, 2020. Lateralized Expression of Cortical Perineuronal Nets during Maternal Experience is Dependent on MECP2. eNeuro 7.

Laurent HK, Ablow JC, 2012. The missing link: mothers' neural response to infant cry related to infant attachment behaviors. Infant Behav Dev 35, 761–772. [PubMed: 22982277]

Laurent HK, Stevens A, Ablow JC, 2011. Neural correlates of hypothalamic-pituitary-adrenal regulation of mothers with their infants. Biol.Psychiatry 70, 826–832. [PubMed: 21783177]

Lee M, 2013. Neurotransmitters and microglial-mediated neuroinflammation. Curr Protein Pept Sci 14, 21–32. [PubMed: 23441898]

Lei B, Mace B, Dawson HN, Warner DS, Laskowitz DT, James ML, 2014. Anti-inflammatory effects of progesterone in lipopolysaccharide-stimulated BV-2 microglia. PLoS One 9, e103969. [PubMed: 25080336]

Leibenluft E, Gobbini MI, Harrison T, Haxby JV, 2004. Mothers' neural activation in response to pictures of their children and other children. Biol.Psychiatry 56, 225–232. [PubMed: 15312809]

Lenz KM, Nelson LH, 2018. Microglia and Beyond: Innate Immune Cells As Regulators of Brain Development and Behavioral Function. Front Immunol 9, 698. [PubMed: 29706957]

Lenzi D, Trentini C, Pantano P, Macaluso E, Iacoboni M, Lenzi GL, Ammaniti M, 2009. Neural basis of maternal communication and emotional expression processing during infant preverbal stage. Cerebral cortex 19, 1124–1133. [PubMed: 18787229]

Leuner B, Glasper ER, Gould E, 2010. Parenting and plasticity. Trends Neurosci 33, 465–473. [PubMed: 20832872]

Leuner B, Gould E, 2010. Structural plasticity and hippocampal function. Annu.Rev.Psychol 61, 111–140, C111-113. [PubMed: 19575621]

Leuner B, Mirescu C, Noiman L, Gould E, 2007. Maternal experience inhibits the production of immature neurons in the hippocampus during the postpartum period through elevations in adrenal steroids. Hippocampus 17, 434–442. [PubMed: 17397044]

Leuner B, Sabihi S, 2016. The birth of new neurons in the maternal brain: Hormonal regulation and functional implications. Front Neuroendocrinol 41, 99–113. [PubMed: 26969795]

Levy F, Batailler M, Meurisse M, Keller M, Cornilleau F, Moussu C, Poissenot K, Migaud M, 2019. Differential effects of oxytocin on olfactory, hippocampal and hypothalamic neurogenesis in adult sheep. Neurosci.Lett 713, 134520. [PubMed: 31562884]

Levy F, Gheusi G, Keller M, 2011. Plasticity of the parental brain: a case for neurogenesis. J Neuroendocrinol 23, 984–993. [PubMed: 21824205]

Levy F, Kendrick KM, Keverne EB, Piketty V, Poindron P, 1992. Intracerebral oxytocin is important for the onset of maternal behavior in inexperienced ewes delivered under peridural anesthesia. Behav.Neurosci 106, 427–432. [PubMed: 1590960]

Lin FG, Galindo-Leon EE, Ivanova TN, Mappus RC, Liu RC, 2013. A role for maternal physiological state in preserving auditory cortical plasticity for salient infant calls. Neuroscience 247, 102–116. [PubMed: 23707982]

Lisofsky N, Gallinat J, Lindenberger U, Kühn S, 2019. Postpartal Neural Plasticity of the Maternal Brain: Early Renormalization of Pregnancy-Related Decreases? Neuro-Signals 27, 12–24. [PubMed: 31112016]

Lisofsky N, Wiener J, de Condappa O, Gallinat J, Lindenberger U, Kühn S, 2016. Differences in navigation performance and postpartal striatal volume associated with pregnancy in humans. Neurobiology of Learning and Memory 134, 400–407. [PubMed: 27614142]

Liu RC, Linden JF, Schreiner CE, 2006. Improved cortical entrainment to infant communication calls in mothers compared with virgin mice. Eur.J Neurosci 23, 3087–3097. [PubMed: 16819999]

Liu RC, Schreiner CE, 2007. Auditory cortical detection and discrimination correlates with communicative significance. PLoS Biol 5, e173. [PubMed: 17564499]

Lomanowska AM, Boivin M, Hertzman C, Fleming AS, 2015. Parenting begets parenting: A neurobiological perspective on early adversity and the transmission of parenting styles across generations. Neuroscience.

Lonstein JS, 2018. The dynamic serotonin system of the maternal brain. Arch Womens Ment Health.

Lonstein JS, Pereira M, Morrell JI, Marler CA, 2014. Parental Behavior, in: Plant TM, Zeleznik AJ (Eds.), Knobil and Neill's Physiology of Reproduction, 4th edition. Elsevier, pp. 2371–2438.

Lorberbaum JP, Newman JD, Horwitz AR, Dubno JR, Lydiard RB, Hamner MB, Bohning DE, George MS, 2002. A potential role for thalamocingulate circuitry in human maternal behavior. Biol.Psychiatry 51, 431–445. [PubMed: 11922877]

Love G, Torrey N, McNamara I, Morgan M, Banks M, Hester NW, Glasper ER, Devries AC, Kinsley CH, Lambert KG, 2005. Maternal experience produces long-lasting behavioral modifications in the rat. Behav.Neurosci 119, 1084–1096. [PubMed: 16187836]

Lowry CA, Evans AK, Gasser PJ, Hale MW, Staub DR, Shekhar A, 2008. Topographic organization and chemoarchitecture of the dorsal raphe nucleus and the median raphe nucleus, Serotonin and Sleep: Molecular, Functional and Clinical Aspects. Birkhauser, Basel, pp. 25–67.

Lucassen PJ, Meerlo P, Naylor AS, van Dam AM, Dayer AG, Fuchs E, Oomen CA, Czeh B, 2010. Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. Eur Neuropsychopharmacol 20, 1–17. [PubMed: 19748235]

Luders E, Kurth F, Gingnell M, Engman J, Yong EL, Poromaa IS, Gaser C, 2020. From baby brain to mommy brain: Widespread gray matter gain after giving birth. Cortex 126, 334–342. [PubMed: 32105976]

Luo H, Liang X, Cheng Z, Cai X, Feng F, Zhou H, Tang X, Zhou J, Wang D, Xiao X, 2020. Effects of normal pregnancy on maternal EEG, TCD, and cerebral cortical volume. Brain and Cognition 140, 105526. [PubMed: 32007788]

Maes M, Lin AH, Ombelet W, Stevens K, Kenis G, De Jongh R, Cox J, Bosmans E, 2000. Immune activation in the early puerperium is related to postpartum anxiety and depressive symptoms. Psychoneuroendocrinology 25, 121–137. [PubMed: 10674277]

Maguire J, Ferando I, Simonsen C, Mody I, 2009. Excitability changes related to GABAA receptor plasticity during pregnancy. J Neurosci. 29, 9592–9601. [PubMed: 19641122]

Marlin BJ, Mitre M, D'Amour J A, Chao MV, Froemke RC, 2015. Oxytocin enables maternal behaviour by balancing cortical inhibition. Nature 520, 499–504. [PubMed: 25874674]

Martinez-Garcia M, Paternina-Die M, Barba-Muller E, Martin de Blas D, Beumala L, Cortizo R, Pozzobon C, Marcos-Vidal L, Fernandez-Pena A, Picado M, Belmonte-Padilla E, Masso-Rodriguez A, Ballesteros A, Desco M, Vilarroya O, Hoekzema E, Carmona S, 2021. Do Pregnancy-Induced Brain Changes Reverse? The Brain of a Mother Six Years after Parturition. Brain Sci 11.

McEwen B, 2002. Estrogen actions throughout the brain. Recent Prog Horm Res 57, 357–384. [PubMed: 12017552]

Medina J, Workman JL, 2018. Maternal experience and adult neurogenesis in mammals: Implications for maternal care, cognition, and mental health. J Neurosci Res.

Musser ED, Kaiser-Laurent H, Ablow JC, 2012. The neural correlates of maternal sensitivity: an fMRI study. Developmental cognitive neuroscience 2, 428–436. [PubMed: 22652538]

Navarrete CD, Fessler DMT, Eng SJ, 2007. Elevated ethnocentrism in the first trimester of pregnancy. Evolution and Human Behavior.

Nelander M, Wikstrom AK, Weis J, Bergman L, Larsson A, Sundstrom-Poromaa I, Wikstrom J, 2018. Cerebral Osmolytes and Plasma Osmolality in Pregnancy and Preeclampsia: A Proton Magnetic Resonance Spectroscopy Study. Am.J.Hypertens 31, 847–853. [PubMed: 29415199]

Ning K, Zhao L, Franklin M, Matloff W, Batta I, Arzouni N, Sun F, Toga AW, 2020. Parity is associated with cognitive function and brain age in both females and males. Scientific Reports 10, 1–9. [PubMed: 31913322]

Niven JE, Laughlin SB, 2008. Energy limitation as a selective pressure on the evolution of sensory systems. J. Exp. Biol 211, 1792–1804 [PubMed: 18490395]

Noriuchi M, Kikuchi Y, Senoo A, 2008. The functional neuroanatomy of maternal love: mother's response to infant's attachment behaviors. Biol. Psychiatry 63, 415–423. [PubMed: 17686467]

Numan M, 2020. The Parental Brain: Mechanisms, Development, and Evolution. Oxford University Press.

Oatridge A, Holdcroft A, Saeed N, Hajnal JV, Puri BK, Fusi L, Bydder GM, 2002. Change in brain size during and after pregnancy: study in healthy women and women with preeclampsia. AJNR Am J Neuroradiol 23, 19–26. [PubMed: 11827871]

Okabe S, Tsuneoka Y, Takahashi A, Ooyama R, Watarai A, Maeda S, Honda Y, Nagasawa M, Mogi K, Nishimori K, Kuroda M, Koide T, Kikusui T, 2017. Pup exposure facilitates retrieving behavior via the oxytocin neural system in female mice. Psychoneuroendocrinology 79, 20–30. [PubMed: 28246032]

Opala EA, Verlezza S, Long H, Rusu D, Woodside B, Walker CD, 2019. Experience of Adversity during a First Lactation Modifies Prefrontal Cortex Morphology in Primiparous Female Rats:

Lack of Long Term Effects on a Subsequent Lactation. Neuroscience 417, 95–106. [PubMed: 31437474]

Orchard ER, , Ward PGD, , Sforazzini F, , Storey E, Egan GF, , Jamadar SD, , 2020. Relationship between parenthood and cortical thickness in late adulthood. 15, 1–16.

Osborne LM, Monk C, 2013. Perinatal depression--the fourth inflammatory morbidity of pregnancy?: Theory and literature review. Psychoneuroendocrinology 38, 1929–1952. [PubMed: 23608136]

Parsons CE, Young KS, Petersen MV, Jegindoe Elmholdt E-M, Vuust P, Stein A, Kringelbach ML, 2017. Duration of motherhood has incremental effects on mothers' neural processing of infant vocal cues: a neuroimaging study of women. Scientific Reports 7.

Paul S, Austin J, Elliott R, Ellison-Wright I, Wan MW, Drake R, Downey D, Elmadih A, Mukherjee I, Heaney L, Williams S, Abel KM, 2019. Neural pathways of maternal responding: systematic review and meta-analysis. Archives of Women's Mental Health 22, 179–187.

Pawluski JL, Barakauskas VE, Galea LA, 2010. Pregnancy decreases oestrogen receptor alpha expression and pyknosis, but not cell proliferation or survival, in the hippocampus. J Neuroendocrinol 22, 248–257. [PubMed: 20136685]

Pawluski JL, Brummelte S, Barha CK, Crozier TM, Galea LA, 2009a. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. Front Neuroendocrinol 30, 343–357. [PubMed: 19361542]

Pawluski JL, Charlier TD, Lieblich SE, Hammond GL, Galea LA, 2008. Reproductive experience alters corticosterone and CBG levels in the rat dam. Physiol Behav.

Pawluski JL, Csaszar E, Savage E, Martinez-Claros M, Steinbusch HW, van den Hove D, 2015. Effects of stress early in gestation on hippocampal neurogenesis and glucocorticoid receptor density in pregnant rats. Neuroscience 290, 379–388. [PubMed: 25655215]

Pawluski JL, Galea LA, 2006. Hippocampal morphology is differentially affected by reproductive experience in the mother. J Neurobiol. 66, 71–81. [PubMed: 16216005]

Pawluski JL, Galea LA, 2007. Reproductive experience alters hippocampal neurogenesis during the postpartum period in the dam. Neuroscience 149, 53–67. [PubMed: 17869008]

Pawluski JL, Galea LA, 2008. The role of reproductive experience on hippocampal function and plasticity, in: Bridges R (Ed.), Neurobiology of the Parental Brain. Academic Press, Boston, pp. 493–508.

Pawluski JL, Lambert KG, Kinsley CH, 2016. Neuroplasticity in the maternal hippocampus: Relation to cognition and effects of repeated stress. Horm Behav 77, 86–97. [PubMed: 26122302]

Pawluski JL, Lieblich SE, Galea LA, 2009b. Offspring-exposure reduces depressive-like behaviour in the parturient female rat. Behav Brain Res 197, 55–61. [PubMed: 18760310]

Pawluski JL, Paravatou R, Even A, Cobraiville G, Fillet M, Kokras N, Dalla C, Charlier TD, 2020. Effect of sertraline on central serotonin and hippocampal plasticity in pregnant and non-pregnant rats. Neuropharmacology 166, 107950. [PubMed: 31935392]

Pawluski JL, Valenca A, Santos AI, Costa-Nunes JP, Steinbusch HW, Strekalova T, 2012. Pregnancy or stress decrease complexity of CA3 pyramidal neurons in the hippocampus of adult female rats. Neuroscience 227, 201–210. [PubMed: 23036618]

Pawluski JL, van den Hove DL, Rayen I, Prickaerts J, Steinbusch HW, 2011. Stress and the pregnant female: Impact on hippocampal cell proliferation, but not affective-like behaviors. Horm Behav 59, 572–580. [PubMed: 21376727]

Pawluski JL, Vanderbyl BL, Ragan K, Galea LA, 2006a. First reproductive experience persistently affects spatial reference and working memory in the mother and these effects are not due to pregnancy or 'mothering' alone. Behav Brain Res 175, 157–165. [PubMed: 17011053]

Pawluski JL, Walker SK, Galea LA, 2005. Reproductive experience differentially affects spatial reference and working memory performance in the mother. Horm Behav.

Pawluski JL, Walker SK, Galea LA, 2006b. Reproductive experience differentially affects spatial reference and working memory performance in the mother. Horm Behav 49, 143–149. [PubMed: 15992800]

Pearson RM, Lightman SL, Evans J, 2009. Emotional sensitivity for motherhood: Late pregnancy is associated with enhanced accuracy to encode emotional faces. Hormones and Behavior.

Penick CA, Ghaninia M, Haight KL, Opachaloemphan C, Yan H, Reinberg D, Liebig J, 2021. Reversible plasticity in brain size, behaviour and physiology characterizes caste transitions in a socially flexible ant (Harpegnathos saltator). Proceedings. Biological sciences / The Royal Society 288, 20210141.

Peper JS, Hulshoff Pol HE, Crone EA, van Honk J, 2011. Sex steroids and brain structure in pubertal boys and girls: a mini-review of neuroimaging studies. Neuroscience 191, 28–37. [PubMed: 21335066]

Pocock JM, Kettenmann H, 2007. Neurotransmitter receptors on microglia. Trends Neurosci 30, 527–535. [PubMed: 17904651]

Posillico CK, Schwarz JM, 2016. An investigation into the effects of antenatal stressors on the postpartum neuroimmune profile and depressive-like behaviors. Behav Brain Res 298, 218–228. [PubMed: 26589802]

Raz S, 2014. Behavioral and neural correlates of cognitive-affective function during late pregnancy: an Event-Related Potentials study. Behavioural Brain Research 267, 17–25. [PubMed: 24671067]

Rehbein E, Hornung J, Sundstrom Poromaa I, Derntl B, 2021. Shaping of the Female Human Brain by Sex Hormones: A Review. Neuroendocrinology 111, 183–206. [PubMed: 32155633]

Rincón-Cortés M, Grace AA, 2020. Adaptations in reward-related behaviors and mesolimbic dopamine function during motherhood and the postpartum period. Front Neuroendocrinol 57, 100839. [PubMed: 32305528]

Rocchetti M, Radua J, Paloyelis Y, Xenaki LA, Frascarelli M, Caverzasi E, Politi P, Fusar-Poli P, 2014. Neurofunctional maps of the 'maternal brain' and the effects of oxytocin: A multimodal voxel-based meta-analysis. Psychiatry and Clinical Neurosciences 68, 733–751. [PubMed: 24734987]

Rolls A, Schori H, London A, Schwartz M, 2008. Decrease in hippocampal neurogenesis during pregnancy: a link to immunity. Mol.Psychiatry 13, 468–469. [PubMed: 18421294]

Roos A, Lochner C, Kidd M, van Honk J, Vythilingum B, Stein DJ, 2012. Selective attention to fearful faces during pregnancy. Progress in Neuro-Psychopharmacology and Biological Psychiatry 37, 76–80. [PubMed: 22154947]

Rosenblatt JS, 1969. The development of maternal responsiveness in the rat. Am J Orthopsychiatry 39, 36–56. [PubMed: 5776164]

Rosselet C, Zennou-Azogui Y, Xerri C, 2006. Nursing-induced somatosensory cortex plasticity: temporally decoupled changes in neuronal receptive field properties are accompanied by modifications in activity-dependent protein expression. J Neurosci. 26, 10667–10676. [PubMed: 17050706]

Ruscio MG, Sweeny TD, Hazelton JL, Suppatkul P, Boothe E, Carter CS, 2008. Pup exposure elicits hippocampal cell proliferation in the prairie vole. Behav Brain Res 187, 9–16. [PubMed: 17913255]

Rutherford HJ, Booth CR, Luyten P, Bridgett DJ, Mayes LC, 2015a. Investigating the association between parental reflective functioning and distress tolerance in motherhood. Infant Behav.Dev 40, 54–63. [PubMed: 26025253]

Rutherford HJ, Wallace NS, Laurent HK, Mayes LC, 2015b. Emotion Regulation in Parenthood. Dev.Rev 36, 1–14. [PubMed: 26085709]

Rutherford HJV, Maupin AN, Mayes LC, 2019. Parity and neural responses to social and non-social stimuli in pregnancy. Social neuroscience 14, 545–548. [PubMed: 30198393]

Rutherford HJV, Potenza MN, Mayes LC, Scheinost D, 2020. The Application of Connectome-Based Predictive Modeling to the Maternal Brain: Implications for Mother-Infant Bonding. Cerebral Cortex 30, 1538–1547. [PubMed: 31690936]

Rutherford JM, Moody A, Crawshaw S, Rubin PC, 2003. Magnetic resonance spectroscopy in pre-eclampsia: evidence of cerebral ischaemia. BJOG. 110, 416–423. [PubMed: 12699805]

Sakamoto M, Imayoshi I, Ohtsuka T, Yamaguchi M, Mori K, Kageyama R, 2011. Continuous neurogenesis in the adult forebrain is required for innate olfactory responses. Proc Natl Acad Sci U S A 108, 8479–8484. [PubMed: 21536899]

Salmaso N, Popeski N, Peronace LA, Woodside B, 2005. Differential effects of reproductive and hormonal state on basic fibroblast growth factor and glial fibrillary acid protein immunoreactivity

in the hypothalamus and cingulate cortex of female rats. Neuroscience 134, 1431–1440. [PubMed: 16054761]

Salmaso N, Quinlan MG, Brake WG, Woodside B, 2011. Changes in dendritic spine density on layer 2/3 pyramidal cells within the cingulate cortex of late pregnant and postpartum rats. Horm Behav 60, 65–71. [PubMed: 21397603]

Salmaso N, Woodside B, 2006. Upregulation of astrocytic basic fibroblast growth factor in the cingulate cortex of lactating rats: time course and role of suckling stimulation. Horm Behav 50, 448–453. [PubMed: 16860801]

Salmaso N, Woodside B, 2008. Fluctuations in astrocytic basic fibroblast growth factor in the cingulate cortex of cycling, ovariectomized and postpartum animals. Neuroscience 154, 932–939. [PubMed: 18472346]

Schaafsma SM, Pfaff DW, Spunt RP, Adolphs R, 2015. Deconstructing and reconstructing theory of mind. Trends in Cognitive Sciences 19, 65–72. [PubMed: 25496670]

Schiavo JK, Valtcheva S, Bair-Marshall CJ, Song SC, Martin KA, Froemke RC, 2020. Innate and plastic mechanisms for maternal behaviour in auditory cortex. Nature 587, 426–431. [PubMed: 33029014]

Schurz M, Radua J, Aichhorn M, Richlan F, Perner J, 2014. Fractionating theory of mind: A meta-analysis of functional brain imaging studies. Neuroscience and Biobehavioral Reviews 42, 9–34. [PubMed: 24486722]

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD, 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 27, 2349–2356. [PubMed: 17329432]

Segman RH, Goltser-Dubner T, Weiner I, Canetti L, Galili-Weisstub E, Milwidsky A, Pablov V, Friedman N, Hochner-Celnikier D, 2010. Blood mononuclear cell gene expression signature of postpartum depression. Mol. Psychiatry 15, 93–100, 102. [PubMed: 19581911]

Shams S, Pawluski JL, Chatterjee-Chakraborty M, Oatley H, Mastroianni A, Fleming AS, 2012. Dendritic morphology in the striatum and hypothalamus differentially exhibits experience-dependent changes in response to maternal care and early social isolation. Behav Brain Res 233, 79–89. [PubMed: 22569575]

Shepard KN, Lin FG, Zhao CL, Chong KK, Liu RC, 2015. Behavioral relevance helps untangle natural vocal categories in a specific subset of core auditory cortical pyramidal neurons. J Neurosci. 35, 2636–2645. [PubMed: 25673855]

Sherer ML, Posillico CK, Schwarz JM, 2017. An examination of changes in maternal neuroimmune function during pregnancy and the postpartum period. Brain Behav Immun 66, 201–209. [PubMed: 28669797]

Shingo T, Gregg C, Enwere E, Fujikawa H, Hassam R, Geary C, Cross JC, Weiss S, 2003. Pregnancy-stimulated neurogenesis in the adult female forebrain mediated by prolactin. Science 299, 117–120. [PubMed: 12511652]

Sierra A, Gottfried-Blackmore A, Milner TA, McEwen BS, Bulloch K, 2008. Steroid hormone receptor expression and function in microglia. Glia 56, 659–674. [PubMed: 18286612]

Slattery DA, Hillerer KM, 2016. The maternal brain under stress: Consequences for adaptive peripartum plasticity and its potential functional implications. Front Neuroendocrinol 41, 114–128. [PubMed: 26828151]

Snyder JS, Drew MR, 2020. Functional neurogenesis over the years. Behav Brain Res 382, 112470. [PubMed: 31917241]

Sorg BA, Berretta S, Blacktop JM, Fawcett JW, Kitagawa H, Kwok JC, Miquel M, 2016. Casting a Wide Net: Role of Perineuronal Nets in Neural Plasticity. J Neurosci. 36, 11459–11468. [PubMed: 27911749]

Stern JM, 1996. Somatosensation and Maternal Care in Norway Rats, in: Rosenblatt JS, Snowden CT (Eds.), Parental Care: Evolution, Mechanisms, and Adaptive Significance. Academic Press, San Diego, pp. 243–294.

Swain JE, 2008. Baby stimuli and the parent brain: functional neuroimaging of the neural substrates of parent-infant attachment. Psychiatry (Edgmont) 5, 28–36.

Tasaka GI, Feigin L, Maor I, Groysman M, DeNardo LA, Schiavo JK, Froemke RC, Luo L, Mizrahi A, 2020. The Temporal Association Cortex Plays a Key Role in Auditory-Driven Maternal Plasticity. Neuron 107, 566–579 e567. [PubMed: 32473095]

Terlecki LJ, Sainsbury RS, 1978. Effects of fimbria lesions on maternal behavior in the rat. Physiol Behav 21, 89–97. [PubMed: 567818]

Tomizawa K, Iga N, Lu YF, Moriwaki A, Matsushita M, Li ST, Miyamoto O, Itano T, Matsui H, 2003. Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. Nat.Neurosci 6, 384–390. [PubMed: 12598900]

Tramontin AD, Brenowitz EA, 2000. Seasonal plasticity in the adult brain. Trends Neurosci 23, 251–258. [PubMed: 10838594]

Udvari EB, Volgyi K, Kekesi KA, Simon D, Hunyadi-Gulyas E, Dobolyi A, 2019. Proteomic Analysis of the Maternal Preoptic Area in Rats. Neurochem Res 44, 2314–2324. [PubMed: 30847857]

Uriarte N, Ferreno M, Mendez D, Nogueira J, 2020. Reorganization of perineuronal nets in the medial Preoptic Area during the reproductive cycle in female rats. Sci Rep 10, 5479. [PubMed: 32214157]

van Heukelum S, Mars RB, Guthrie M, Buitelaar JK, Beckmann CF, Tiesinga PHE, Vogt BA, Glennon JC, Havenith MN, 2020. Where is Cingulate Cortex? A Cross-Species View. Trends Neurosci 43, 285–299. [PubMed: 32353333]

Vegeto E, Bonincontro C, Pollio G, Sala A, Viappiani S, Nardi F, Brusadelli A, Viviani B, Ciana P, Maggi A, 2001. Estrogen prevents the lipopolysaccharide-induced inflammatory response in microglia. J Neurosci. 21, 1809–1818. [PubMed: 11245665]

Veyrac A, Wang G, Baum MJ, Bakker J, 2011. The main and accessory olfactory systems of female mice are activated differentially by dominant versus subordinate male urinary odors. Brain Res. 1402, 20–29. [PubMed: 21683943]

Walker CD, Deschamps S, Proulx K, Tu M, Salzman C, Woodside B, Lupien S, Gallo-Payet N, Richard D, 2004. Mother to infant or infant to mother? Reciprocal regulation of responsiveness to stress in rodents and the implications for humans. J Psychiatry Neurosci 29, 364–382. [PubMed: 15486606]

Wan L, Tu T, Zhang QL, Jiang J, Yan XX, 2019. Pregnancy Promotes Maternal Hippocampal Neurogenesis in Guinea Pigs. Neural Plast 2019, 5765284. [PubMed: 31097956]

Wohleb ES, 2016. Neuron-Microglia Interactions in Mental Health Disorders: "For Better, and For Worse". Front Immunol 7, 544. [PubMed: 27965671]

Workman JL, Gobinath AR, Kitay NF, Chow C, Brummelte S, Galea LAM, 2016. Parity modifies the effects of fluoxetine and corticosterone on behavior, stress reactivity, and hippocampal neurogenesis. Neuropharmacology 105, 443–453. [PubMed: 26808316]

Xerri C, Stern JM, Merzenich MM, 1994. Alterations of the cortical representation of the rat ventrum induced by nursing behavior. J Neurosci. 14, 1710–1721. [PubMed: 8126565]

Zaki J, Ochsner KN, 2012. The neuroscience of empathy: progress, pitfalls and promise. Nat.Neurosci. 15, 675–680. [PubMed: 22504346]

Zhang K, Wang M, Zhang J, Du X, Chen Z, 2020. Brain Structural Plasticity Associated with Maternal Caregiving in Mothers: A Voxel-and Surface-Based Morphometry Study. Neurodegenerative Diseases 19, 192–203.

Zhao M, Janson Lang AM, 2009. Bromodeoxyuridine infused into the cerebral ventricle of adult mice labels nigral neurons under physiological conditions--a method to detect newborn nerve cells in regions with a low rate of neurogenesis. J Neurosci Methods 184, 327–331. [PubMed: 19699232]

Zheng JX, Chen YC, Chen H, Jiang L, Bo F, Feng Y, Tang WW, Yin X, Gu JP, 2018. Disrupted spontaneous neural activity related to cognitive impairment in postpartum women. Frontiers in Psychology.

Zheng JX, Ge L, Chen H, Yin X, Chen YC, Tang WW, 2020. Disruption within brain default mode network in postpartum women without depression. Medicine 99, e20045. [PubMed: 32358387]

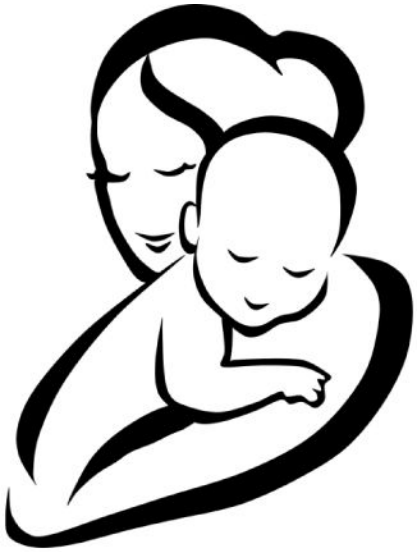
Highlights

- Motherhood involves widespread changes in structure, function, and neural/glial plasticity
- This plasticity often involves regressive events refining maternal neurocircuitry
- Brain plasticity underlies mothers' physiology, behavior, and health
- How these brain changes promote the transition to motherhood remains to be determined
- Maternal experience needs to be considered when studying the female brain

Neurosci Biobehav Rev. Author manuscript; available in PMC 2023 February 01.

Table 1.

Summary of key changes in the maternal brain of humans with structural and functional neuroimaging. EEG = electroencephalography ; fMRI = functional magnetic resonance imaging; rsFC = resting-state functional connectivity

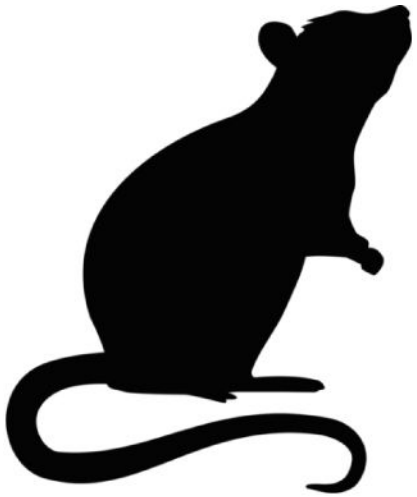
	**Pregnancy** Structural neuroimaging ↓ overall brain size [1] ↓ grey matter volume across pregnancy in medial frontal cortex, precuneus, posterior cingulate cortex, inferior frontal gyri, superior temporal sulci, hippocampus, ventral striatum [2,3] ↓ volume associated with ↑ maternal attachment [2] and ↑ neural reactivity to infant [3] Functional neuroimaging ↑ EEG response in a number of tasks [5,11,12]
	**Postpartum** Structural neuroimaging ↓ cortical thickness [4,5,6] ↑ grey matter volume in various brain regions in the weeks or months postpartum in frontal areas, occipital cortex, and cerebellar areas [7,8] ↓ grey matter volume in many brain regions compared to pre-conception up to 6 years postpartum [2,9,10] ↑ grey matter volume in hippocampus [2] ↑ white matter volume and gyrification [6] Functional neuroimaging ↑ fMRI response to offspring cues in many areas including the insula, orbitofrontal gyrus, inferior frontal gyrus, precentral gyrus, thalamus, amygdala, striatum [13,14,15] ↑ fMRI response to infant cries in frontal regions associated with ↑ attachment [16], ↑ sensitive behaviors to their infants [17] ↑ connectivity with the anterior cingulate gyrus, left nucleus accumbens, right caudate and left cerebellum using rsFC [18] ↑ rsFC between the left amygdala and left nucleus accumbens associated with ↑ maternal structuring during a mother-child interaction [18]

1. Oatridge et al., 2002
2. Hoekzema et al 2017
3. Hoekzema et al., 2020
4. Carmona et al., 2019
5. Luo et al 2020
6. Zhang et al., 2020

7. Kim et al., 2010a
8. Luders et al., 2020
9. Martinez-Garcia et al., 2021
10. Lisofsky et al., 2016
11. Rutherford et al., 2019
12. Fiterman and Raz, 2019
13. Bjertrup et al., 2019
14. Paul et al., 2019
15. Rocchetti et al., 2014
16. Laurent and Ablow, 2012
17. Musser et al., 2012
18. Dufford et al., 2019

Table 2.

Summary of key changes in the maternal brain of rodents with regards to neurogenesis, measures of dendritic complexity, glial cells and grey matter volumes. mPOA = medial preoptic area; SVZ=subventricular zone; OB = olfactory bulb; DR = dorsal raphe nucleus; mPFC = medial prefrontal cortex; FGF = fibroblast growth factor; GFAP = glial fibrillary acidic protein; BNST = bed nucleus of the stria terminalis.

		Pregnancy	**Postpartum**
	Cell Proliferation and/or Survival	↓ hippocampus[1,2]	↓ hippocampus[2], mPOA[3], DR[4] ↑ SVZ/OB[5] (↓ hippocampus and SVZ/OB in sheep[6])
	Dendritic complexity	↓ ↑ hippocampus[1,2] ↑ mPOA[7]	↓ hippocampus[2] ↑ mPOA[7,8], mPFC[9]
	Glia	↓ microglia in nucleus accumbens, amygdala, hippocampus, mPFC[10,11] ↑ FGF/GFAP cingulate gyrus 2[12]	↓ microglia in nucleus accumbens, amygdala, hippocampus, mPFC[10,11] ↑ FGF/GFAP in mPOA, cingulate gyrus 2[13]
	Grey matter volume		↑ mPOA, BNST, amygdala, hippocampus[14]

1. Pawluski et al., 2020
2. Pawluski et al., 2016, review
3. Akbari and Fleming, 2007
4. Holschbach and Lonstein, 2017
5. Shingo et al., 2003
6. Brus et al., 2010
7. Keyser-Marcus et al., 2001
8. Shams et al., 2012
9. Leuner et al., 2010

10. Haim et al., 2017
11. Posillico and Schwarz, 2016
12. Salmaso et al., 2005
13. Salmaso et al., 2011
14. Barriere et al 2021