The transition to motherhood: linking hormones, brain and behaviour

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Abstract

We are witnessing a stark increase in scientific interest in the neurobiological processes associated with pregnancy and maternity. Convergent evidence suggests that around the time of labour, first-time mothers experience a specific pattern of neuroanatomical changes that are associated with maternal behaviour. Here we provide an overview of the human neurobiological adaptations of motherhood, focusing on the interplay between pregnancy-related steroid and peptide hormones, and neuroplasticity in the brain. We discuss which brain plasticity mechanisms might underlie the structural changes detected by MRI, which hormonal systems are likely to contribute to such neuroanatomical changes and how these brain mechanisms may be linked to maternal behaviour. This Review offers an overarching framework that can serve as a roadmap for future investigations.

1 Introduction

Becoming a mother is a transformative event both at a physiological and psychological level. The arrival of a newborn entails a set of behavioural adaptations in mothers directed at ensuring the well-being of the offspring (Box 1). In the past decade, MRI studies have consistently shown that brains of women also undergo substantial neuroanatomical changes during pregnancy and the postpartum period [1, 2]. These structural brain changes and behavioural adaptations are accompanied by extreme fluctuations in hormones, which are potent modulators of brain plasticity. However, the specific relationship among hormones, brain plasticity and behaviour during the transition to motherhood still needs to be unravelled.

Brain plasticity is the lifelong ability of the nervous system to adaptively change in response to physiological and environmental demands through processes that regulate cellular function, brain structure and connectivity. For over 100 years, hormones have been known to coordinate neuroplasticity during sensitive periods of development as in early life and adolescence [3, 4]. Hormonal fluctuations during pregnancy exceed those of any other neuroendocrine event in the lifetime of a human. However, researchers only recently started to consider the possibility that pregnancy and the postpartum period are also sensitive windows of hormone-driven brain plasticity. Non-human animal models have paved the way for understanding the hormonal effects on the brain and behaviour of mothers. Studies with rodents indicate that *pregnancy hormones* prime a neural circuit known as the 'maternal caregiving circuit' [5], which facilitates the onset of maternal behaviour. The functional activation of the maternal caregiving circuit is accompanied by structural neuroplasticity, which includes modifications in the proliferation and morphology of brain cells.

In the current work, we present potential pathways in which hormone-driven neuroplasticity at the cellular level may translate into neuroanatomical and behavioural changes during the human motherhood transition. We start by reviewing recent evidence on the neuroanatomical and hormonal changes associated with human pregnancy and the *postpartum period*. Functional MRI brain changes are discussed, when necessary, but are out of the scope of this Review. Next, we outline pathways in which pregnancy-related hormones facilitate the activation of the neural circuits responsible for maternal behaviour. We then describe how such hormones trigger neuroplasticity mechanisms that translate into neuronal and glial structural changes in the rodent maternal brain. Finally, we discuss the potential links among hormones, neuroplasticity and maternal behaviour in humans and set a series of questions that can serve as a roadmap for future investigations.

2 Neuroanatomical changes in mothers

For decades, the life-changing event of becoming a mother remained out of the bounds of magnetic resonance research. The first controlled neuroimaging study describing widespread and pronounced neuroanatomical changes associated with pregnancy was published only a few years ago [6]. We begin

this Review by summarizing the key findings of the first study together with subsequent efforts to understand what happens in the brain through human pregnancy and the postpartum period.

Pregnancy leads to changes in the brain structure of the mother. First-time mothers have been found to display widespread grey matter brain volume reductions when assessed before conceiving and again at 2–3 months after giving birth compared with *nulliparous* women [6, 7]. Pregnancy-related brain decreases are prominent, with a mean decrease of 3% in total cortical grey matter volume [8]. Such grey matter volume reductions are primarily located in midline regions (extending from the medial prefrontal cortex (mPFC) to the anterior cingulate cortex and from the precuneus to the posterior cingulate cortex), lateral prefrontal cortex (primarily middle and inferior frontal gyri), superior and middle temporal cortex (extending to the insula, fusiform gyri and temporoparietal junction) [6, 7]. Grey matter reductions also affect subcortical regions such as the hippocampus (and parahippocampal gyrus) [6, 7], the ventral striatum [9] — a subcortical region containing the nucleus accumbens — and the dorsal striatum, specifically the caudate nucleus [7]. Morphometric studies also reveal that these grey matter reductions co-occur with a flattening of the cortex similar to that taking place during adolescence, that is, a thinner and less-gyrified cortex with shorter, narrower and shallower sulci [8]. This pronounced cortical flattening is long-lasting, remaining years after parturition [6, 8, 10].

Longitudinal studies comparing brain anatomy of women after giving birth and again after a few months reveal brain volume increases throughout the postpartum period [7, 11–13]. Specifically, although mothers display reduced grey matter volumes in the immediate postpartum period compared with non-mothers, this volume difference partially diminishes as the postpartum period progresses [7, 12, 14]. Many of the regions whose grey matter volume decreases during pregnancy coincide with regions that increase during the postpartum period (Fig. 1). These include the precuneus, superior temporal gyrus, inferior frontal and medial prefrontal gyrus extending into the anterior cingulate, medial temporal areas (including the hippocampus, parahippocampal gyrus and insula), visual areas such as the middle occipital gyrus, posterior cerebellum, ventral striatum including the nucleus accumbens, and dorsal striatum including the caudate. These findings draw a dynamic trajectory of volumetric decreases during pregnancy that, at least in part, tend to recover during the postpartum period (Fig. 2). Importantly, the complete longitudinal time course of grey matter changes during human pregnancy and the postpartum period remains to be elucidated.

2.1 Neuroanatomy and maternal behaviour

Gray matter changes during the transition to motherhood may promote maternal behaviour. In humans, the degree of pregnancy-related neuroanatomical changes has been associated with different self-reported indirect measures of the mother-to-infant relationship, including higher quality of attachment [6], lower presence of hostility towards the newborn [6] and an increased social selectivity (for example, strong preference for close friends or family) [7]. During the postpartum period, grey matter volume increases in a midbrain cluster comprising the hypothalamus, amygdala and globus

pallidus were associated with mothers attributing a higher number of positive adjectives to their babies [11]. Moreover, volume decreases in the nucleus accumbens of a woman during pregnancy have been positively associated with increased neural activation in response to photographs of their baby after birth [9]. All in all, the structural brain changes observed during pregnancy and the postpartum period could function as a neural adjustment that facilitates sensitive and timely behaviours towards the newborn.

2.2 Neuroanatomy and pregnancy hormones

Human pregnancy is a dynamic but coordinated process involving large and intricate hormonal fluctuations (Box 2). Yet, when adopting a panoramic view, we see a clear shift in how hormones fluctuate before and after parturition (Fig. 2). The steroid hormones that are upregulated during pregnancy plummet in the postpartum period [15–17]. Similarly, there is a rise and fall in oxytocin and prolactin levels, but their secretion during the postpartum period becomes linked to breastfeeding episodes and mother-to-infant interaction [18–21]. Of note, the hormonal timeline depicted in Fig. 2 represents the fluctuations occurring in the peripheral circulation. In the case of steroid hormones, these changes may be similar to the fluctuations occurring inside the brain, as steroids readily cross the blood–brain barrier via non-saturable processes (Box 3). Protein hormones, by contrast, are mainly produced in the brain and then exported to the periphery. In this case, it is common to assume that peripheral levels indicate, to some extent, central production. However, we still do not know the exact relationship between peripheral and central levels, and extrapolations should be made carefully.

Brain structural changes in mothers are often attributed to pregnancy hormones. Several rodent studies have documented how hormones — including oestradiol, progesterone, *corticosterone*, prolactin and oxytocin — trigger neuroplasticity during the transition to motherhood (see the section 'Hormonal-mediated neural plasticity'). However, endocrine factors are almost never considered in human neuroimaging studies [22], and even when collected, they are rarely combined with neuroimaging data [6, 12]. Despite that, some emerging evidence suggests a relationship between pregnancy hormones and structural brain changes in humans. For instance, greater pregnancy-related total grey matter volume reductions have been associated with higher circulating oestradiol levels during the third trimester of pregnancy [7]. Moreover, the transition from decreasing grey matter volumes during pregnancy to increasing grey matter volumes during the postpartum period is aligned with a stark shift in the hormonal milieu before and after delivery (Fig. 2). Finally, the similarity between structural brain changes during pregnancy and adolescence [8] — another period marked by utmost steroid hormonal fluctuations — suggests that overlapping hormonal factors may prompt the neural changes observed in both the periods. Overall, these observations suggest that hormonal factors may trigger neuroplasticity during human pregnancy.

3 Hormones and maternal behaviour

Non-human animal studies have provided a great understanding of the hormonal regulation of maternal behaviour. One of the first pieces of evidence for the humoral basis of maternal behaviour dates from 1972, when Terkel and Rosenblatt [23] transfused pregnant animal blood into non-maternal virgin females, resulting in a rapid induction of maternal behaviour in the latter. In addition, ovariectomized virgin females treated with a hormonal regimen of oestradiol, progesterone and prolactin reduced their latency to behave maternally from typical 6–7 days to 35–40 h [24, 25]. Moreover, newer studies using conditional transgenic approaches have found that the actions of oestrogen and prolactin in promoting maternal behaviour may be mediated via specific receptors located in the medial preoptic area (MPOA), a central region of the maternal brain circuit [26–28] (see the section 'Maternal circuit activation in rodents').

Along with these hormones, several other studies suggest that oxytocin has an additional role in stimulating maternal behaviour. Specifically, a combination of oxytocin and oestradiol stimulates maternal behaviour in ovariectomized virgin female rats, whereas oxytocin alone takes longer to induce the maternal response [29, 30]. Finally, corticosterone administration modulates the intensity of maternal behaviour in adrenalectomized dams [31]. These findings suggest that *peripartum* steroids (oestradiol, progesterone and corticosterone) and peptide hormones (oxytocin and prolactin) together facilitate and regulate maternal behaviour.

In humans, the evidence linking hormones and maternal behaviour is scarcer and based on correlational data. Moreover, the literature has mainly focused on one hormone: oxytocin. Similar to what has been observed in other mammalian species, peripheral oxytocin levels measured across pregnancy and the postpartum period relate to maternal behaviour [32–34]. These include increased mother-to-infant synchrony, sensitive mothering, positive communication and affectionate contact (Box 1). It should be noted, however, that oxytocin derived from the hypothalamus may exert a more substantial influence on maternal behaviour.

Beyond oxytocin, other less-explored hormones have been associated with the expression of maternal care in humans. For example, hormonal changes in oestradiol and progesterone during early and late gestation have been linked to higher maternal sensitivity, affectionate contact, lack of intrusiveness [35] and more positive feelings of attachment [36] towards the newborn during the postpartum period. During the early postpartum period, studies have also correlated higher plasma cortisol levels with the feeling of mothers drawn to their scent of newborn [36]. After the early postpartum period, when cortisol has returned to pre-pregnancy levels, lower maternal cortisol seems to be positively associated with higher maternal sensitivity when playing with their infant [37]. Finally, during the lactation period, high prolactin levels after feeding the infant are positively associated with exhibiting higher levels of maternal sensitivity when interacting with the infant [38].

4 Hormonal control of maternal circuits

Despite the aforementioned evidence, the brain mechanisms through which pregnancy hormones facilitate human maternal behaviour are still unknown. Maternal behaviour is a multifactorial construct that does not rely exclusively on hormonal stimulation (Box 1). Fortunately, the neurobiological bases of maternal behaviour have been extensively studied in murine models, thus providing a reference framework. Next, we provide an overview of the rodent maternal brain literature as a roadmap to infer how hormones activate specific brain networks to elicit maternal behaviour in humans.

4.1 Maternal circuit activation in rodents

In rats, peripartum hormones target hormone-sensitive neural regions to initiate maternal behaviour (Fig. 3). Following a decrease in progesterone right before parturition, oestradiol and prolactin bind to receptors in the MPOA in the rostral hypothalamus (and the adjacent bed nucleus of stria terminalis (BNST)). This region is considered the initial hub for the onset of maternal behaviour. Among the different MPOA neuronal populations, optogenetic studies in mice highlight the role of MPOA galanin-expressing neurons in the control of parental behaviour [39].

Upon binding to specific MPOA receptors, oestradiol and prolactin activate cytoplasmic kinase cascades and genomic signalling pathways, which produce functionally active and pup-responsive MPOA neurons [5]. Cytoplasmic and genomic mechanisms result in two types of brain plasticity: molecular and structural. Molecular plasticity includes increased neurotransmitters, neuromodulators and receptor levels, to modulate neural electrical activity. Structural plasticity affects neuronal morphology including changes in the soma size, 'dendritic' length and branching and 'spine' density (see the section 'Hormones and neuroplasticity' for a detailed review of the structural plasticity of the rodent maternal brain, including morphological and cellular plasticity). In parallel, oxytocin derived from the paraventricular hypothalamic nucleus reaches multiple regions of the maternal circuit, including the MPOA, mPFC, BNST, ventral tegmental area, nucleus accumbens, ventral pallidum, olfactory bulb and the amygdala [40]. In these brain regions, oxytocin enhances neural excitability through various mechanisms, including the reduction of presynaptic inhibitory inputs [41] and the increase of postsynaptic depolarization [42]. Together, these hormone-driven changes may enhance the functionality of the circuit so the new dam can respond effectively to pup signals. Of note, the current understanding of these hormonal-induced intracellular mechanisms primarily relies on studies conducted in virgin females or lactating dams [43–45]. The specific cytoplasmic, genomic and neural excitability pathways through which prolactin, oestradiol and oxytocin activate the maternal circuit during late pregnancy remain an active area of investigation.

The activation of MPOA neurons near parturition stimulates maternal behaviour through a dual pathway that modifies the valence and saliency of the pup stimuli, switching it from irrelevant or aversive to highly relevant and rewarding stimuli [5, 46] (Fig. 3). This on and off switch motivates and guides the behaviour of the dam. At the neural level, this involves the inhibition of a

defensive-avoidance neural circuit and the stimulation of a reward-motivational neural circuit. MPOA projections inhibit the defensive-avoidance circuit, which involves projections from the olfactory bulb to the medial amygdala, and thence to the periaqueductal grey via the anterior and ventromedial nuclei of the hypothalamus. Along with the inhibition of the defensive-avoidance circuits, the hormonal activation of MPOA mobilizes reward-motivational circuits by stimulating dopamine release from the ventral tegmental area to the nucleus accumbens. The action of dopamine on D1 receptors of the nucleus accumbens shell increases the responsiveness of ventral pallidum to the pup stimuli incoming from the basolateral and basomedial amygdala. Projections from the ventral pallidum to other basal ganglia and motor areas are key to eliciting maternal approach behaviours. Once the maternal circuit has been activated with late pregnancy and parturition hormones and maternal behaviour has been established, maternal behaviour is maintained and adapted through sensory-related inputs from the pups. Olfactory, tactile, suckling and visual pup-originated stimuli are first processed by the primary sensory cortices. The information is then integrated into the thalamus and association cortices such as the mPFC and incorporated into key nodes of the maternal circuit such as the MPOA and the amygdala (basolateral, basomedial and medial nucleus). This process feeds back into the circuit to maintain and adapt maternal behaviour to the needs of the pup through the postpartum period. Besides the crucial regions of the maternal circuit, other areas such as the hippocampus [47, 48] and the mPFC [49] impact maternal behaviour, modulating aspects involved with spatial learning and memory and aiding organization and cognitive flexibility to maternal care, respectively.

4.2 Maternal circuit activation in humans

Maternal circuits in humans not only share core regions of the rodent network but also include later-evolved components that are unique to humans. Functional magnetic resonance studies suggest that human maternal behaviour is governed by a highly conserved mammalian subcortical network, connected via multiple projections to later-evolving cortical networks involved in higher-order socio-affective functions [5, 50]. Similar to rodents, subcortical regions commonly activated in human mothers in response to their infant cues include the hypothalamus, the amygdala and dopaminergic reward regions such as the nucleus accumbens and the ventral tegmental area [50–52].This network may maintain aspects of parental behaviour highly conserved among mammals such as vigilance and reward towards the infant. Beyond subcortical networks, cortical regions also activate in human mothers who are exposed to infant-related stimuli [50–53]. These regions commonly include the anterior cingulate cortex, the insula, the mPFC and the temporoparietal junction [53]. These brain areas have been associated with key cognitive processes for parents such as empathy, mentalizing and emotion regulation [5, 50, 54].

Brain regions belonging to the maternal circuit in humans are rich in receptors for ‘pregnancy hormones’. Post-mortem studies have reported mRNA expression of oestrogen, prolactin and oxytocin receptors in the hypothalamus [55–61]. Beyond these regions, researchers have also reported mRNA expression of the oxytocin receptor in the amygdala and anterior cingulate cortex [55, 56]. This

reinforces the possibility that humans use similar hormonal pathways to rodents to facilitate maternal behaviour. In the next section, we discuss which hormonally induced neuroplasticity processes found in rodents could underlie the neuroanatomical changes observed in humans.

5 Hormones and neuroplasticity

Hormonal-mediated plasticity in the rodent maternal brain involves changes on multiple scales, ranging from molecular to cellular and morphological changes (Table 1). The latter two are referred to as structural plasticity. Structural plasticity involves neural or glial morphological changes and larger-scale changes in the number of neuronal and glial brain cells. These include decreases in *neurogenesis* and reduced proliferation of *microglia*, as well as increases in myelin production and repair. Here, we focus on structural brain plasticity changes affecting the morphology and number of brain cells (Table 1), as this form of plasticity is more likely to impact neuroanatomy than changes at a molecular level. We mainly discuss findings from rat studies as these are the best-studied rodents to understand the structural plasticity of the maternal brain (for a comprehensive review of all neuroplasticity processes described in the rodent maternal brain, including mice, see refs. [48, 62, 63]).

5.1 Hormonal-mediated neural plasticity

Maternal rats, also known as dams, display changes in the production of functional neurons (that is, neurogenesis) and neuronal morphology in crucial regions of the maternal brain circuit. In the following paragraphs, we present these two cellular-level mechanisms in further detail.

5.1.1 Neurogenesis

The peripartum period of rats is accompanied by changes in neurogenesis within the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles [63]. Regarding the subventricular zone, robust evidence in mouse studies indicates that surges in prolactin during pregnancy promote neurogenesis in this region [64]. These neurons then migrate to the olfactory bulb, presumably facilitating the recognition of familiar odours and promoting maternal behaviour. The implications of hippocampal neurogenesis in maternal behaviour is not that well understood. However, in this section, we focus on the hippocampus because it is currently the only brain region in which neurogenesis has been confirmed in humans [65]. Future studies should examine the possibility of neurogenesis occurring in other sites during human pregnancy.

Studies indicate that, compared with nulliparous rats, hippocampal cell proliferation is reduced in dams across the transition to motherhood, including mid [66] and late pregnancy [67], early [68–70], mid [66, 69, 71] and late postpartum periods [70, 72] and weaning [73]. From the mid-postpartum period onwards, survival of hippocampal proliferating cells is also reduced [68, 69, 71].

In non-reproductive conditions, hippocampal neurogenesis is generally stimulated by oestradiol and inhibited by corticosterone [74, 75]. However, studies examining the hormonal correlates of neurogenesis during pregnancy found no association between neurogenesis and oestradiol levels [66, 76]. By contrast, reduced hippocampal neurogenesis during the postpartum period has been associated with the plummet of oestradiol levels [68] and the sustained corticosterone levels associated with lactation [66, 69, 70]. Thus, peripartum steroid hormonal fluctuations may inhibit neurogenesis in the hippocampus from mid-pregnancy to the late postpartum period in female rats.

5.1.2 Neuronal morphology

In rats, the maternal brain circuit, including subcortical (MPOA and supraoptic hypothalamic nuclei, hippocampus and nucleus accumbens) and cortical regions (mPFC and cingulate cortex), undergoes neuronal morphological changes in the soma size, dendritic length, branch number and *dendritic spine* number during pregnancy and the postpartum period. Compared with nulliparous rats, pregnant rats at late gestation display increased dendritic spine density on CA1 hippocampal neurons [77, 78] and decreased dendritic complexity (fewer intersections) of CA3 hippocampal neurons [79]. Pregnant rats also exhibit increased soma size, dendritic length and dendritic branches within MPOA neurons, which return to a basal state in the early postpartum period [80]. During the early-to-mid postpartum period, female rats display increased dendritic spine density within the hippocampus [77, 78, 81], the nucleus accumbens [82], the mPFC [83, 84], and the cingulate cortex [81]. Dendritic length and arborization have also been found to increase in the MPOA [85], the nucleus accumbens [82, 85] and the mPFC [83] and decrease in the caudate [85] and the hypothalamic supraoptic nucleus [86] during early postpartum and mid-postpartum periods. mPFC spine density remains increased during the late postpartum period [83] and around weaning [87] but decreases thereafter [84]. In the hippocampus, spine density appears unaltered in the late postpartum period [81] and after weaning [88], although other studies report increased hippocampal spine density around weaning [87] and thereafter [78]. At weaning, mPFC dendritic length and branching normalize [87], whereas these measures decrease in the hippocampus [88].

Late pregnancy steroid hormones seem to have an essential role in some of these morphological changes. The administration of a progesterone and oestradiol regime mimicking pregnancy not only facilitates maternal behaviour but also produces neuronal morphology changes similar to those observed in dams during the postpartum period: dendritic spine density increases in the hippocampus [77] and dendritic length, branching and soma size expand in the MPOA [80]. After weaning, neither oestradiol nor corticosterone correlates with the hippocampal dendritic branching [88]. Importantly, throughout pregnancy, oestradiol and progesterone facilitate the gradual formation of perineural nets in the MPOA [89]. These extracellular proteins surround neurons and, during neuroplasticity phases, stabilize neural connections. Thus, pregnancy steroid hormones may activate dendritic growth and consolidate neural circuits in the maternal brain circuit during late pregnancy in female rodents.

5.2 Hormonal-mediated glial plasticity

Brain plasticity in the maternal brain is not limited to neurons. Modifications in glial cells including microglia, *oligodendrocytes* and *astrocytes* have also been documented. We provide an overview of the main mechanisms in which glial cells have been found to yield structural brain changes in female rats in the peripartum period. These mechanisms include reduced microglial proliferation, increased myelination and astrocyte remodelling.

5.2.1 Microglia changes

The transition to motherhood appears to alter the resident innate immune cells of the brain, microglia. Microglia act as macrophages to eliminate microorganisms, cellular debris and dead neurons and are the primary source of cytokine secretion in the brain, hence facilitating neuroinflammatory processes [90]. In addition, microglia are important in sculpting neuronal networks by dynamically modulating synaptic plasticity [90–94]. Compared with virgin rats, pregnant rats show lower density of microglial cells during late gestation (gestational day 20) and the early postpartum period (postpartum days 1 and 8), a trend that reverses at weaning[95]. These microglial decreases specifically affect maternal circuits, including the hippocampus, the nucleus accumbens, the amygdala and the mPFC.

There is no direct evidence to date linking pregnancy hormones to microglial reduction. Yet, microglial cells have receptors for pregnancy-related hormones whose levels reach peak at different stages of late pregnancy, such as glucocorticoids [96], oestrogen [96], progesterone [97] and oxytocin [98]. These hormones have been found to attenuate microglial-induced neuroinflammation [99–102] and suppress microglial proliferation to protect neurons from prolonged neuroinflammation [103–105]. Thus, these hormones may underlie the downregulation of microglial numbers observed during pregnancy and the postpartum period. Notably, the reduction in the number of microglia is due to reduced microglial proliferation and is specific to the ramified microglia95 that typically survey the environment for debris or pathogens [106]. This suggests that neuroimmune surveillance may be diminished during the peripartum period. Indeed, neuroimmune responses to immune challenges are suppressed in the maternal brain, especially in the peripartum period [107]. These findings suggest that, at least in rodents, pregnancy-related hormones may contribute to microglial adaptations during pregnancy.

5.2.2 Myelination

Rat studies report pregnancy-related changes in oligodendrocytes, a type of brain cell responsible for the myelination of neuronal axons. Specifically, oligodendrocyte progenitor cells accelerate their proliferation and the number of mature oligodendrocytes across pregnancy [108, 109] and lactation [110]. As a result, the number of myelinated axons rises [108], suggesting an enhanced capacity for myelination in the rodent maternal brain. Pregnancy also induces boosted re-myelination or myelin repair after a white matter insult in rats [108]. These pro-myelination processes associated with

pregnancy are, at least in part, due to an enhanced GABAergic tone induced by progesterone [108]. The hormone prolactin has also been shown to promote oligodendrocyte production during pregnancy in mice, leading to increased myelination in the rodent maternal brain [111], but this has not been investigated in rat models. Thus, pregnancy hormones may confer increased myelination capacity in female rodents.

5.2.3 Astrocytic remodelling

Finally, the transition to motherhood in rats also entails morphological changes in astrocytes, glial cells that regulate synaptic function. These changes occur in brain regions such as the cingulate cortex and hypothalamic regions. In rats, the cingulate cortex [112–114] and MPOA [112, 113] display increases in markers of astrocytic morphology such as the glia-activating basic fibroblast growth factor (bFGF) and the astrocyte cytoskeleton glial fibrillary acidic protein from late pregnancy through lactation. Studies suggest that steroid hormones and maternal experience interact to induce astrocytic plasticity in the cingulate cortex. Specifically, a regimen of progesterone and oestradiol mimicking pregnancy and 3 h of maternal experience produced a similar profile of astrocytic changes in the cingulate cortex of virgin rats [115].

Astrocytic morphological changes also occur within another hypothalamic nucleus: the supraoptic nucleus. Under basal conditions, oxytocin-expressing neurons in the hypothalamic supraoptic nucleus are highly packed but remain separated by astrocytic processes. Around parturition, astrocytic coverage in the oxytocin-expressing cells of the supraoptic nucleus of the hypothalamus is significantly reduced in rats, resulting in direct contact between cell bodies and *dendrites* [116]. Such astrocytic retraction is thought to upregulate oxytocin secretion during this period [117]. Thus, rat studies suggest that pregnancy hormones regulate synaptic transmission in key nodes of the maternal circuit through astrocytic plasticity.

Overall, rodent studies provide evidence that pregnancy-related hormonal fluctuations slow down neurogenesis, activate dendritic growth, alter brain immune function, promote myelination and regulate synaptic transmission through plasticity processes that affect both neurons and glial cells. These processes are especially prominent during the late stages of pregnancy, contributing to reshaping the brain of mothers through the postpartum period.

6 Neuroplasticity observed by MRI

Previous sections have reviewed ex vivo histology studies that analyse cellular and morphological markers of brain plasticity. However, in vivo neuroanatomical measures using MRI can also shed light on neuroplasticity processes at a macroscopic level [118]. Unfortunately, MRI studies have rarely established associations with pregnancy hormones.

In pregnant rats, MRI has only been applied using diffusion-based MRI, which captures the microstructural arrangement of the brain by measuring the diffusion properties of water within tissues. In particular, one longitudinal study found increased grey matter and white matter diffusion in late pregnant rats, suggesting that the brain tissue microstructure became more permeable to diffusion movements of water molecules during pregnancy [119]. Additionally, in mice, a longitudinal MRI study with 12 dams revealed transient grey matter increases during the postpartum period in multiple maternal brain regions including MPOA, BNST, paraventricular hypothalamic nucleus, caudate, putamen, amygdala, insula and hippocampus [120]. A few of these grey matter increases started at late gestation, including those in MPOA, BNST and the insula, which contrasts with the general decreasing trend observed in humans [120] (see the section 'Neuroanatomical changes in mothers'). This inconsistency may arise from variations in the specific brain regions investigated (subcortical versus cortical) and disparities in the imaging acquisition parameters and processing pipelines. Also, human neuroimaging studies have mainly included whole-brain analyses, which could mask trends specific to certain regions. Finally, the slight differences in the hormonal milieu of the peripartum period, as well as differences in maternal demands, should also be taken into account when aiming to translate rodent findings to humans. To date, further research is needed to establish whether pregnancy-induced grey matter changes in rodents resemble those observed in humans.

In humans, the dynamic grey matter volume trajectories during the transition to motherhood are accompanied by hormonal shifts mothers experience before and after parturition (Fig. 2). Grey matter volume reductions are thought to occur during pregnancy when prolactin and steroid hormones (progesterone, oestradiol and cortisol) are steadily increasing. By contrast, postpartum grey matter volume increases coincide with the plummet in steroid hormones and with oxytocin and prolactin pulses related to lactation and mother-to-infant contact. This timeline supports the hypothesis that hormones may be directly or indirectly linked to changes in the structure of the human brain. Although we count on evidence that pregnancy hormones reach the brain (Box 3), how they influence pregnancy-related neuroplasticity and maternal behaviour is not well understood.

In the next section, we discuss how this relationship may be based on the evidence reviewed in previous sections and propose directions for future research. Specifically, we discuss potential pathways in which pregnancy-related hormones may orchestrate neuroplasticity changes that facilitate maternal behaviour in humans.

7 Future directions

In the previous sections, we provided an overview of human and rodent studies relevant to the question of how the endocrine system stimulates neuroplasticity to initiate and sustain maternal behaviour. We focused on hormones as the main elicitors of maternal neuroplasticity and adopted a multiscale perspective by describing neuroplasticity from molecular processes to entire brain tissues. In this last section, we discuss which neuroplasticity processes are likely to contribute to the neuroanatomical

changes detected in humans with MRI and how they may relate to pregnancy hormones and maternal behaviour. We also outline current limitations in human studies and propose future research questions within the maternal brain field.

7.1 Underpinning cellular mechanisms

Given the standard MRI resolution, it is unlikely that the large-scale grey matter volume changes observed in humans are produced by neuroplasticity exclusively at the morphological and molecular levels. Instead, larger changes affecting the proliferation of brain cells are likely to be the main contributors to volumetric changes. Because the neuroanatomical changes detected in human mothers are dynamic (that is, decreased grey matter during pregnancy and increased grey matter during the postpartum period), brain cells that regenerate slowly, such as neurons, are unlikely to support these changes. Besides, human adult neurogenesis has only been observed within the hippocampus [64, 121]. A more likely candidate is microglia, which exhibits a much higher regeneration rate across the brain [122, 123]. Although microglial changes occurring in key maternal brain circuits in rats have been found to follow a similar dynamic trajectory to grey matter changes observed in humans [96], future studies should address the role of microglia in pregnancy-related neuroanatomical changes in humans. Notably, alterations in myo-inositol levels, a widely used glial marker, have been detected during and after pregnancy [7, 124]. However, the precise direction and temporal patterns of these metabolite changes require further investigation in the light of conflicting results. For instance, Hoekzema et al. [7] report an increase in myo-inositol levels from pre-conception to the early postpartum period, whereas Nelander et al. [124] indicate decreased myo-inositol levels during late pregnancy. A higher sampling rate of MRI data across the motherhood transition, including MRI sessions during pregnancy, will help to delineate the grey matter trajectories more accurately and identify a specific turning point. Also, future studies should apply MRI markers optimized to target microglia activity or proliferation to help confirm the contribution of microglia to grey matter changes during pregnancy. In addition, as microglia is an immune-competent cell, it would be interesting to study glial markers along with peripheral and central markers of immune activity and monitor pregnancies that have atypical immune environments, such as multiple sclerosis and pregnancies through egg donation. If the dynamics of these markers are associated with the evolution of grey matter changes across pregnancy and the postpartum period, we could have indirect evidence of immune contribution to these changes. Beyond changes in microglia, myelination has been also proposed to induce apparent decreases in grey matter by misclassifying voxels at tissue interfaces as white matter. However, in humans, the few studies that examined pregnancy-induced white matter changes did not find a significant effect [6, 7]. Besides, although cross-sectional studies indicate no differences in cerebral perfusion between pregnant and non-pregnant women [125], longitudinal studies are required to rule out the potential contribution of the pronounced vascular adaptations that accompany pregnancy on MRI changes.

7.2 Role of the hormonal system

The hormonal fluctuations accompanying motherhood, which exceed the levels of any other period of the life of a woman, are expected to have a primary role in the induction of pregnancy-related neuroplasticity. In humans, however, few studies have reconciled neuroanatomical changes with the hormonal climate of this life stage. Recently, Hoekzema et al. [7] have studied how oestradiol, oestriol, progesterone and cortisol relate to the structural brain reorganization observed in first-time mothers. In this study, only late pregnancy oestradiol levels were found to be positively associated with the reductions in grey matter volume observed across pregnancy [7], suggesting that this steroid hormone contributes to the structural brain reorganization occurring in humans. It is unknown, however, whether other untested hormones or specific hormonal ratios may also contribute to the observed structural changes in the maternal brain. Given the interactive nature of hormones, it is likely that the neuroanatomical changes do not rely on discrete hormonal effects but on the complex interplay between multiple steroid and peptide hormones. The hormonal milieu during pregnancy and the postpartum period is substantially more complex than the presence of a handful of active hormones. As previously stated, this environment is dynamic during pregnancy and the early postpartum period (Fig. 2). Additionally, the unique hormonal and enzymatic placental composition causes a substantial alteration of the active components present in the circulation of the mother. These alterations include variations in the hormone levels, the equilibrium between different hormones and metabolites and even the generation of hormone-related metabolites exclusive of pregnancy, such as oestriol and human placental lactogen. For instance, although not yet linked to neuroplasticity in the maternal brain, oestriol and human placental lactogen levels heavily increase during pregnancy [17, 18, 126] and can act through the same receptors as oestradiol [127] and prolactin [128]. Hence, the shifts observed in the human brain during pregnancy may result from a dynamic cocktail of hormones and metabolites. To better understand how this complex milieu contributes to the observed brain changes, future studies should evaluate a higher number of hormones and metabolites along with MRI data at different time points of the motherhood transition. Furthermore, owing to the invasive nature of measuring hormonal changes within the brain, human research relies on peripheral hormonal levels to explain the potential link between hormonal fluctuations and the observed brain changes. Hence, future research should better elucidate the relationship between peripheral and central hormonal changes in human and non-human species, especially for pivotal pregnancy neuropeptides such as oxytocin and prolactin. At a cellular and molecular level, rodent studies indicate that steroid and peptide hormones (including oestradiol, progesterone, glucocorticoids, prolactin and oxytocin) trigger and regulate neuroplasticity across the transition to motherhood (see Table 1 and the section 'Hormonal-mediated neural plasticity'). These include the synthesis of neurotransmitters and their receptors, neuronal morphology, neurogenesis and myelination. Concerning fluctuations in the number of microglia, they could result from the combined effects of glucocorticoids and oestradiol levels in late pregnancy and oxytocin levels in the early postpartum period.

7.3 Link with maternal behaviour

Structural brain changes — probably supported by cellular-level neuroplasticity processes — may only affect maternal behaviour indirectly. Instead, neuroplasticity changes affecting the activity and morphology of neurons may have a more direct relationship with maternal behaviour. In rodent studies, the molecular and morphometric neuroplasticity events that accompany the emergence of maternal care have been related to fine-tuning the connectivity and excitability of the neural circuitry controlling maternal care. In turn, cellular plasticity might be collaterally related to maternal behaviour by ensuring that the molecular and morphological changes occur optimally, thus securing the correct functioning of the maternal circuit. In fact, depletion of microglia to mimic decreased microglial tone in late pregnancy and the early postpartum period facilitates maternal behaviour in virgin female rats [129]. Exactly how a reduction in microglia might be shaping the maternal neural circuitry is unknown. One plausible way is by creating a less inflammatory and more excitable environment that favours brain remodelling [130]. In humans, the associations between pregnancy-related neuroanatomical changes and different aspects of maternal behaviour (for example, quality of mother-to-infant attachment) are scarce and have sometimes failed to replicate [6, 7, 11, 14]. Future studies should evaluate how changes in different brain metrics (including functional, anatomical, diffusion or spectroscopic data) interact to facilitate human maternal behaviour. These studies will shed light into how structural brain modifications translate into functional adjustments and foster maternal behaviour. These investigations should actively contribute to the ongoing rebranding of motherhood, portraying it as a phase of constant brain adaptations, thereby dispelling outdated notions of the maternal brain being dysfunctional or inadequate [131, 132]. Regarding the metrics to infer maternal behaviour, we believe that metrics with higher ecological validity could benefit this research field. In humans, studies analysing the neuroanatomical changes associated with the transition to motherhood have inferred maternal behaviour indirectly through questionnaires. Although these can help us to understand the mother's subjective experience of motherhood, they are also affected by the 'social desirability bias', which can skew their interpretation. Future research should include measurements of maternal behaviour in more naturalistic settings, using paradigms such as the still face paradigm [133], strange situation [134] or free play [135]. This would allow us to better infer bond quality and associate brain changes with different components of maternal behaviour.

7.4 Contribution of extrinsic factors

Human maternal behaviour probably depends on the combination of intrinsic gestational factors and extrinsic postpartum factors. Extrinsic factors include not only continuous interaction with the infant, which can lead to experience-induced neuroplasticity, but also type of breastfeeding, sleep, stress, hydration, weight and nutrition. Extrinsic factors could shape maternal behaviour through subcellular neuroplasticity processes in maternal care circuits rather than through neuroanatomical changes. As parental care in humans is highly dependent on socio-cultural factors, studies that control for sex and

potential gender roles on child rearing are important to disentangle the contribution of gestational and childrearing factors. The addition of groups of non-gestational parents including same-sex partners or adoptive parents will capture the influence of extrinsic postpartum factors while also excluding potential influences of sex and gender.

8 Conclusions

In sum, we currently count on some evidence of the role of hormones in activating and regulating neuroplasticity processes during pregnancy and the postpartum period. However, more studies are needed to elucidate the types of neuroplasticity processes involved in the transition to motherhood in humans and how they affect maternal behaviour. A current frontier lies in how cellular and subcellular neuroplasticity that affect both neurons and glial cells shape human maternal behaviour. Future research should tackle these questions to shed light into how hormones and environmental factors trigger neural adjustments that support adaptive maternal behaviour in humans.

9 Display items

9.1 Tables

Table 1 | Neuroplasticity of the maternal brain in primiparous dam rats

Neuroplasticity process	Brain region (regions)	Pregnancy to postpartum periods						
		Early gestation (GD1–GD7)	Mid gestation (GD8–GD14)	Late gestation (GD15–GD21)	Early postpartum (PD1–PD7)	Mid postpartum (PD8–PD14)	Late postpartum (PD15–PD21)	Postweaning (>PD21)
Microglial proliferation	HCC, NA, BLA, mPFC	–	–	↓[95]	↓[95]	↓[95]	Ø[95]	–
	MCTX	–	–	Ø[95]	Ø[95]	–	–	Ø[95]
Neurogenesis (neuronal proliferation)	HCC	Ø[76,136] (¬E2[76])	↓ (¬E2)[66]	↓[67]; Ø[77,136–139]	↓ (*E2)[68]; ↓ (*Cort)[69,70]	↓[66,69,71] (*Cort[66,69])	↓[70]	↓[66,72,73]; Ø[69]
	DR	–	–	–	Ø (¬Cort)[140]	–	–	–
Neurogenesis (neuronal survival)	HCC	–	–	Ø[76,77,137,138] (¬E2[76])	–	↓[69]	Ø[69,70]	↓[68,71]
	DR	–	–	–	–	↑[140]	↓[140]	–
Myelination	CC	↑[109]	–	↑ (*P)[108]; Ø[109,110]	–	↑[110]; Ø[108]	–	–
Neuronal soma size	MPOA	–	–	↑ («P, E2)[80]	Ø («P, E2)[80]	–	–	–
Neuronal dendritic branching	HCC	–	–	$\downarrow_{CA3}$[79]; $Ø_{CA1}$[78,79]	–	$Ø_{CA1}$[78]	–	$\downarrow_{CA1/3}$ (¬E2 or Cort)[88]; $Ø_{CA1}$[78]
	MPOA	–	–	↑ («P, E2)[80]	Ø («P, E2)[80]	↑[85]	–	–
	SON	–	–	–	–	↓[86]	–	–
	NA	–	–	–	–	$\uparrow_{shell}$[85]	–	–
	CAUD	–	–	–	–	↓[85]	–	–
	mPFC	–	–	–	–	–	–	Ø[87]
	CG	–	–	Ø[81]	Ø[81]	–	↑[81]	–
Neuronal dendritic length	HCC	–	–	ØCA1[78]	–	ØCA1[78]	–	$\downarrow_{CA1/3}$[88]; $Ø_{CA1}$[78]
	MPOA	–	–	↑ («P, E2)[80]	Ø («P, E2)[80]	Ø[85]	–	–
	NA	–	–	–	–	$\uparrow_{core}$[82]; $Ø_{shell}$[82,85]	–	–
	CAUD	–	–	–	–	↓[85]	–	–
	mPFC	–	–	–	↑[83]	–	Ø[83]	Ø[87]
Neuronal spine density	HCC	–	–	$\uparrow_{CA1}$ («P, E2)[77,78]; $Ø_{CA1}$[81]	$\uparrow_{CA1}$ («P, E2)[77,81]	$\uparrow_{CA1}$[78]	$Ø_{CA1}$[81]	$Ø_{CA1}$[88]; $\uparrow_{CA1}$[78]; $\uparrow_{CA1/DG}$[87]
	NA	–	–	–	–	↑[82]	–	–
	mPFC	–	–	–	↑[83]	↑[84]	↑[83]	↑[87]; Ø[84]
	OFC	–	–	–	–	–	–	Ø[87]
	CG	–	–	Ø[81]	↑[81]	–	Ø[81]	–
Astrocytic processes	SON	–	–	↓ (*Oxt)[116]	–	–	–	–

Information in parentheses summarizes (where known) hormone findings related to given neuroplasticity processes and time periods. ↑, Increase in neuroplasticity process; ↓, decrease in neuroplasticity process; Ø, no neuroplasticity changes detected; *, association between hormone and neuroplasticity process; ¬, no association between hormone and neuroplasticity process; «, hormonal regimen-induced change in neuroplasticity process; –, no data; BLA, basolateral amygdala; CA1, CA1 hippocampal region; CA3, CA3 hippocampal region; CAUD, caudate; CG, cingulate cortex; core, core region of the NA; Cort, corticosterone; DG, dentate gyrus; DR, dorsal raphe nucleus; E2, oestradiol; GD, gestational day; HCC, hippocampus; MCTX, motor cortex; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; NA, nucleus accumbens; OFC, orbital frontal cortex; Oxt, oxytocin; P, progesterone; PD, postpartum day; shell, shell region of the NA; SON, supraoptic nucleus (hypothalamus). [136–140]

9.2 Figures

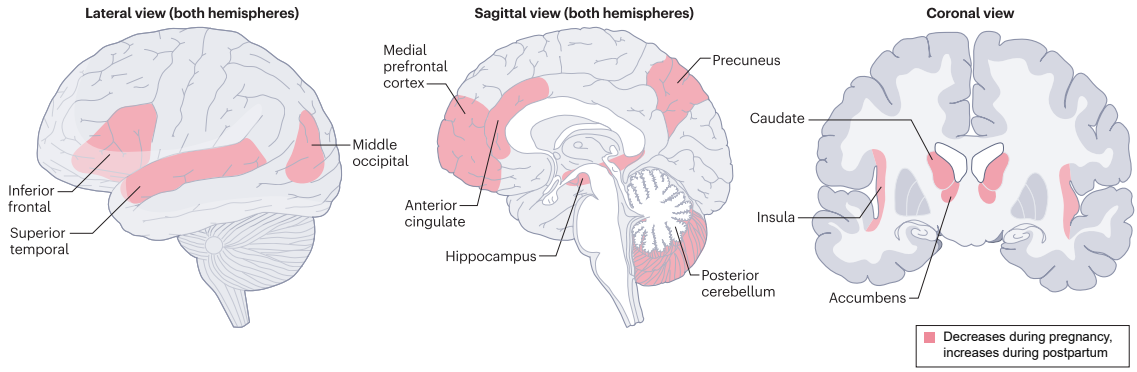

Fig. 1 Changes in grey matter volume during the transition to motherhood. Shaded areas represent brain regions whose grey matter volume has been reported to decrease during pregnancy [6, 7, 9] and to increase during the postpartum period [7, 11–13]. Of note, the figure only shows regions where concurrent decreases and increases have been documented, leaving out additional brain regions reported to decrease during pregnancy but not to increase during the postpartum period or vice versa.

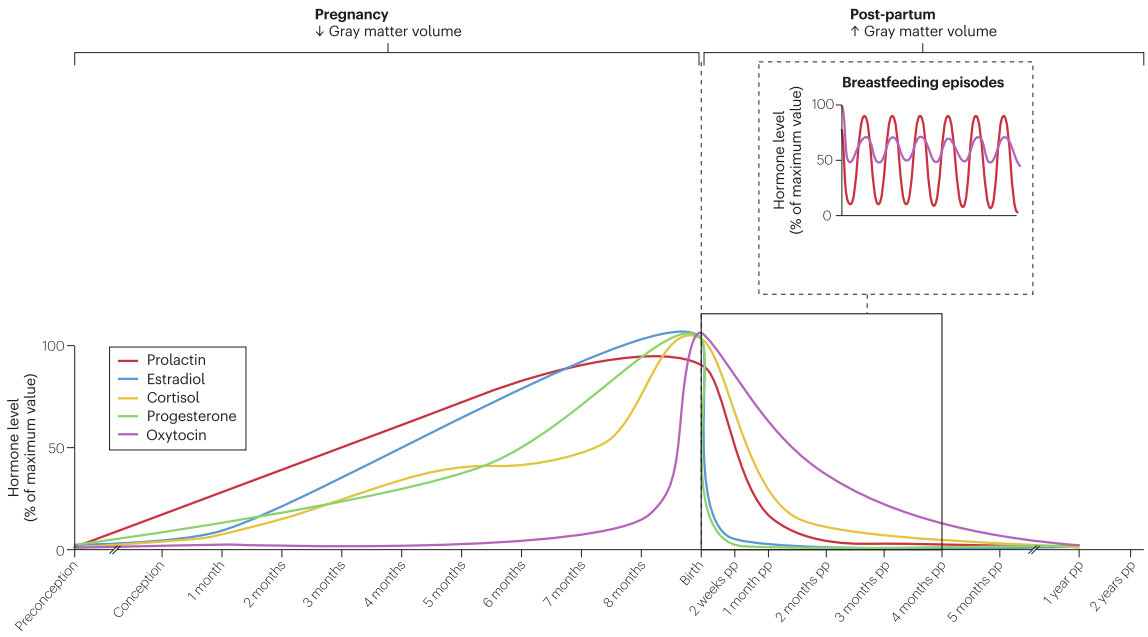

Fig. 2 Grey matter and hormonal trajectories across motherhood transition in humans. Top: structural changes in grey matter reported before and after pregnancy in MRI studies. The left side represents the general grey matter volume decrease observed during pregnancy [6, 7, 141]. The right side represents the general grey matter volume increase observed during the postpartum period [7, 11–13, 141]. Bottom: timeline showing idealized basal hormonal levels across pregnancy, birth and the postpartum period. The inset illustrates the prolactin and oxytocin fluctuations observed in response to suckling during breastfeeding, with each peak corresponding to a breastfeeding episode. These idealized trajectories were compiled from studies that measured hormones at multiple time points during pregnancy or the postpartum period [16, 20, 21, 142–147]. Preconception hormonal levels are based on reference values for non-pregnant women. pp, Postpartum; ↑, increases in grey matter; ↓, decreases in grey matter.

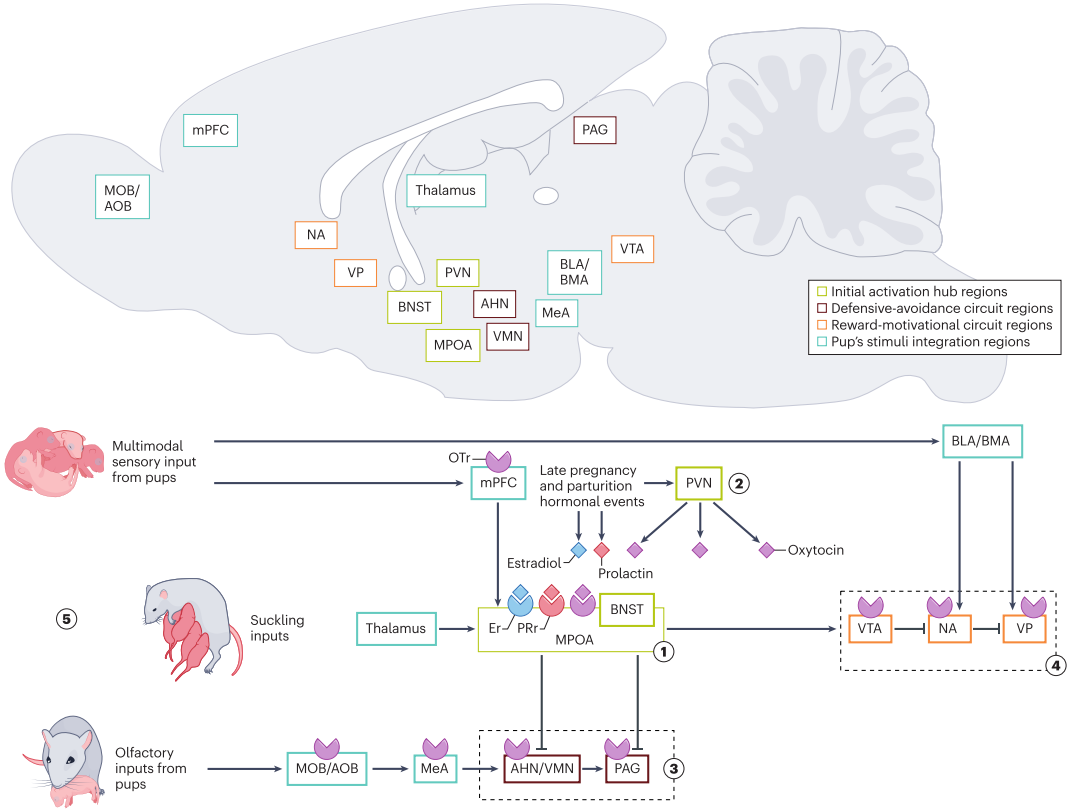

Fig. 3 Maternal circuit in rodents.Maternal circuit in rodents. Top: sagittal section of rodent brain showing the main regions comprising the maternal circuit. Regions acting as the initial hub for the circuit are depicted in green. Regions of the reward motivational and defensive-avoidance subcircuits are depicted in orange and maroon, respectively. Regions that receive sensory inputs from the pups are depicted in blue. Bottom: scheme of the rodent maternal circuit including the brain regions of the top figure, and the receptors for and activated by late pregnancy and parturition hormones: oestradiol (blue), prolactin (red) and oxytocin (purple). The activation of the circuit comprises the following actions: (1) before parturition, oestradiol and prolactin bind to receptors in the MPOA and the adjacent BNST, considered the initial hubs for the onset of maternal behaviour; (2) oxytocin derived from the PVN reaches and enhances neural excitability of multiple regions of the circuit; (3) MPOA-activated neurons inhibit the defensive-avoidance subcircuit, which is guided by olfactory inputs from the pups; (4) MPOA-activated neurons also activate the reward-motivational subcircuit, releasing the VP from inhibition from the NA and thus increasing its responsiveness to pup stimuli; (5) then, sensory inputs from pups received by the thalamus, medial prefrontal cortex and amygdala maintain and adapt maternal behaviour during the postpartum period. These numbers are intended to guide the reader through the figure and do not imply that the activation of the circuit follows this specific order. Activations and inhibitions may overlap in time. Of note, oestrogen–prolactin receptors are also expressed in other brain regions besides the MPOA (not shown). AHN/VMN, anterior–ventromedial hypothalamic nucleus; BLA/BMA, basolateral–basomedial amygdala; BNST, bed nucleus of the stria terminalis; Er, oestrogen receptor; MeA, medial amygdala; MOB/AOB, medial–anterior olfactory bulb; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; NA, nucleus accumbens; PAG, periaqueductal grey; PRr, prolactin receptor; PVN, paraventricular nucleus; VP, ventral pallidum; VTA, ventral tegmental area; OTr, oxytocin receptor.

9.3 Boxes

Box 1. Maternal behaviour

Maternal behaviour is defined as the collection of behaviours displayed by the mother with the ultimate goal of increasing offspring survival and well-being [5]. Multiple factors can modulate maternal care in placental mammals, including species-specific conditions such as the level of maturity of the young at birth, litter size or environmental variables related to food shortages or predation. In rodents, maternal care has been operationalized as a set of observable behaviours, including nest building, pup grooming and licking, retrieving all pups to the nest, lactation and nursing [148]. In humans, however, the influence of cultural factors makes maternal behaviour more challenging to operationalize. Hence, researchers in this field commonly turn to mother-to-infant relationship metrics as an indicator of maternal care.

Human maternal behaviour can be quantified through self-reported questionnaires [149, 150], which provide information about specific emotions of the mother with her infant. These include how much pleasure they experience when interacting with their infant, how competent they feel in understanding or meeting the needs of the infant or how well they accept and tolerate the demands of motherhood [149, 150]. Because these measures rely on self-report, they assess the subjective experience of mothers and are subjected to a 'social desirability bias'.

Another way of characterizing human maternal care is through behavioural and observational paradigms (for example, videotaped free play [135], still face paradigm [133] and 'strange situation' [134]). In free play [135] paradigms, researchers describe the behaviour of mothers as they freely interact with their infant and assess the main components of maternal behaviour, including expressions of positive emotions, gaze direction towards the infant, high-pitched vocalizations and displays of affectionate touch [135]. Conversely, the still face paradigm [133] and the strange situation [134] focus on the affective response of an infant to maternal unavailability and the attachment style of an infant as an indirect measure of maternal behaviour. The expression of an infant of positive affect and secure attachment have been associated with appropriate and consistent maternal responses to the needs of an infant.

Box 2. Hormonal timeline across pregnancy

The hormonal fluctuations observed during pregnancy far exceed those of any other period in the life of a human. The primary driver of such intense hormonal dynamics is the placenta, which secretes numerous hormones to prepare the maternal body for gestation, labour and

lactation [128]. Here, we briefly describe the hormonal timeline of five hormones critical for maternal neuroplasticity: progesterone, oestradiol, cortisol, prolactin and oxytocin.

Hormonal changes during gestation

During early pregnancy, chorionic gonadotropin sustains progesterone synthesis in *corpus luteum* cells, which is essential for the early maintenance of pregnancy [17]. At 6–8 weeks of gestation, however, the placenta becomes the principal source of progesterone production [151–154]. Around the same time, the placenta starts synthesizing oestradiol [155], and circulating levels of these steroid hormones rise progressively throughout pregnancy and peak before parturition [15]. Lactotroph cells also increase during pregnancy [156], resulting in a steady rise in prolactin secretion until parturition and a fivefold change in its abundance across gestation. [18, 19, 156]. Moreover, cortisol levels increase around mid-gestation mainly owing to a positive feedback mechanism with placental corticotropin-releasing hormone, which also increases over gestation [157, 158]. Cortisol levels peak before delivery at levels two to four times higher than those observed during the non-pregnant state [16].

Hormonal changes during parturition

Unlike most mammalian species, human progesterone levels do not plummet before parturition. Evidence suggests that its pregnancy-maintaining action may get withdrawn, contributing to the onset of labour [159, 160]. During parturition, oxytocin levels experience a threefold to fourfold increase relative to before parturition and a sixfold to eightfold increase compared with basal levels in non-pregnant women [20]. Along with oestrogen-mediated upregulation of oxytocin uterine receptors, this stimulates uterine contractions [161, 162]. Of note, other hormones (for example, relaxin, prostaglandins and corticotropin-releasing hormone) act in parallel to promote labour [17].

Hormonal changes during the postpartum period

After parturition, all placental-derived hormones plummet in the maternal circulatory system, including progesterone, oestradiol and placental corticotropin-releasing hormone. Cortisol levels decrease to pre-pregnancy levels during the first month of the postpartum period [16]. Oxytocin and prolactin levels also fall gradually over the first months of the postpartum period but are tightly linked to breastfeeding [21]. Contact of mothers with their infants also modulates oxytocin synthesis during the postpartum period [163].

Box 3. How hormones reach the brain

The brain is an endocrine organ with a dual role as both a producer and a target of hormones [164]. The mechanisms to reach or exit the brain, however, depend on the type of hormone.

Steroid hormones

Steroid hormones, including oestradiol, progesterone and cortisol, are mainly synthesized in peripheral organs. Owing to their lipophilic composition, they readily cross the blood–brain barrier and reach their target cells in the central nervous system by diffusion, a passive and non-saturable mechanism [165]. Importantly, steroid hormones, such as allopregnanolone, can also be synthesized de novo in the brain by glial cells and neurons [39, 166–168].

Peptide hormones Prolactin is mainly synthesized in the anterior pituitary gland, from where it is released into the peripheral circulation. Hence, to act as a neuropeptide, it has to re-enter the brain. It was first suggestedbthat blood-borne prolactin might be transported into the brain via the prolactin receptors in the choroid plexus [169]. However, in genetically modified mice that lack the prolactin receptor, prolactin can still access the brain [170]. This evidence has led to the current hypothesis that transport occurs at the cerebrovascular level via an unidentified transporter molecule. Oxytocin is synthesized by magnocellular and parvocellular hypothalamic neurons. Through magnocellular collateral axons, oxytocin reaches numerous forebrain regions [40, 171]. Through projections of parvocellular neurons, it reaches the spinal cord and cerebellum. In addition, oxytocin diffuses to other nearby or remote brain regions through extracellular spaces [172, 173]. Alternatively, oxytocin acts as an endocrine hormone after being released into the blood via the magnocellular nerve endings in the posterior pituitary [172, 173]. Once in the periphery, it has been recently suggested that circulating oxytocin can be transported back into the brain by the receptor for advanced glycation end-products on brain capillary endothelial cells [174]. However, it is still unclear the extent to which circulating oxytocin levels in the bloodstream can affect the brain.

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Author contributions

O.V., C.S.-B., M.M.-G., A.S., O.J.P., S.C. and O.K. researched data for the article. O.V., C.S.-B., M.M.-G., C.P., M.P.-P. and S.C. made substantial contributions to discussion of content. The article was written by O.V., C.S.-B., M.M.-G., C.P., A.S., O.J.P., S.C. and O.K. O.V., C.S.-B., M.M.-G., C.P., M.P.-P., S.C and B.L. reviewed and edited the manuscript before submission.

Competing interests

The authors declare no competing financial interests.

Glossary

Astrocytes

Most abundant glial cells that participate in the maintenance of ionic and chemical homeostasis of the synaptic cleft, are involved in the response to injury and affect neuronal development and plasticity.

Corpus luteum

A transient endocrine gland that forms in an ovary by residual follicular wall cells following ovulation.

Corticosterone

Main glucocorticoid in several species including rodents. In humans, the main glucocorticoid is cortisol. Thus, corticosterone effects in rodents are commonly associated with cortisol effects in humans.

Dendrites

Branched extensions of neurons that serve as the entry site of synaptic inputs into neurons. They can be pruned, lengthened and branched out as necessary to refine synaptic function.

Dendritic spine

Small membranous protrusion from the dendrite of a neuron that receives a synaptic input from axons, constantly forming and disappearing in response to neuronal activity.

Microglia

Macrophage-like glial cells that are involved in immune responses, as well as in surveying the development and remodelling of the nervous system.

Neurogenesis

Multistage process consisting of neural stem cell proliferation, differentiation into neuronal cell types, migration to target regions, maturation and integration within specific neural circuits.

Nulliparous

A woman who has never given birth.

Oligodendrocytes

Glial cells that produce the myelin sheath that insulates neuronal axons, enhancing the speed of the signal conduction.

Parturition

Action of giving birth to offspring; childbirth.

Peripartum

The period shortly before, during and immediately after giving birth.

Postpartum period

Period starting after parturition and lasting up to 6 months.

Pregnancy hormones

Hormones that significantly fluctuate during pregnancy.

Weeks of gestation

The time between the beginning of the last menstrual period and birth.

Additional information

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