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# Neural plasticity supporting parental behaviors

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Becoming a parent involves extraordinary changes that allow caregivers to attend to and nurture infants. Neural circuits must adapt to the demands of caregiving to orchestrate various complex nurturing behaviors. These changes occur between two opposing circuits: a circuit primed for the expression of parenting to execute caregiving, and a circuit that suppresses this behavioral expression when the timing is not appropriate. In this review, we provide an overview of the neural circuits supporting the positive and negative control of parental behaviors and discuss mechanisms by which these opposing circuits are altered to facilitate the onset of parental care.

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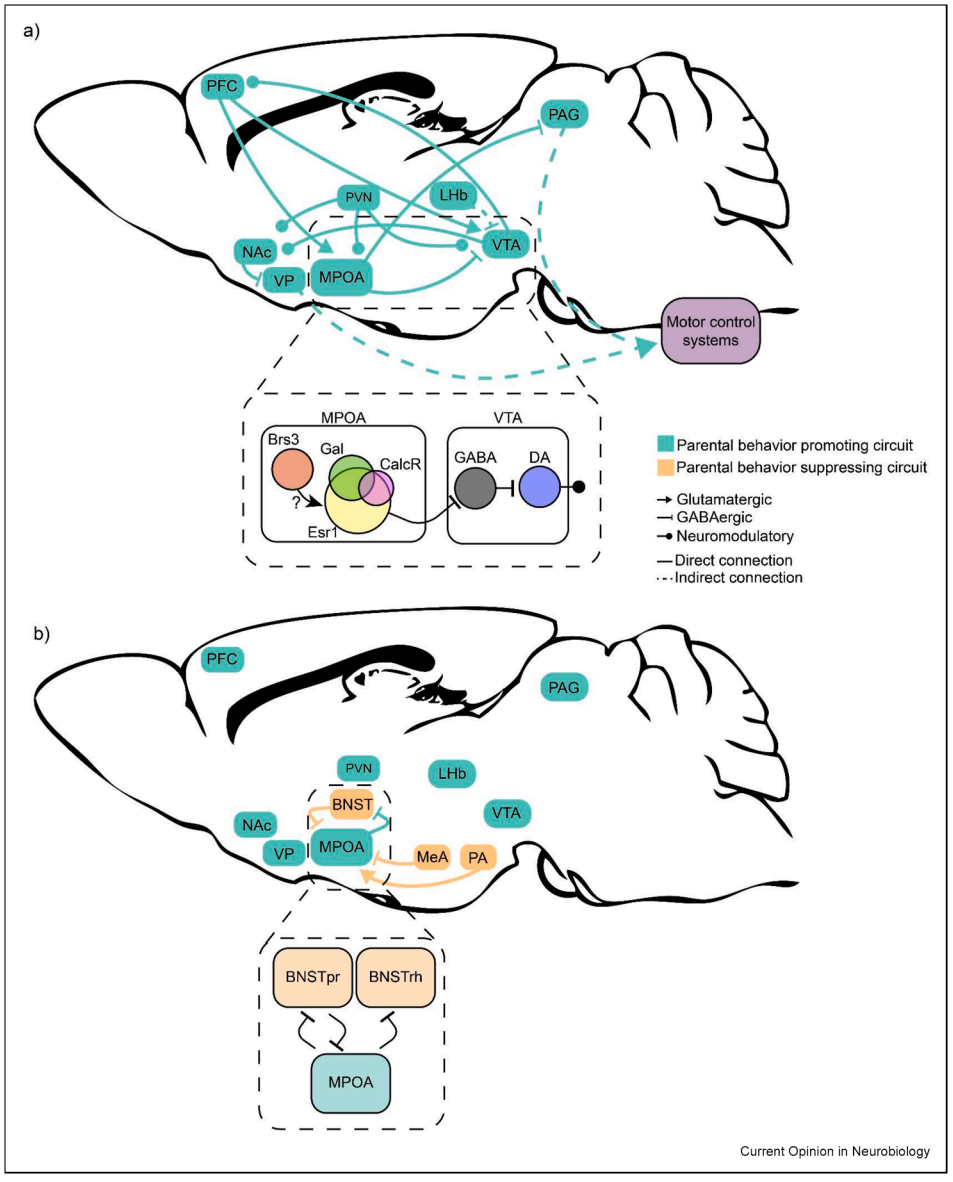
Parenting encompasses a suite behaviors that ensure offspring survival and well-being, and is observed throughout the animal kingdom [1]. Rodents, particularly rats and mice, are widely used to study parenting due to their robust parental care and neural circuit access. Parental animals display a variety of non-pup-directed behaviors, like nest-building and maternal aggression, and pup-directed behaviors to provide nutrition, safety, and warmth. Among pup-directed behaviors, pup retrieval is extensively used as a metric for parental responsiveness. When isolated from the nest, pups emit ultrasonic vocalizations that trigger parental animals to approach [2]. Adults then sniff the pup to sample chemosensory cues, and pick up the pup and carry it to the nest. Pup retrieval is typically followed by repetitive pup grooming, nest building, and nursing (in mothers) or crouching over pups [3]. While female rodents typically provide the majority of parental care, both males and females possess the circuitry to exhibit parenting [4].

The expression of parental behaviors depends on sex and experience. Mothers are highly parental, while nulliparous females range from infanticidal, avoidant of pups, or spontaneously maternal [5], depending on the species and strain. Nulliparous male rats and mice are non-parental or infanticidal [6]. Mating is capable of inducing parental behaviors. Females are primed by surges of hormones during pregnancy to robustly care for pups [7]. Male mice switch from infanticidal to pup caring behaviors several weeks after mating — a timeline that coincides with the birth of their pups [6]. Rodents can also show parental behaviors without mating; seminal work by Jay Rosenblatt illustrated that repeatedly exposing virgin rats to pups, a process termed pup sensitization, elicits parenting [8]. This sensitization process is additionally regulated by development; young rats acquire parental behaviors more readily than adults [9]. Additionally, nulliparous female mice can display maternal behaviors spontaneously, and co-housing with a dam and her litter can accelerate the onset of maternal care [10]. These findings highlight diverse plasticity mechanisms — hormonal and experiential — that initiate parenting.

Several reviews have outlined the core neural circuits regulating parental behaviors, [1,4,11–13]. Given the various triggers that can initiate parenting, it is important to understand the components of the circuit undergoing plasticity. Various circuit nodes can instruct a parental state transition, while others integrate physiological or environmental signals to modify the likelihood of parental onset. We propose that two interacting circuits regulate parenting: one promotes its expression and another suppresses it (Figure 1). The behavior-promoting circuit drives the expression of specific parenting behaviors, such as pup retrieval, pup grooming, and nursing. The behavior-suppressing circuit blocks the activation of the behavior-promoting circuit, and in many cases, drives hostile behaviors towards the pups. We discuss the primary functions of these opposing circuits and highlight plasticity mechanisms that promote parental onset.

**Figure 1**




Neural circuitry underlying the promotion and suppression of parenting.

## Parental behavior promoting circuit

At the center of the parental behavior-promoting circuit is the medial preoptic area (MPOA) (Figure 1a). At the output level, it projects to the ventral tegmental area (VTA) and periaqueductal gray (PAG) to promote various aspects of parental behaviors. At the input level, the paraventricular nucleus of the hypothalamus (PVN) and prefrontal cortex (PFC) project to the MPOA and modulate parental behaviors, although they are not the typical "sensory" regions that relay pup cues to the MPOA.

### Medial preoptic area

The MPOA is a central node in the parental behavior circuit [14]. Lesioning the MPOA virtually abolished parental behaviors across species [14—16]. Over the last decade, substantial progress has been made to uncover genetically defined cell types within the MPOA governing parenting. Galanin (Gal)-, estrogen receptor alpha (Esr1)-, prolactin receptor (Prlr)-, calcitonin receptor (CalcR)-, and bombesin receptor (Brs3)-expression cells in the MPOA have all been found to be critical for parenting [12,17—21]. A snRNAseq and multiplexed

error-robust fluorescence in situ hybridization (MERFISH) study identified six MPOA subpopulations relevant for parenting, and two were recently investigated — one featuring CalcR and another featuring Brs3 [22]. Yoshihara et al. found that silencing MPOA$^{CalcR}$ cells or knocking down CalcR expression in the MPOA disrupts maternal behaviors [23]. A recent study found that MPOA$^{Brs3}$ neurons also play a role in maternal behaviors [20]. The cells are inhibited by hunger-signaling cells in the arcuate nucleus, allowing females to switch between food seeking and parental care according to energy demands [20]. MPOA$^{CalcR}$ and MPOA$^{Brs3}$ cells are enriched in Esr1 and Prlr, which themselves may control distinct aspects of parenting; MPOA Esr1 knockdown reduces pup retrieval [24], while Prlr deletion impairs nursing but not retrieval [21]. With the refinement of molecularly-identified cell types, future work should explore the heterogeneity and signaling mechanisms within these cells to understand their recruitment during the transition to parenting.

### Mesolimbic dopamine system

The VTA sits downstream of the MPOA and plays a key role in parental behaviors [25]. Activating VTA-projecting MPOA$^{Gal}$ neurons increases a general motivation to interact with pups [12], while VTA-projecting MPOA$^{Esr1}$ neurons induce pup retrieval by targeting non-dopaminergic cells, which are mainly GABAergic and likely disinhibit dopaminergic (VTA$^{DA}$) neurons [18]. VTA$^{DA}$ neurons show phasic bursts of activity during pup retrieval [18,26], leading to dopamine release in the nucleus accumbens (NAc) [27]. VTA appears to be a gate for expressing pup retrieval; activating MPOA$^{Esr1}$ neurons while blocking VTA activity nearly abolishes pup retrieval [18]. Beyond generating acute parental actions, Xie et al. found that VTA$^{DA}$ activity acts as a reinforcement signal to improve pup retrieval over time [26].

Early studies suggested that NAc, a major downstream target of VTA$^{DA}$ neurons, could interface with motor control systems that permit parenting. However, the exact function of NAc remains poorly understood. Blocking dopamine signaling in the NAc disrupts maternal behavior [28], but lesioning the NAc did not impair maternal behaviors [29,30]. Interestingly, lesioning one side of the ventral pallidum (VP), a major downstream target of the NAc, and MPOA on the contralateral side impaired maternal behaviors, leading to the hypothesis that MPOA inhibits NAc, which then disinhibits VP to drive parenting [29]. However, if this model is correct, lesioning NAc should tonically disinhibit VP, causing improperly expressed parental behaviors. This prediction is inconsistent with the normal parental behaviors after NAc lesion [29,30]. The exact function of NAc and other brain regions downstream of VTA$^{DA}$ remains unclear.

The lateral habenula (LHb) is a major upstream input to the VTA. It sends dense glutamatergic projections to GABAergic cells in the rostromedial tegmental nucleus (RMTg), which in turn inhibit VTA DA cells [31]. Given that the MPOA-VTA projection, which activates VTA$^{DA}$ cells, promotes parental behaviors, LHb activation, which inhibits VTA$^{DA}$ cells, is expected to suppress parental behaviors. However, Lecca et al. reported that pup distress calls activate LHb neurons, triggering a negative affective state in virgin female mice but are functionally crucial for pup retrieval [32]. When LHb cells were inhibited, pup retrieval was impaired in parental virgin females [32].

How could we reconcile these seemingly contradictory results? The first step of parental behavior is to gain access to the pup. This step typically involves approaching a pup at a distance. While approaching is often considered an appetitive behavior, reflecting the positive valence of the target, this is not always the case. Animals can also approach a stimulus that is annoying and negative, with the hope of terminating it. As an analogy, if your neighbor plays loud music at night, you may go and talk to your neighbor to try to stop the music. For mice, there are two ways to terminate pup distress calls: retrieving the pups or killing them. The LHb likely does not determine which strategy will be implemented; instead, it is likely determined by the animal's parental state. In a highly parental animal, pup retrieval is likely to be implemented, as in Lecca's study [32]. In a low parental state animal, e.g., virgin males, infanticide is expected to occur. The LHb may merely signal the aversive nature of the pup calls. When LHb is inhibited, the animals are less motivated to stop the pup calls, hence reducing retrieval in parental virgin females. One prediction based on this hypothesis, and remains to be tested, is that LHb inhibition will also reduce pup attack in naturally infanticidal animals.

### Periaqueductal gray

The PAG, another MPOA target, also regulates motor components of parenting. Lesioning the lateral and ventrolateral caudal PAG reduced the kyphotic nursing posture by 85 %, significantly reducing pup weight gain [33]. More recently, it was found that MPOA$^{Gal}$ projections to the PAG bidirectionally regulate pup grooming [12], similar to the effects of whole MPOA$^{Gal}$ manipulations [17]. The PAG's innervation of the jaw muscles [34] could explain its effect on active pup-directed behaviors, like pup grooming, but future studies are needed to establish this relationship.

### Paraventricular nucleus of the hypothalamus

The PVN contains neuropeptidergic cells that can modulate the parental expression circuit. The PVN is bidirectionally connected with the MPOA [12] and

contains oxytocin- and vasopressin-expressing neurons, which have extensive roles in parenting [35,36]. In females, tyrosine hydroxylase (TH)-expressing neurons in the anteroventral periventricular nucleus (AVPV) control PVN oxytocin release to promote maternal behavior [37]. PVN oxytocin neurons also project widely throughout the brain, and their connections to the MPOA, VTA, and auditory cortex enhance animals' readiness to exhibit parenting [38–41].

### Prefrontal cortex

The prefrontal cortex (PFC) has been implicated in parental behaviors for decades. However, its exact function remains elusive and appears subregion-specific. Lesioning medial PFC (mPFC) slowed down pup retrieval, although females eventually retrieved most pups within the 10-min testing period [42]. Conversely, acute pharmacological inactivation of mPFC, including both prelimbic cortex (PL) and infralimbic cortex (IL), virtually abolished pup retrieval in female rats [43]. Pereira and Morell inactivated PL and IL separately and observed opposite behavioral changes: while PL inactivation increased the preference for a pup-associated environment, IL inactivation increased the preference for a cocaine-associated environment, suggesting that PL suppresses, whereas IL enhances maternal motivation [44]. More recently, Corona et al. showed increased neural activity during pup retrieval in the female anterior cingulate cortex (ACC), another subregion of the PFC [45]. Chemogenetic inhibition of ACC excitatory neurons decreased pup interaction time by approximately 25 % [45]. Cells in the orbitofrontal cortex (OFC) are also activated during pup interaction and retrieval [46]. Ablating OFC cells delayed the emergence of pup retrieval behavior in virgin females over days. These results collectively suggest that multiple PFC subregions could influence parental behaviors. With the exception of PL, PFC regions promote parental motivation and behavioral expression. However, unlike MPOA, the role of PFC appears to be compensable, especially when the lesion is permanent. PFC cells activated during pup retrieval overlap with cells activated during sucrose reward [46], suggesting that PFC's role in maternal behavior likely reflects its general role in facilitating rewarding goal-directed behaviors.

PFC potentially influences parenting through its projection to the MPOA [47]. IL projects to MPOA more densely than PL, consistent with the positive role of IL, but not PL, in promoting maternal motivation [47]. PFC may also influence parental behavior through its bidirectional connection with $VTA^{DA}$ neurons [48]. Inactivating OFC reduces $VTA^{DA}$ activity and dopamine release in the NAc during pup retrieval in parental virgin females, suggesting a modulatory role in enhancing the pup's reward value [46].

## Parental behavior suppressing circuit

Recent studies revealed that three regions — the bed nucleus of stria terminalis (BNST), medial amygdala (MeA), and posterior amygdala (PA) — can drive negative pup-directed behaviors, i.e., infanticide (Figure 1b). These regions all project densely to the MPOA, enabling strong influence over the parenting circuit.

### Bed nucleus of stria terminalis

The BNST, a region bidirectionally connected with MeA and MPOA, contains several subregions. While ventral BNST (vBNST) has been suggested to play a similar role as MPOA in promoting parenting [5,49], the rhomboid nucleus (BNSTrh) and principal nucleus (BNSTpr) both direct infanticide [50,51].

Our recent study discovered that BNSTpr Esr1 cells ($BNSTpr^{Esr1}$) are necessary and sufficient for infanticide in female mice [51]. Optogenetically activating $BNSTpr^{Esr1}$ inputs to MPOA suppresses maternal behavior and induces infanticide. These cells mutually inhibit $MPOA^{Esr1}$ cells. During motherhood, $BNSTpr^{Esr1}$ cell excitability decreases while $MPOA^{Esr1}$ cell excitability increases, shifting the circuit and behavior toward maternal care.

BNSTrh is also linked to infanticide. BNSTrh neurons show elevated c-Fos following infanticide, and BNSTrh lesions suppress infanticide [50]. BNSTrh cells receive inhibitory inputs from the MPOA, but unlike BNSTpr cells, do not project back to MPOA [50]. Inhibitory inputs to BNSTrh, putatively from MPOA, are potentiated following paternal experience in mice [52], offering another pathway by which MPOA can suppress infanticidal drive.

### Medial amygdala

The MeA receives olfactory information directly from the accessory olfactory bulb and indirectly from the main olfactory system [53], and projects densely to the MPOA. Thus, MeA is well-positioned to facilitate parental behaviors by transmitting pup olfactory cues to the MPOA. However, early lesion studies found that damaging MeA promotes parental behaviors [54], suggesting an inhibitory role of MeA in parenting. Concordantly, Chen et al. found that high-intensity optogenetic stimulation of MeA GABAergic cells ($MeA^{Vgat}$) elicits infanticide in males [55]. Our study further showed that activating MeA to MPOA projecting cells induces infanticide in virgin female mice [51]. These results suggest that MeA sends GABAergic inputs to the MPOA to suppress parenting.

The MeA undergoes retuning as parental behaviors emerge. Bulk $Ca^{2+}$ recording revealed that $MeA^{Vgat}$ neurons are more active during infanticide in virgin males than during pup grooming in parental males and

females [55], and sexual experience allows MeA neurons to better discriminate pups from other conspecifics [56]. MeA may reduce the response towards pups in parents, which may decrease its suppression of the MPOA.

Importantly, weak activation of GABAergic MeA neurons promotes pup grooming in males and females [55]. When MeA-MPOA cells were chemogenetically activated, pup attack and grooming were simultaneously enhanced [51]. Thus, MeA may also contain a set of cells that promote aspects of parental behaviors. How parenting-promoting and suppressing cells are organized in the MeA remains an open question.

### Posterior amygdala

The PA is enriched with Esr1. $PA^{Esr1}$ neurons send direct excitatory inputs to $MPOA^{Esr1}$ cells, making it well-positioned to facilitate parental behaviors [57]. Surprisingly, two studies reported that activation of PA cells instead elicits infanticide [58,59]. However, we found that MPOA-projecting PA cells show higher c-Fos expression after parental behaviors than infanticide [51]. A recent study revealed that PA neurons projecting to the MPOA contain two distinct cell populations — one relevant for infanticide and one for parenting [60]. Serotonin receptor 7 is highly enriched in the parenting-activated cells, and activating these cells suppresses infanticide in virgin females [60]. The PA also contains oxytocin receptor-expressing interneurons [58], which may interface between infanticide- and parental behavior-related populations and bias the behavioral drive based on oxytocin level. Thus, both MeA and PA can suppress parental behavior-promoting circuit, although these regions also contain a subset of cells that may facilitate pup caring.

## Plasticity of the parental circuits

The parental behavior-promoting and suppressing circuits push and pull throughout the lifespan. Recent studies have described various mechanisms that enable the parental behavior-promoting circuit to prevail in this tug-of-war during parenthood, including facilitating the recognition of pup cues, hormonal and peptidergic modulation as a function of reproductive state, circuit remodeling during development, and neuromodulatory state transitions.

### Changes in responses to pup cues during parenthood

Parental care relies on a combination of sensory inputs [61], and sensory systems adapt during the transition to parenting. In particular, primary olfactory, auditory, and somatosensory regions are extensively modified by parental experience. In mice, pregnancy stimulates neural stem cells to produce transient olfactory bulb interneurons, which allow mothers to recognize their pups following parturition [62]. Additionally, responses to natural odors strengthen in the main olfactory bulb of mothers [63], and pup odors modulate auditory responses, sharpening auditory cortical tuning to pup vocalizations [64]. Compared to non-parental females, neurons in the auditory cortex of maternal mice respond more reliably to pup vocalizations [40] and generalize across a range of pup vocalizations to initiate pup retrieval [65]. Mothers also receive somatosensory input from pups to facilitate milk letdown [66]. In nursing mothers, the representation of nipple-bearing skin is about twofold larger than in nonlactating females [67]. To what extent these changes in sensory coding occur in fathers remains largely unknown.

### Role of sex hormones and neuropeptides in parental circuit plasticity

Parenting behavior is highly sensitive to hormonal regulation. Estrogen, progesterone, prolactin, and oxytocin, play crucial roles in the induction of maternal behavior [7] and have largely conserved roles in males and females in the absence of pregnancy [13]. These hormones act directly on the parental circuit, and their receptor expression in the brain is dynamically modulated by reproductive state [68]. Moreover, these hormones trigger a cascade of changes within the circuit, regulating transcription, synaptic transmission, biophysical properties, and morphology of the cells [7]. The MPOA is enriched in hormone receptors [22], making it a popular site for exploring the neuroendocrine regulation of parenting.

In lactating females, the basal firing of $MPOA^{Esr1}$ and $MPOA^{Gal}$ neurons decreases, but responses elicited by pup interactions increase, effectively enhancing the signal-to-noise ratio and heightening selectivity for pups [18,69]. During pregnancy, estrogen increases cell excitability and progesterone facilitates excitatory inputs to MPOA cells [69]. The elevated excitability of MPOA cells can inhibit infanticide-driving cells in the BNSTpr, thereby suppressing infanticidal motivation in favor of maternal care [51]. These hormones also influence pup non-directed behaviors that prepare the animal for motherhood; progesterone modulates the neural activity of the Edinger–Westphal nucleus, a midbrain structure important for preparatory nesting before sleep, to promote nest building during pregnancy [70]. These physiological changes are accompanied by morphological plasticity. Rat MPOA cell bodies increase by nearly 50 % as a result of pregnancy [71], and dendritic spine density increases in pregnant mice and rats [69,71]. These changes offer mechanistic insight into the well-described phenomenon that estrogen and progesterone facilitate maternal behaviors [72,73].

Prolactin administration in the MPOA stimulates maternal behavior, and MPOA Prlr antagonism delays

the onset of maternal behavior in hormone-primed rats [7,74]. Interestingly, deletion of Prlr from MPOA neurons indiscriminately, but not from GABAergic or glutamatergic MPOA neurons, significantly impairs nursing [21]. This suggests that even a small amount of prolactin signaling is sufficient to sustain maternal behavior, and prolactin likely operates through a distributed circuit. In particular, prolactin has been linked to maternal motivation; systemic antagonism of Prlr impairs pup retrieval and nursing in rats introduced to a novel cage [75], and congenital knockout of Prlr in all GABAergic neurons impairs females' ability to retrieve pups in a T-maze [76]. Thus, while Prlr MPOA neurons influence nursing, the distributed action of prolactin in parental circuits may orchestrate other components of maternal behaviors.

Systemic injections of oxytocin facilitate maternal behavior in nulliparous female rodents [40], and oxytocin action in the MPOA and VTA promotes the onset of maternal care [41]. Several recent studies have detailed the mechanisms by which oxytocin can act on the parental circuit. Valtcheva et al. identified that the posterior intralaminar thalamus relays pup call information to PVN oxytocin neurons to promote pup retrieval [77]. This is accomplished through the long-term depression of inhibition on oxytocin neurons via internalization of postsynaptic GABA receptors, which allows for delayed, persistent firing of these cells and oxytocin release [77]. Oxytocin release can stimulate plasticity in the auditory cortex; when paired with pup vocalizations, oxytocin transiently decreases inhibitory transmission and facilitates excitatory long-term potentiation to enhance coding of pup cues and accelerate maternal behavior onset [40]. In a similar vein, oxytocin can work with serotonin in the NAc to induce long-term depression on medium spiny neurons and promote social reward [78]. Thus, oxytocin is capable of modifying multiple components of the parental circuit, both enhancing the salience of pup sensory cues and modifying social reward.

### Hormonal actions in male parental behaviors

Although males do not receive the same pregnancy-related hormonal cues as females, many of these same hormones serve important functions in paternal behavior. Esr1 represents a common cell type for parenting in males [19], and stimulation of MPOA$^{Esr1}$ cells promotes paternal behaviors [19]. Likewise, prolactin is correlated with paternal behavior. Deleting the prolactin receptor from CamKIIα-expressing cells disrupts pup retrieval in sires [79]. Using MPOA$^{Gal}$ neurons as an entry point, Stagkourakis et al. showed that prolactin directly depolarizes the cell membrane, facilitates spontaneous excitatory currents, and increases neuronal firing rate by closing calcium-dependent small conductance potassium channels [80]. Interestingly, male rats have lower circulating levels of prolactin than mice and do not show paternal behavior. Tuning the oscillatory frequency of mouse tuberoinfundibular dopamine cells, a key population that tonically suppresses lactotroph cells to decrease prolactin secretion, to a rat-like frequency can lower prolactin levels and suppress paternal behaviors in mouse sires [80]. A recent study found that oxytocin plays a critical role in the induction of parenting in male mice; deleting oxytocin from the PVN impairs paternal behaviors [38]. However, it remains unclear if these hormonal signals produce the same physiological changes in males as in females, such as increased signal-to-noise ratio mediated by estrogen in the MPOA [18,69] and oxytocin in the auditory cortex [40]. Moreover, the hormonal changes from insemination to fatherhood and their effects on parental circuits are poorly understood. For example, circulating prolactin levels do not differ between non-parental virgins and sires [79,80]. Prolactin surges transiently during mating, but blocking this surge does not affect the subsequent transition to paternal care [79]. Investigating the action of these hormones on neural circuit function in males would inform us to what degree parental onset differs between the sexes.

### Change in parental behaviors during development

Parental behaviors also change over development. Juvenile rats are more readily parentally responsive than adults [9], and juvenile male mice do not attack pups, but become infanticidal in adulthood [81]. Sex hormones appear to be responsible for the behavioral switch during development. Estrogen supplementation during puberty enhances synaptic transmission in the BNSTrh during adulthood [82], suggesting the estrogen rise during puberty could lead to increased infanticide. Indeed, pubertal development is accompanied by drastic changes in steroid hormones, which can alter gene expression and synaptic wiring [83]. Importantly, a recent study from Jamieson et al. discovered a form of pre-pubertal synaptic plasticity; microglia engulf immature dendritic spines and enhance excitatory transmission to MPOA$^{Gal}$ neurons, to facilitate parenting in juvenile mice [84].

### Neuromodulators as dial knobs on the parental circuit

In addition to hormones, neuromodulators fine-tune parenting circuits. In addition to dopamine, serotonin has been found necessary for postpartum maternal care [7], possibly by interacting with the oxytocin system to mediate the reward value of pups [78]. Norepinephrine (NE) is a useful example for examining how neuromodulators interact with hormones to facilitate maternal behaviors. Locus coeruleus NE neurons are active acutely during pup retrieval and modulate their tonic activity throughout maternal behaviors to convey a state of maternal arousal [85]. NE can directly act on the MPOA to influence pup retrieval [86] and modulate the

sensitivity of ACC neurons to pups [45], allowing maternal behaviors to be expressed flexibly. Knocking out dopamine β-hydroxylase, the enzyme that synthesizes NE, reduces pup retrieval and pup survival, but restoration of NE prior to parturition reinstates maternal behavior [87]. Together with hormones and experience, NE can act on the parental circuit to effectuate a maternal state shift.

## Conclusions and future directions

Over the last several decades, considerable progress has been made in identifying the discrete circuit components involved in parenting. We have outlined the neural pathways mediating the positive and negative control of parental behaviors, as well as several mechanisms by which these regions can be recruited. However, many questions remain. First, parental onset occurs at diverse timescales; nulliparous females show maternal behavior within days of sensitization, while males become parental weeks after mating. What governs the activation of the parental circuit over these timescales? Long-term behavioral recordings [10] and neuromodulatory monitoring tools [88] could clarify how circuit plasticity unfolds. Additionally, while this review focused on the onset of parenting in adults, there is a paucity of mechanistic studies investigating how these behaviors are developmentally regulated or how they wane across time. Addressing these questions is important to advancing our basic understanding of how the parental circuit functions and how it may be dysregulated in psychiatric conditions.

## Declaration of competing interest

The authors declare no competing interests.

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## Data availability

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

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