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The hormonal and neural control of maternal aggression

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In mice and many other species, aggression levels are low in virgin females but increase dramatically during lactation to protect vulnerable offspring. This aggression, aimed at protecting the young, is known as maternal aggression. It emerges abruptly after parturition, peaks during early lactation, and declines after weaning. Given its stereotyped temporal profile, hormones associated with pregnancy and lactation are believed to play critical roles in its rise and fall. In addition, maternal aggression diminishes within hours of pup separation and rapidly recovers upon pup reunion, indicating a secondary, pup-dependent regulation of its expression. Here, we review current knowledge of the female aggression circuit and the hormonal and neural mechanisms that reshape it during pregnancy and lactation. We propose a two-step model in which pregnancy-associated sex hormone surges refine the aggression circuit, while lactation-associated neuropeptide signals gate circuit output in response to the need to protect offspring.

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Introduction

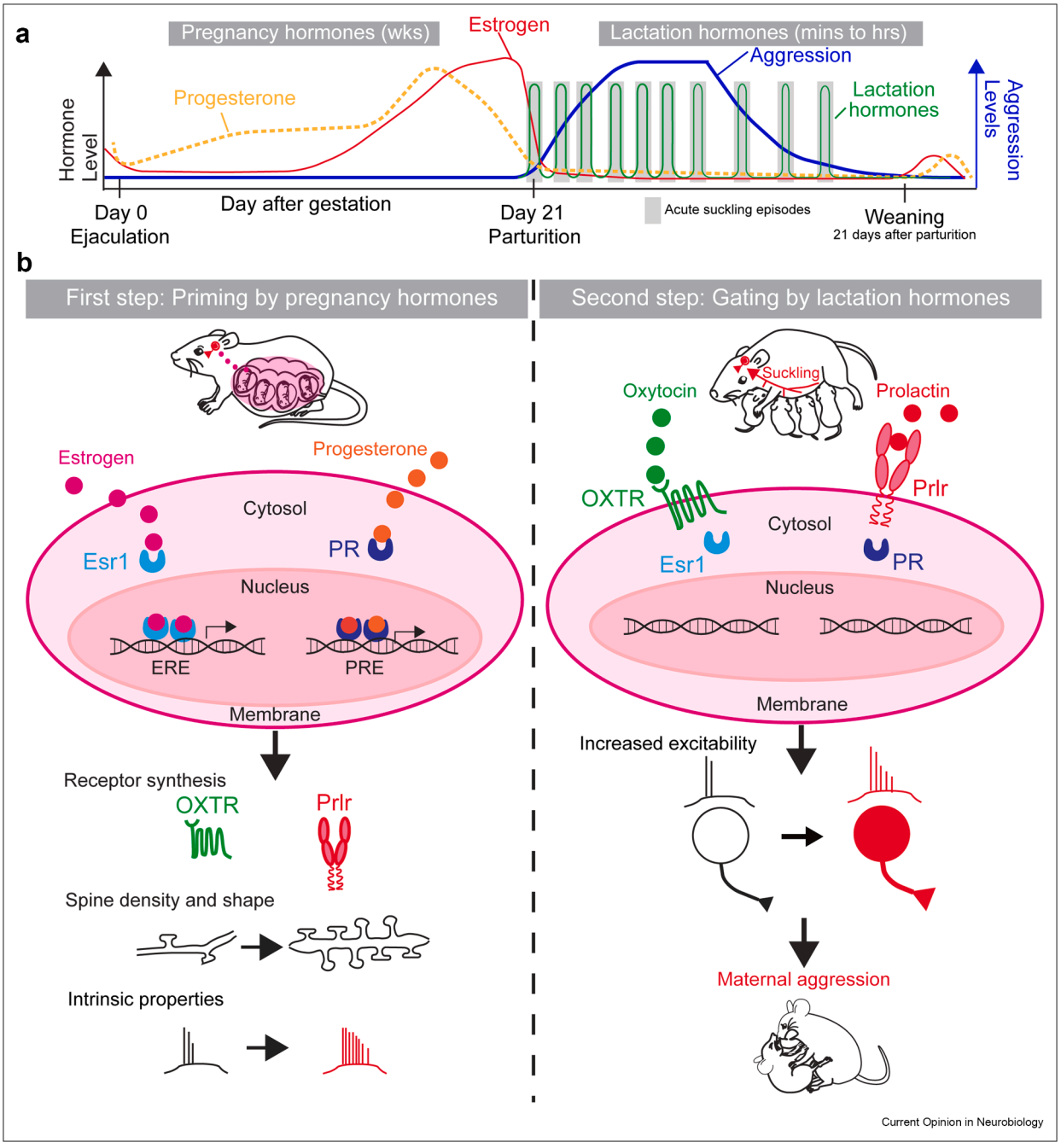
Newborn animals are vulnerable and defenseless. To ensure their survival, females in mammalian species, including mice and humans, undergo drastic behavioral changes during pregnancy and motherhood. While virgin females mainly focus on their own needs and survival, lactating mothers prioritize the care and well-being of their offspring [1,2]. They display various maternal behaviors, providing the offspring with nutrition, warmth, and sanitary care. Additionally, aggression levels in females increase dramatically during lactation to protect offspring from potential infanticidal intruders, known as maternal aggression [3–5]. Similar to maternal care, maternal aggression increases the offspring's chance of survival. While many brain regions implicated in male aggression also modulate female aggression, the female aggression circuit undergoes pronounced reproductive-state-dependent changes, with activity markedly increasing during lactation. In this review, we will discuss recent advances regarding the female aggression circuit and our current understanding of the hormonal and neural changes that support the changes in female aggression during motherhood. Although females in non-mammals could also aggressively protect their young [6,7], this review will focus on studies in mammals, especially mice.

The rise and fall of female aggression during lactation

In rodents, females consistently show increased aggression during lactation, although aggression levels during the non-lactating period vary across species [5,8]. In laboratory mice, virgin females rarely attack unfamiliar conspecific intruders, whereas mothers readily attack intruders within a few hours after giving birth. Mice and rats show similar trajectories of female aggression during lactation, with the highest levels occurring during the first postpartum week, declining in the second week, and disappearing after weaning (Figure 1a) [3,5,8].

In contrast to maternal aggression in mice, maternal care behaviors emerge later in pregnancy and typically persist after weaning [9,10]. In virgin females, repeated exposure to pups can also induce all aspects of pup caring behaviors, including retrieving, grooming, and crouching over pups, while the same "pup sensitization" protocol fails to induce aggression towards conspecific intruders [11]. These behavioral observations suggest that hormonal and neural changes that trigger maternal care and maternal aggression are likely different.

Figure 1



A two-step hormonal control supporting the rise of female aggression during motherhood.
(a) In mice, estrogen (red) and progesterone (orange) levels rise over the course of pregnancy and decline sharply before parturition, whereas lactation-associated hormones driven by pup suckling fluctuate on timescales of minutes to hours during lactation. Female aggression (blue) emerges after parturition, peaks during early lactation, and gradually declines as pups approach weaning.
(b) In the first step, pregnancy-associated surges of sex hormones remodel the female aggression circuit by altering gene expression, neuronal morphology, synaptic connectivity, and electrophysiological properties. In the second step, pup suckling–induced release of oxytocin and prolactin transiently boosts circuit output, enabling the expression of maternal aggression.
Esr1, estrogen receptor alpha; ERE, estrogen response elements; OXTR, oxytocin receptor; PR, progesterone receptor; PRE, progesterone response elements; Prlr, prolactin receptor.

Hormone changes essential for the emergence of maternal aggression

Unlike inter-male aggression, the emergence of maternal aggression does not require prior fighting experience or intruder exposure [12]. Instead, it appears to arise "automatically" within hours after parturition, implicating pregnancy-associated hormonal changes in priming the aggression circuit. In mice, progesterone levels increase from early pregnancy, peak around gestational day 16, and decline rapidly before parturition, whereas estrogen levels remain low during the first two-thirds of pregnancy and then rise sharply before parturition, followed by a rapid decrease (Figure 1a) [13,14]. However, in virgin females, estrogen and progesterone regimens that mimic pregnancy fail to induce aggression [15]. Moreover, administration of estrogen and progesterone in lactating females either inhibits or has no effect on maternal aggression [5,16]. Together, these findings indicate that pregnancy-associated sex hormones alone are insufficient to activate the female aggression circuit.

Because maternal aggression does not emerge until several hours after birth, pup-related stimuli are likely essential for its initiation. Consistent with this idea, removal of pups immediately after parturition prevents the emergence of maternal aggression [17]. Moreover, blocking suckling by removing nipples before lactation disrupts the initiation of maternal aggression, whereas nipple removal during late lactation accelerates its decline [15,18]. Similarly, separating lactating females from their pups for 5 h markedly reduces aggression, an effect that is fully reversed within 10 min of pup reunion [19,20]. Together, these findings indicate that the presence of pups—particularly their ability to suckle—is critical for the expression and maintenance of high levels of maternal aggression. How does suckling stimulation promote maternal aggression? The answer likely lies in endocrine changes induced by suckling. Suckling robustly triggers the release of lactation-associated hormones, including oxytocin and prolactin [2,21]. However, exogenous prolactin and oxytocin administration to virgin female mice fails to induce aggressive behavior [22,23].

While neither pregnancy-related sex hormones nor suckling-induced neuropeptide hormones are sufficient to induce maternal aggression, their combination appears to be the key. Savare and Gandelman applied a mixture of estrogen and progesterone to ovariectomized virgin females, which induced nipple growth, and then co-housed the females with foster pups [15]. Three days after pup co-housing, over 50% of treated females attacked a conspecific intruder, whereas hormones or pup exposure alone had little effect [15]. Notably, aggression only emerged in virgin females that showed nipple growth and received suckling from pups, suggesting that sex hormones and suckling-induced neuropeptide hormones are likely the right "recipe" to activate the female aggression circuit.

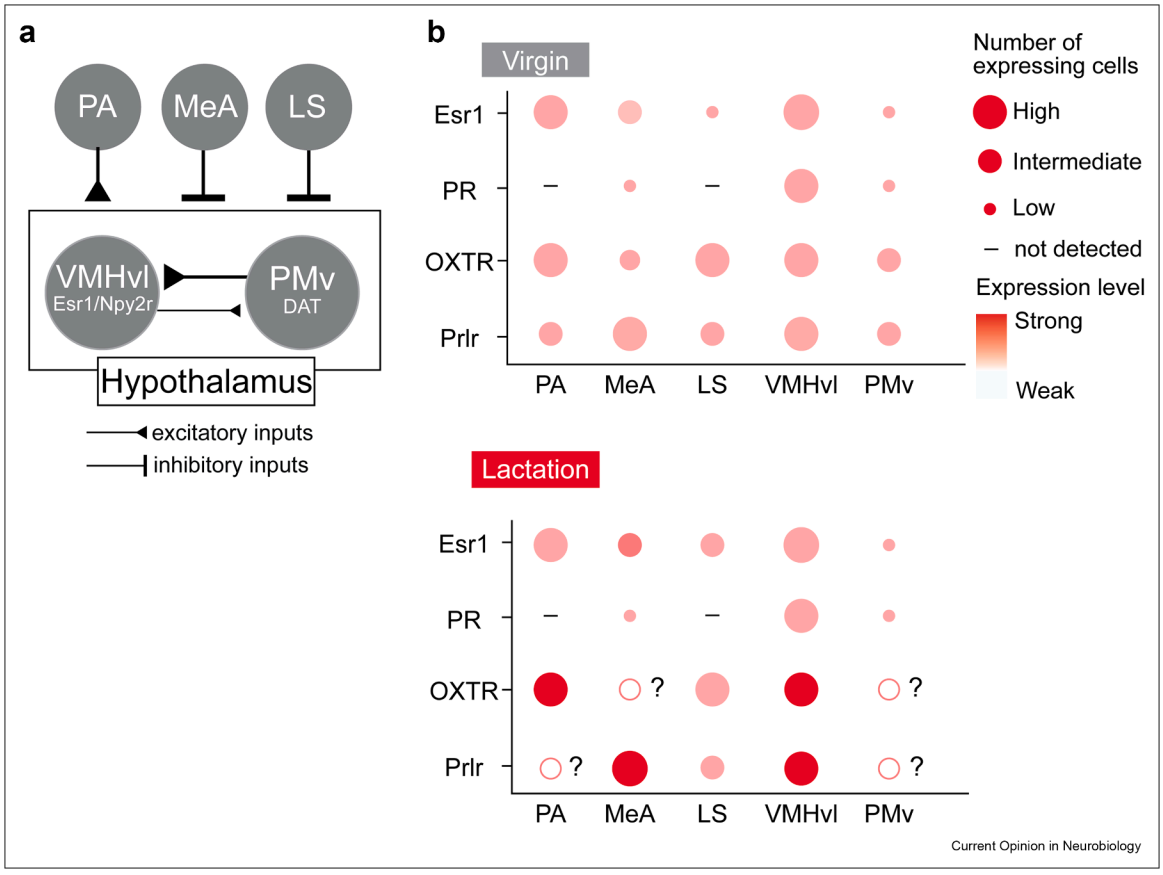
Neural circuits for female aggression

Before we discuss how hormones may change the female aggression circuit to support the behavior, we will review our current understanding of the circuit. The ventrolateral part of the ventromedial hypothalamus (VMHvl) has now been established as a critical region for both male and female aggression, and the molecular identity of aggression-related VMHvl cells is continuously refined (Figure 2a) [24–26]. Estrogen receptor alpha-expressing cells in the VMHvl ($VMHvl^{Esr1}$) are necessary and sufficient for maternal aggression in female mice [25]. Furthermore, $VMHvl^{Esr1}$ cells are not homogenous: the medially (VMHvlm) located $VMHvl^{Esr1}$ cells are preferentially activated during female aggression, while the lateral (VMHvll) $VMHvl^{Esr1}$ cells are mainly activated during female sexual behaviors [25]. Using activity-dependent single-cell RNA sequencing (Act-seq), Liu et al. identified neuropeptide Y receptor Y2 (Npy2r), a VMHvlm-biased gene, as a genetic marker for the female aggression-relevant population [26]. Optogenetic activation of $VMHvl^{Npy2r}$ cells elicited time-locked attack against adult conspecific intruders in non-aggressive virgin females, whereas optogenetic silencing of these cells suppressed maternal aggression in lactating female mice [26].

Another hypothalamic region that has been indicated in maternal aggression is the ventral premammillary nucleus (PMv) [27,28]. Lesioning PMv decreased maternal aggression in lactating rats and attenuated attack-induced c-Fos expression in the VMHvl, suggesting that the PMv is likely an upstream region of the VMHvl (Figure 2a), potentially relaying conspecific olfactory cues [29]. Optogenetic inhibition or targeted ablation of dopamine transporter expressing PMv (PMv^{DAT}) cells diminished aggressive behaviors in lactating female mice. Conversely, optogenetic stimulation of PMv^{DAT} cells facilitated maternal aggression, although only in mothers, not virgin females [22]. Notably, PMv^{DAT} cells are also critical for inter-male aggression [28,30].

Esr1-expressing (PA^{Esr1}) cells in the posterior amygdala (PA) are a main source of excitatory inputs to the VMHvl, and we previously found that the PA-VMHvl pathway is functionally important for driving aggression in male mice (Figure 2a) [31]. Although PA shows sexually dimorphic connectivity [32], our recent study demonstrated that PA^{Esr1} cells and their projection to the VMHvl are similarly essential for aggression in lactating females [12]. Chemogenetic inhibition of VMHvl-projecting PA^{Esr1} cells abolished maternal aggression, while optogenetic stimulation of PA^{Esr1} to

Figure 2



Pregnancy and lactation hormone receptors in the female aggression circuit.
Brain regions that have been indicated in maternal aggression and their connectivity.
A summary of hormone receptor expression in maternal aggression-related brain regions in virgin and lactating females based on [12,49,68–72].
LS, lateral septum; MeA, medial amygdala; PA, posterior amygdala; PMv, the ventral premammillary nucleus; Npy2r, Neuropeptide Y receptor type 2.

VMHvl terminal induced time-locked attacks in mothers [12].

Both VMHvl and PMv receive substantial inputs from the medial amygdala (MeA), principal nucleus of the bed nucleus of stria terminalis (BNSTpr), and lateral septum (LS) (Figure 2a). Ablating the aromatase-expressing cells in the posterodorsal division of MeA decreased both inter-male aggression and maternal aggression [33]. Chemogenetic inhibition of MeA cells non-selectively prevented aggression escalation in lactating females across repeated exposure to conspecific adult males [34].

The roles of the BNSTpr in female aggression appear to be relatively minor. Chemogenetic inhibition of aromatase cells or Esr1 cells in the BNSTpr has little effect on maternal aggression in lactating females [35,36]. These functional results are consistent with the cells' lack of *in vivo* responses during female aggressive behaviors [35]. In contrast, inhibiting BNSTpr aromatase cells reduced inter-male aggression [35].

Pharmacological activation of LS by antagonizing the $GABA_A$ receptor decreased both male aggression and maternal aggression, suggesting its naturally suppressive effect on aggression in both sexes [37,38]. However, recent studies indicate the role of LS in female aggression is likely complicated. Activating oxytocin receptor in the ventral LS promotes attack in female rats, whereas activating vasopressin receptor in the dorsal LS has the opposite effect [39]. We found that dopamine signaling in the dorsal LS is non-essential for maternal aggression, although it is critical for the increased male aggression over repeated fighting [40].

Overall, with the notable exception of the BNSTpr, the core regions regulating aggressive behavior are largely shared between males and females [8], Nevertheless, differences in neuromodulation, cell-type composition,

and functional organization give rise to sexually dimorphic patterns of aggression in expression, intensity, and context dependence.

Plasticity of the female aggression circuit during pregnancy and lactation

As discussed earlier, pregnancy-related sex hormones, together with suckling-induced neuropeptide hormones, are likely essential for activating the aggression circuit in females, enabling the mothers to attack the intruder fiercely upon their first encounter. In support of this hypothesis, all female aggression-related regions, including VMHvl, PMv, PA, MeA, and LS, express abundant estrogen, progesterone, oxytocin, and prolactin receptors, allowing aggression cells to sense the neurochemical environment (Figure 2a and b) [4,8,21,22,25,41]. Estrogen and progesterone receptors (PR) are nuclear receptors that act as transcription factors upon activation and can influence the expression of various ion channels and receptors [42,43]. Interestingly, both the oxytocin and prolactin receptor (OXTR and Prlr) genes contain estrogen response elements (EREs), and receptor expression levels increase in response to estrogen [44,45]. During lactation, likely due to the actions of sex hormones, OXTR expression in females broadly increases in many brain regions, including all maternal aggression-related regions [46–50]. A comprehensive comparison of transcriptomic profiles in ovariectomized females with and without estrogen supplementation revealed hundreds of genes in the VMHvl, MeA and BNSTpr that are significantly altered by sex hormones [51]. Thus, at the molecular level, estrogen and progestogen surges during pregnancy can dramatically alter the transcriptomic landscape of aggression-related cells, preparing them to sense neuropeptide release induced by pup suckling.

Molecular changes induced by sex hormones are reflected in corresponding morphological and physiological alterations of neurons. VMHvl neurons typically possess one long primary dendrite and two to three shorter secondary dendrites. In ovariectomized females, estradiol shortens the primary dendrite while increasing both the length and spine density of the shorter dendrites [52]. In contrast, progesterone reverses the estradiol-induced increase in spine density [53,54]. At the electrophysiological level, estradiol increases the responsiveness of VMHvl neurons to excitatory inputs [55]. Consistent with this shift toward excitation, estradiol reduces GABA A receptor expression in the VMH, an effect that is reversed by subsequent progesterone treatment [56]. Importantly, some physiological changes require synergistic actions of estradiol and progesterone: progesterone following estradiol, but not estradiol alone, increases GluA1 and GluA2 levels in the VMHvl, indicative of synaptic potentiation [57]. Similar hormone-dependent plasticity is likely to occur in other nodes of the aggression circuit, given their abundant expression of sex hormone receptors.

The initiation of aggression depends on increased output in the aggression circuit. Indeed, VMHvl^{Npy2r} cells in lactating females responded more strongly to conspecific intruders than virgin or post-lactation females [12,26]. In our recent study, we further examined the physiological changes of VMHvl^{Npy2r} cells during lactation that may explain the increased *in vivo* responses (Figure 3) [12]. We found that a higher fraction of VMHvl^{Npy2r} cells form synaptic connections with PA cells during lactation than in the virgin state. Moreover, the excitability of VMHvl^{Npy2r} cells increases significantly during lactation (Figure 3). As a combined result, PA input becomes more effective in evoking action potentials of VMHvl^{Npy2r} cells in lactating females than in virgin females [12]. This is functionally consequential as optogenetic activation of the PA-VMHvl pathway induces attack in lactating, but not virgin, females [12].

PMv^{DAT} cells show similar state-dependent excitability changes as the VMHvl^{Npyr2r} cells [22]. In virgin females, most PMv^{DAT} cells (74%) are silent, whereas most cells (76%) in aggressive dams are tonically active (Figure 3) [22]. PMv^{DAT} cells in non-aggressive dams showed a lower spontaneous firing rate than in aggressive dams [22]. Consistent with the cell excitability difference, conspecific intruders induce higher c-Fos expression in aggressive dams than in non-aggressive dams [22,29].

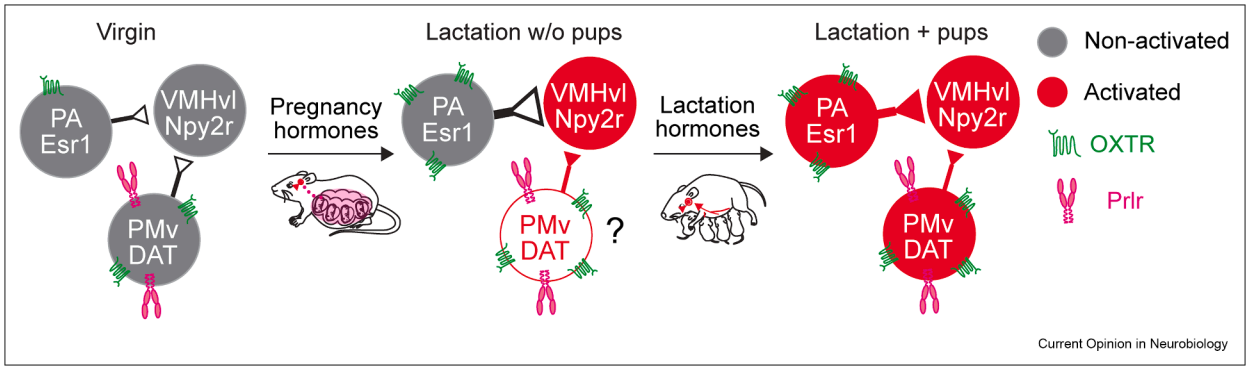
Beyond the hypothalamus, PA^{Esr1} cell responses to intruders also increase during lactation [12]. However, PA^{Esr1} cell excitability remains unchanged. With regard to the synaptic transmission, although both spontaneous excitatory and inhibitory synaptic currents (sEPSC and sIPSC) of PA^{Esr1} cells increase, the E/I ratio does not [12].

Thus, synaptic and cellular changes occur in multiple hypothalamic nodes in the aggression circuit during lactation, enhancing the overall circuit output. These changes could also occur in other aggression-related regions, such as MeA and LS, representing interesting future directions.

Lactation hormones boost the maternal aggression circuit

Maternal aggression critically depends on pup suckling. Separating the pups from lactating females for a few hours reduces female aggression to intruders, which could be recovered after merely 10 min of reunion with the pups [19,20]. This rapid and reversible modulation is ethologically adaptive: maternal aggression is energetically costly and risky, and should be expressed only when it serves the function of protecting vulnerable offspring. When pups are absent or inactive, such as due

Figure 3



Reproductive state- and pup-dependent activation of the female aggression circuit.
During pregnancy, VMHvl^{Npy2r} cell excitability increases and PA to VMHvl^{Npy2r} connectivity strengthens. During lactation, suckling and pup interaction-induced oxytocin and prolactin release further enhances the activity of PA^{Esr1} and PMv^{DAT} cells via their respective receptors, thereby increasing the input–output gain of the female aggression circuit.

to predation and illness, engaging in aggressive defense would provide little benefit. The fast timescale of these behavioral changes suggests that neurochemicals associated with pup interaction, particularly suckling-induced oxytocin and prolactin release, play a key role in dynamically gating the aggression circuit (Figure 1a).

VMHvl expresses abundant OXTR and Prlr, both of which increase expression levels during lactation [49,50]. However, antagonizing OXTR in the VMHvl or knocking out VMHvl OXTR do not affect maternal aggression in female mice, suggesting that OXTR signaling may not modulate female aggression through the VMHvl [12]. Conditional knockout of Prlr in the VMHvl drastically increases aggression in lactating female mice, leading to the idea that VMHvl Prlr restrains maternal aggression [23]. However, prolactin primarily excites VMHvl cells, arguing against its role in dampening the VMHvl activity. Notably, OXTR and Prlr are expressed in both aggression-related VMHvlm and mating-related VMHvll cells [25]. As mating and aggression VMHvl cells counteract each other [58], oxytocin and prolactin likely affect aggression in opposite ways through VMHvlm and VMHvll. When VMHvlm and VMHvll simultaneously receive oxytocin or prolactin, the net effect on aggression could be hard to predict. Therefore, VMHvl aggression cell-specific OXTR or Prlr knockout is essential to elucidate the role of VMHvl OXTR and Prlr signaling in maternal aggression.

PMv^{DAT} cells express abundant Prlr and OXTR [22]. *In vitro* application of prolactin or oxytocin depolarizes the cells and increases the cell firing, which suggests that pup's presence, especially suckling, could lead to higher baseline activities of PMv^{DAT} cells (Figure 3) [22]. This change is due to the activation of the T-type calcium channel, as ML218, a T-type channel antagonist, occluded the prolactin effect [22]. Oxytocin acts through OXTR. TGOT, a specific OXTR agonist, also induces PMv^{DAT} cell depolarization. However, oxytocin likely also acts through other receptors, such as Avpr1a, to modulate the cells, as when OXTR is blocked with an antagonist, oxytocin remains effective in depolarizing PMv^{DAT} cells. The functional importance of OXTR and Prlr signaling in maternal aggression remains unclear. Stagkourakis et al. reported that 28-day administration of either one or both peptide hormones failed to increase aggression in virgin females [22]. However, it remains possible that PMv Prlr and OXTR signaling play a role in permitting instead of initiating maternal aggression, as in the case of PA.

OXTR is expressed in virtually 100% Esr1 cells in the PA (PA^{Esr1}), while Prlr is sparsely expressed in the area [31,59]. OXTR signaling in the PA is crucial for maternal aggression. Specifically, OXTR antagonist injection or OXTR knockout in the PA significantly reduced maternal aggression in mice [12]. Oxytocin increases the excitability of PA^{Esr1} cells, likely contributing to the increased responses of PA cells to intruders during lactation (Figure 3) [12]. When mothers were separated from pups for one day, maternal aggression, together with the oxytocin level, plummeted. When oxytocin cells in the paraventricular nucleus (PVN) were optogenetically activated, female aggression recovered to the pre-separation level. When PA OXTR is blocked prior to PVN oxytocin cell stimulation, female aggression failed to recover [12]. Consistent with functional manipulation results, after 24 h pup separation, neural responses of VMHvl-projecting PA cells during intruder introduction decrease and this decreased response can be

restored after 1-h PVN^{OXT} cell stimulation. These results demonstrate a critical role of PA OXTR signaling in linking pup's active presence to maternal aggression level.

OXTR and prolactin receptor (Prlr) are also expressed in the LS, and exhibit heightened signaling during lactation [60,61]. Notably, levels of phosphorylated STAT5, a key downstream effector of Prlr signaling, increase in the ventral LS (LSv) of pregnant and lactating female mice, although the functional role of LS prolactin signaling in maternal aggression remains unclear [60]. Several lines of evidence suggest that enhanced oxytocin signaling in the LS may facilitate maternal aggression. First, Oliveira et al. showed that oxytocin levels increase in the LS of single-housed, aggressive virgin female rats—but not in group-housed, non-aggressive females—following encounters with intruders [39]. Second, optogenetic activation of oxytocin fibers originating from the PVN and supraoptic nucleus within the LS promotes aggression in virgin metestrous and diestrous female rats [39]. Third, OXTR signaling in the LS is critical for suppressing social fear. LS injection of OXTR antagonist increases social fear in lactating females, whereas oxytocin infusion suppresses social fear in virgin females [61]. Reduced social fear may be essential for sustaining high levels of maternal aggression. Together, these findings suggest that oxytocin in the LS may modulate maternal aggression both by directly facilitating aggressive behavior and indirectly by suppressing social fear. At the synaptic level, oxytocin exerts region-specific effects within the LS, increasing sIPSC frequency in dorsal LS neurons while decreasing sIPSC frequency in ventral LSv neurons [39]. Given that dorsal and ventral LS subregions play opposing roles in aggression, and that reduced intra-LS inhibition is critical for aggression initiation [38,40,62], these differential effects provide a plausible circuit-level mechanism through which oxytocin shapes maternal aggression.

Together, these findings indicate that pup suckling rapidly gates maternal aggression through oxytocin- and prolactin-dependent modulation of multiple aggression-related nodes—including VMHvl, PMv, PA and LS—thereby linking the pups' active presence to dynamic, reversible tuning of the maternal aggression circuit rather than long-lasting circuit reorganization.

Summary and future directions

Based on current knowledge, we propose a two-step hypothesis to explain the rise and fall of female aggression during motherhood (Figure 1b). In the first step, pregnancy-associated fluctuations in sex hormones remodel the female aggression circuit over the course of weeks by acting on multiple nodes. This remodeling alters gene expression, inter-regional connectivity, and the morphological and electrophysiological properties of aggression-related neurons. Given the widespread expression of sex hormone receptors, these changes are likely circuit-wide, although their magnitude and direction may be region- and cell-type-specific. For example, neurons in the VMHvl and PMv show increased excitability, whereas PA neurons do not. Notably, Esr1-expressing neurons in the medial preoptic nucleus (MPOA), a population essential for maternal behaviors, exhibit a marked increase in excitability during lactation, whereas Esr1-expressing neurons in the BNSTpr, which regulate infanticide, show more modest changes toward the opposite direction [36]. These observations suggest that medial hypothalamic neurons may be particularly susceptible to hormone-driven plasticity compared to neurons in non-hypothalamic regions. How sex hormones differentially influence hormone receptor—expressing cells across regions, remain open questions and important directions for future research.

In the second step, pup suckling—induced elevations in oxytocin and prolactin permit the female aggression circuit to respond to intruders and drive attacks on short timescales (minutes to hours). This additional layer of control ensures that maternal aggression is expressed selectively, in accordance with the immediate need to protect offspring. When pups are absent or become inactive, often indicating illness or death, maternal aggression diminishes within hours, allowing females to conserve energy, avoid unnecessary risk, and potentially reengage in mating. We propose that oxytocin and prolactin act as signals of offspring presence, enabling reversible adjustment of aggression levels. Consistent with this idea, most nodes of the aggression circuit express OXTR, and several also express Prlr, allowing them to sense circulating peptide hormones (Figure 2b). In the brain regions examined to date, activation of OXTR and Prlr similarly depolarizes neurons and increases excitability, supporting synergistic roles in promoting circuit output. Whether oxytocin and prolactin gate the aggression circuit broadly across many nodes or primarily through a limited subset (e.g., the PA) remains unclear and represents an important direction for future investigation.

Maternal aggression is a distinctive form of aggression. Unlike inter-male aggression, it is restricted to a specific reproductive state [5,8,11,25] and is not associated with nucleus accumbens dopamine release or positive valence [63,64]. Instead, it appears to be largely "pre-programmed," governed by pregnancy-associated sex hormones and peptide hormones that signal active engagement with pups. This two-step control is likely

conserved across mammalian species, although its relative contribution—such as the degree to which maternal aggression depends on oxytocin—may vary with the intrinsic set point of the aggression circuit. Intriguingly, the same hormonal systems and receptors are also present in males. Whether they contribute to increased aggression in fathers remains an open question [65–67].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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** of outstanding interest

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