Parenting as a model for behavioural switches

Shanice Bailey[1] and Yoh Isogai[1,2]

[1] Sainsbury Wellcome Centre for Neural Circuits and Behaviour, University College London

26 Howland Street, London W1T 4JG, United Kingdom

[2] Corresponding author: y.isogai@ucl.ac.uk

Summary

- Broad behavioural characterisation provides an understanding of the organisation of parenting and infanticide in mice
- Modular organisation of circuits underlies parental and nonparental behaviours
- Neuronal substrates underlying behavioural switches are localised both in the sensory periphery and central brain
- Functional and structural plasticity likely drives parental and nonparental transitions

Abstract

Adaptability to ethologically relevant cues is fundamental for social interactions. As such, reproductive success relies on the ability of an animal to transition between parental and nonparental states. Though driven by genetically pre-programmed circuits, these instinctive repertoires are reshaped by internal state and experience, making parenting a robust model for

the study of behavioural flexibility. As a functional wiring diagram for parenting emerges in mice, we are well placed to identify neural substrates and posit associated mechanisms underlying caregiving transitions. In this review, we discuss the importance of comprehensively characterising behaviour, highlight the role of shared circuit elements for behavioural malleability and explore plastic mechanisms that might guide switches between parental and nonparental repertoires.

Total: 3233 words

Introduction

Parental care encompasses a broad suite of instinctive behaviours that facilitate the survival of an infant and can be observed across the animal kingdom [1]. Over recent decades, mice (*Mus musculus*) have emerged as a model to investigate the neural basis of parenting, which is underpinned by circuitry shared in males and females [2].

Although all adult mice are capable of exhibiting infant-directed caregiving [1], the expression of parental behaviour is highly variable. Hormonal fluctuations during pregnancy and parturition ensure that mothers, the primary caregivers, are immediately responsive to the needs of their young [3]. However, stressful environmental conditions can suppress maternal intent [4]. In contrast, virgin males attack neonates but copulation with a female mating partner is sufficient to initiate paternal care time-dependently [5–7]. In laboratory breeds, some virgin females largely ignore infants, yet exposure to pups through cohousing with a highly motivated mother can convert ambivalence to competent caregiving [8]. Clearly, the circuits that regulate parental behaviours are strongly modulated by internal state and social experience. As we grasp the core circuitry underlying parental and nonparental behaviours [2], it will also be important to identify

the neural mechanisms that enable transitions between parental caregiving and infanticide or neglect, and vice versa.

In this review we propose that thorough behavioural characterisations of pup-directed behaviours are needed to better understand the role of the neural circuits underlying parenting or lack thereof. We then review current knowledge of core parental and infanticidal circuits, highlighting potential nodes within each pathway governing behavioural flexibility. Finally, we discuss candidate neural mechanisms that might underlie switches between parental and nonparental responses in the presence of infants.

The organisation of pup-directed actions

Mice display a broad diversity of stereotyped motor patterns in response to pups to ensure reproductive success [9]. To answer basic questions regarding how animals express coherent pup-directed behaviours, it is often useful to identify incremental elements of specific motor patterns and organise them in groups [10,11]. Subsequently, one could organise these behaviours in a hierarchical manner, given that no two behaviours can be expressed at a specific time. The top of this hierarchy should identify the overall goals of the behaviours, whether parenting, attack, or absence of either, which can be defined as an animal's behavioural "state" (Figure 1A). Motor patterns can be further modularised within these states. This type of behavioural framework provides insight for understanding the interrelations of different activity subsets. For example, parenting and pup-directed attack are mutually exclusive, whilst parental pup-directed responses such as retrieval, grooming, and nest building are often displayed consecutively towards infants [12]. In addition, the transition probabilities from one of the motor patterns to another can be quantitatively mapped (Figure 1B,C) [12,13]. Thus, we can systematically define

the appropriate selection and coordination of each of these behaviours across a range of different contexts. Below we discuss how specific motor patterns involving parental and nonparental responses within the context of infant caregiving have been studied so far.

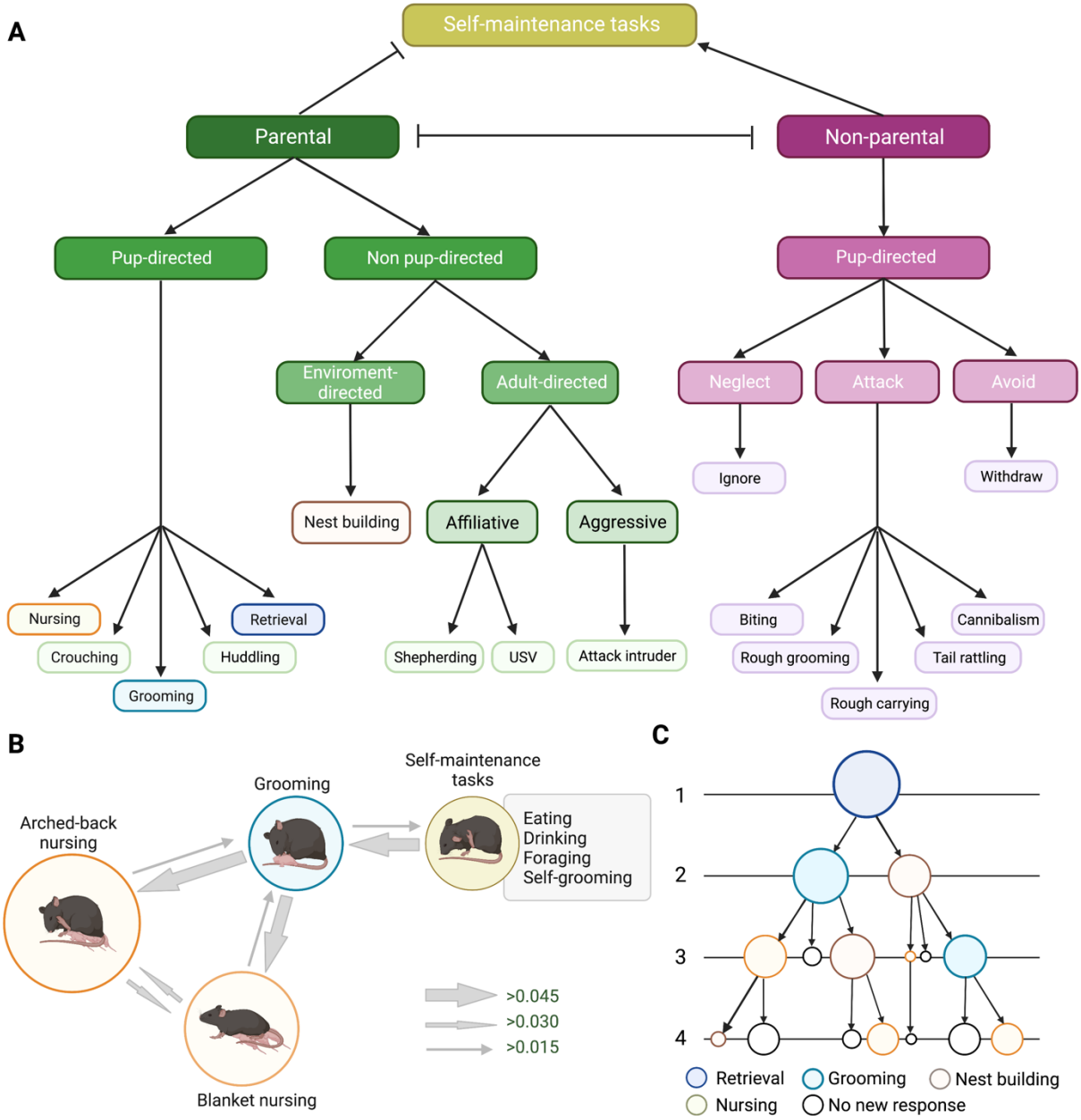

Figure 1. Parental and non-parental behaviour of mice: Pup-centred responses can be organised by state, serial order and transition probability. (A) Hierarchical organisation of behavioural components for parental and nonparental responses. Double-headed blunt arrows represent mutually inhibitory actions. (B) Adapted from Carola et al., 2011 [13], Hidden Markov Model analysis of three pup-directed maternal responses (arched-back nursing, blanket nursing, grooming) and self-maintenance tasks in C57BL/6 mice. Size of circle indicates duration of action and arrow thickness represents transition probabilities between actions. For example, self-maintenance tasks are most likely to lead to grooming, whereas grooming will most likely be followed by either arched-back nursing (active) or blanket nursing (passive). (C) Adapted from Noirot, 1962 [12], sequence of four parental motor patterns or no new response in the order of observed transition frequency across 115 outbred albino mice. Numbers 1-4 indicate order of action performed, and size of circle indicates proportion of animals performing that action. For example, the most common action sequence is retrieval, grooming, nest building, nursing.

A diverse repertoire of motor actions is necessary for parenting

Parenting can be classified based on whether actions are typically performed pre- or post-natally [14] and by motivational factors that can determine actions as appetitive or consummatory [15]. Here, we consider parenting as a repertoire of actions that promotes the survival of neonates to sexual maturity [9], whereas non-parental responses encompass any behaviour that threatens the long-term wellbeing of an infant. First, parenting behaviours can be categorised broadly as pup-directed and non-pup-directed (Figure 1A) [9]. Generally, non-pup-directed parental responses actively establish an environment in which offspring are well protected, such as nest building and defence against intruders. In contrast, pup-oriented parental responses, which are the focus of most parental studies, involve close interaction with infants to provide nourishment (lactating females only), thermoregulation, cleaning, and proximal protection. Despite the wide range of observable pup-directed behaviours, pup retrieval is disproportionately selected in many studies as a proxy for parental care. Pup retrieval is

unambiguously measurable for parental responsiveness, rapidly inducible by the experimenter, and multicomponent. Specifically, the caregiver must (1) search for, (2) pick up, and (3) carry a displaced pup back to the safety of the nest. However, the definition of pup retrieval varies widely. For example, should an animal be considered parental only when performing pup retrieval within a short period (*e.g.*, 2 min) [6,16]? Should successful pup retrieval be scored on one retrieval event [8]? In any case, one important future direction is to incorporate other elements of parental behaviours to understand the organisation of different parental actions, which could vary between sex, strain, age and experience.

Parental repertoires also involve behaviours observed outside of infant caregiving. Whilst affiliative allogrooming during adult–adult interactions strengthens social bonds [17], maternal pup grooming additionally involves anogenital licking to stimulate urination and induces water transfer from the litter to the dam [18]. Similarly, parental nest building is more elaborate than nests solely created for sleeping, as the structure serves as a thermoregulatory and predator protective mechanism [19,20]. In the absence of additional caregiving behaviours or sufficient nesting materials, it may be difficult to determine the intent of these actions.

A decrease in time dedicated to self-maintenance and voluntary activity also characterises efficient parental care [21–23]. It is postulated that balancing the needs of neonates and nurturers, is an adaptive strategy for mothers to conserve energy resources for the costly metabolic demands afforded by parenting. In the wild, this balance may be achieved by communal nesting whereby the responsibility of caregiving is shared with related females and sires [14,24]. Long term video recordings of female co-carers cohabiting with experienced dams showed that the mother “shepherded” the virgin female into the nest with pups to encourage caretaking [8]. The dam also frequently picked up and deposited pups in front of the

accompanying virgin female. Additionally, a study found that 38-kHz ultrasonic vocalizations emitted by the dam in response to pup removal to be important signals for the initiation of pup retrieval in fathers [25]. Likewise, semi-natural paradigms such as communal nesting in a large enclosure likely uncover previously unknown features of co-parenting [26]. One pitfall of this approach is the quantification of behaviours, which have been traditionally performed manually. In addition to limited behavioural categorisation and experimenter bias, manual annotation is particularly time-consuming for numerous animal subjects. Therefore, recent advances in automated analysis of multiagent behaviours [27,28] provide a promising avenue to more closely examine the organisation of parenting repertoires in ecologically relevant conditions. By broadening the evaluation of parental behaviour, it is possible to deepen our understanding of the context-dependent selection of activities between carers.

Pup-directed attack can be expressed flexibly in different environmental conditions

Infanticide is considered an adaptive behaviour that contributes to reproductive success in many species and is sex-independent [29]. In the literature, biting to wound is most often used to behaviourally characterise infanticide, however cannibalism, rough handling, and tail rattling [5,30,31] are observed during pup-directed attack. For virgin male mice, killing unrelated offspring opens mating opportunities with the dam [32]. For wild virgin and peripartum female mice infanticide could improve the availability of more resources for their own progeny [33]. Additionally, internal factors such as strain, social dominance and stress can influence the likelihood of an animal committing infanticide. For example, dominant males commit infanticide more frequently than subordinate males [32,34] and lactating females are capable of displaying infanticide in unfavourable environmental conditions such as limited food supply or high risk of predation [4,33].

The flexible expression of infanticide is also demonstrated in a mating-induced switch from pup-directed attack to parental care in male mice [7,29]. Intriguingly, this behavioural transition is temporally matched with the maternal gestation period, ensuring that the sire nurtures his own offspring. However, recent sexual experience can induce a transient elevation in pup-directed attack [7]. Given the striking temporal dynamics of these changes in behaviour, several studies have sought to identify neural substrates that might regulate this switch during or immediately following male ejaculation. A marked release of prolactin [35] and oxytocin [36] have been reported during sexual behaviour in male mice, however a causal link between ejaculation-associated hormonal signalling and acutely heightened infant-directed aggression remains to be demonstrated [37]. It is possible that hormonal modulation may induce more long-term changes (see 'Hormonal and structural perturbations underlying parental transitions').

Sensory triggers that lead an animal to commit to caregiving or aggression, and whether reliance on these signals changes state-dependently have also been examined. Using silicone pup dummies coated with pheromones, the sensing of pup-specific morphology in addition to vomeronasal cues was shown to be critical for infant-directed attack [30]. In contrast, different cues may be responsible for triggering parental behaviour. For example, the playback of intact and manipulated infant vocalisations showed inter-syllable rate to be critical for pup retrieval [38]. Therefore, it will be important to further investigate how different infant-specific stimuli determine parental and nonparental responses.

Infant neglect: active or passive state?

Infant neglect is often defined as a failure to provide infant care [39] and is demonstrated by laboratory-bred nulliparous female mice prior to pup exposure as well as by sexually

experienced males as they transition to a paternal state [5,16]. This phenotype is distinct from parenting and infanticide in that neglect is characterised by a lack of motivation to interact with pups, despite having the physical capacity to nurture or attack. In rats, pups are aversive to adults and generate avoidance behaviour initially [40]. Comparatively, neglectful mice ignore neonatal cues that would otherwise trigger consummatory behaviour [15] and choose to engage in other activities [41]. Furthermore, maternal neglect by lactating females, as observed in naturally occurring and transgenic models of neglect [41–44], results in complete litter mortality.

Many readouts of parental decision-making (lever press [45], crossing a cage wall [46], elevated plus maze [42] to obtain a pup) have proven to be useful measures of infant-driven motivation or lack thereof. Interestingly, neural circuit manipulations that suppress the expression of parenting or infanticide often produce neglectful behaviour. It is possible that these manipulations may perturb the reward system. The study of infant neglect therefore sheds light on the cognitive and motivational processes that guide an animal to abstain from pup-directed interactions.

Altogether, parental, infanticidal and neglect behaviours have been studied diversely, but details of each repertoire are still being expanded. To capture the full breadth of individual actions and their ethological relevance, the ecology of the animal species studied, sensory triggers, and motivational drives must be further investigated.

Modular circuits support a distinct repertoire of pup-directed behaviours

What are the neural substrates that control individual motor patterns of infant-associated behaviours and what mechanisms organise these circuits in a state-dependent fashion? As discussed above, circuits controlling behavioural patterns within a specific state often govern the

opposing pup-directed behaviours between states (*e.g.,* parental versus non-parental). Identifying the neural substrates underlying modular units of behaviours and the functional connectivity between these loci is the first step to addressing these questions.

A substantial body of literature has outlined the core circuitry underlying parental or infanticidal behaviours [2,47]. Among them, the medial preoptic area (MPOA) in the hypothalamus has long been known to direct the expression of parental behaviours [9]. Perturbations of MPOA neurons particularly have propelled our understanding of parental circuit logic. Activating MPOA Galanin (*Gal*) positive terminals in the periaqueductal grey and medial amygdala (MeA) promoted pup grooming and supressed interactions with conspecifics, respectively, whereas efferents in ventral tegmental area (VTA) enhanced pup retrieval [46]. The inhibition of VTA-projecting, Estrogen receptor alpha (*Esr1*) expressing MPOA neurons, some of which express *Gal*, suppressed both pup retrieval and approach [48]. Moreover, the silencing of Calcitonin receptor (*Calcr*) expressing neurons in the MPOA (60 % $Esr1^{+}$ and 20 % Gal^{+}) generated deficits in pup retrieval, nursing, and huddling behaviours in postpartum mothers [42]. These results suggest that distinct MPOA neuronal clusters, defined either by molecular identity and/or projection targets, underlie some of the incremental modules of parenting. Determining the local connectivity of these clusters could clarify the circuit logic subserving the coherent coordination of behaviour.

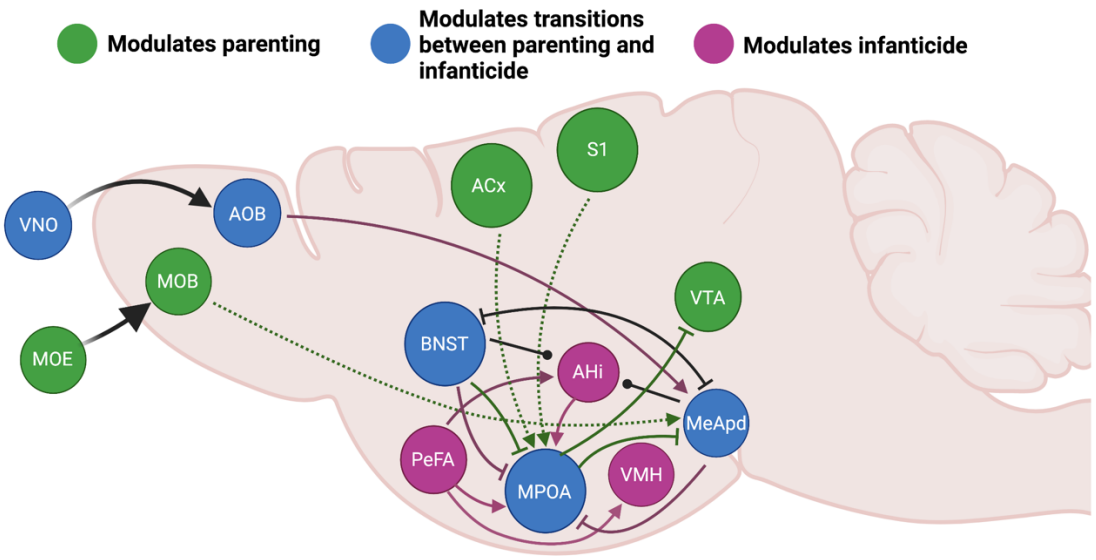

Figure 2. Neural circuitry underlying parental and infanticidal behaviours is highly interconnected. Shown are areas regulating the expression of parental behaviours (green), areas regulating the expression of infanticide (pink), and areas involved in transitions between parenting and infanticide (blue). Arrows indicate excitatory connections. Blunt-end arrows which indicate inhibitory connections. Dashed arrows indicate indirect connections. ACx, auditory cortex, AHi, amygdalohippocampal area, AOB, accessory olfactory bulb, BNST, bed nucleus of stria terminalis, MeApd, posterodorsal medial amygdala, MOB, main olfactory bulb, MOE, main olfactory epithelium, MPOA, medial preoptic area, PeFA, perifornical area, S1, somatosensory cortex, VMH, ventromedial hypothalamus, VNO, vomeronasal organ, VTA, ventral tegmental area.

Are nonparental circuits also modularly organised? Urocortin 3 (*Ucn3*) expressing neurons in the hypothalamic perifornical area (PeFA), for example, were strongly activated in virgin males following infant-directed attack but not after general agonistic displays [31], suggesting that pup-directed aggression is controlled by a unique circuit [49]. Crucially, optogenetic activation of *Ucn3*$^{+}$ PeFA axon terminals in the lateral septum (LS) and amygdalohippocampal area (AHi) induced an escape response and/or aggressive handling and

biting in parental females. Intriguingly, activating terminals in the ventromedial hypothalamus (VMH), an area associated with adult-directed aggression [50], suppressed only parental behaviour. Thus, at least one node of nonparental circuitry appears to be modularly organised.

Interrelation of parental and nonparental circuits

As the neural subpopulations underlying distinct components of parental and nonparental behaviours are further defined, we are well placed to evaluate how groups of opposing behaviours may be coordinated. Indeed, circuits underlying these behaviours appear to be intimately linked (Figure 2).

For example, surgical or genetic ablation of vomeronasal organ or associated ion channels TRPC2 and *Gai2* are sufficient to abolish pup-directed attack but instead initiate paternal behaviour in virgin males [5,6,51]. In contrast, anosmic *Cnga* mutants exhibit significantly reduced pup-directed maternal care [52]. While there are clear differences in the role of distinct olfactory organs for parental care and infanticide, both types of chemosensory information is necessary to elicit the full complement of infant-oriented behaviours within each state [6,51].

Neural substrates that enable a bidirectional control of parental and infanticidal behaviours extend beyond the sensory periphery. The activation of GABAergic neurons within the posterodorsal subdivision of the MeA (MeApd) in males can generate an acute behavioural switch from paternal pup grooming to pup-directed attack as a function of increasing optogenetic stimulation intensity [53]. Furthermore, pup-induced MeApd neuron activity can be modulated by sexual experience and cohabitation with a mating partner [54], suggesting an internal state influence.

Bed nucleus of stria terminalis (BNST), a region densely interconnected with MeA, has also been implicated in both parental and infanticidal behaviour. For example, increase *c-fos* activity was seen in the rhomboid division of BNST (rhBNST) following infanticide, with subsequent rhBNST lesions significantly delaying the onset of infanticide in virgin males [55]. In contrast, ventral BNST (vBNST) neurons are activated during parenting [37,55,56]. The AHi has also emerged as a critical region driving the behavioural switch from pup-oriented attack to caregiving in males. The activation of AHi neurons sending excitatory inputs to the MPOA promoted aggressive behaviour in paternal males [57]. Notably, AHi interneurons express oxytocin receptors, the activation of which inhibits the activity of MPOA-projecting AHi neurons.

Therefore, some brain areas facilitate the expression of parental or infanticidal behaviours and a proportion of highly interconnected brain regions could mediate transitions between the two states. What mechanisms then might underlie behavioural transitions in ethologically relevant scenarios?

Hormonal and structural perturbations underlying parental transitions

As discussed above, differential activity of specific nodes or different subpopulations within a node in parental and nonparental circuits could account for behavioural switching between states (Figure 3A,B). Therefore, a critical challenge has been to uncover specific mechanisms that differentially regulate these circuit modules. Here we outline converging evidence that neural changes necessary to support the behavioural transition to parenting occur at molecular, synaptic, biophysical, and circuit levels.

First, in mothers, parental behaviours are initiated and facilitated by the precise fluctuation of hormones [3]. Among them prolactin and oxytocin, which rise during early pregnancy and following parturition, have been extensively studied for their principle roles in nursing and pup retrieval [8,16,38,43,44]. Acquisition of caregiving behaviour by alloparents and suppression of infanticide also appears to be regulated by hormonal signalling. Oxytocin expressing paraventricular nucleus (PVN-OT) neurons were activated in sexually naïve females while observing maternal pup retrieval and performing pup retrieval for the first time [8]. In fathers, the ablation and silencing of PVN-OT neurons elevated infanticidal behaviours [58]. Additionally, oxytocin administration caused lower pup-evoked vomeronasal activity in virgin males, concurrent with reduced pup-directed aggression [59]. In the case of prolactin, genetic deletion of prolactin receptor (Prlr) from CaMKIIα-expressing forebrain neurons impaired pup retrieval in fathers [37]. Altogether, these data suggest that hormonal signalling in the central brain and sensory periphery may be required for infant caretaking. What precise mechanisms might underlie the effects of this signalling?

Changes in molecular and electrophysiological properties can be mediated by hormones [60] (Figure 3C). Prominently, prolactin has been shown to mediate transcriptional and biophysical responses among hypothalamic neurons [61]. For example, gonadotropin-releasing hormone (GnRH) neurons and tubero-infundibular dopaminergic (TIDA) neurons express Prlr and regulate anterior pituitary hormone secretion critical for reproductive behaviours. Bath application of prolactin induced phospho-STAT5, a marker of prolactin-induced signal transduction, in both types of neurons, but an acute ~3-fold increase in firing rate was seen only in TIDA neurons. Since current data reports serum prolactin to be comparable between virgin

and sexually experienced males [37,62], cell-specific modulation along distinct time courses likely accounts for differential neural circuit activity between physiological states.

Second, oxytocin receptor activation can induce synaptic plasticity in addition to transcriptional and biophysical changes in neurons via intracellular cascades [60]. During motherhood, oxytocin-mediated disinhibition increases auditory cortical neurons responsivity to pup calls through NMDA-dependent long-term potentiation [16,63]. Furthermore, sustained PVN-OT neuron firing to pup vocalisations is facilitated by long-term depression of inhibition in maternal mice by NMDAR-induced internalisation of postsynaptic GABA receptors [64]. Such mechanisms could explain altered neuronal excitability to social stimuli in other brain regions between parental and nonparental states [5,53,65], though synaptic plasticity has also been demonstrated in hypothalamic areas through experience-dependent processes [66].

Third, several studies uncovered structural plasticity concomitant with changes in behaviour towards infants (Figure 3C). Quantitative analysis of the afferents of *Calcr*$^{+}$ MPOA neurons revealed higher presynaptic inputs from the nucleus accumbens (NAc) in mothers than in virgin females [42]. The role of NAc in motivation and reward [15] could explain lower caregiving motivation in virgin females. In fathers, denser MPOA projections to PVN-OT neurons was observed relative to virgin males [58]. Since both oxytocin and prolactin can induce morphological plasticity [60,67], it is possible that a mechanism similar to cyclic, estrogen-mediated circuit remodelling for female sexual receptivity [68] also regulates the expression of parental, neglect and infanticidal behaviours.

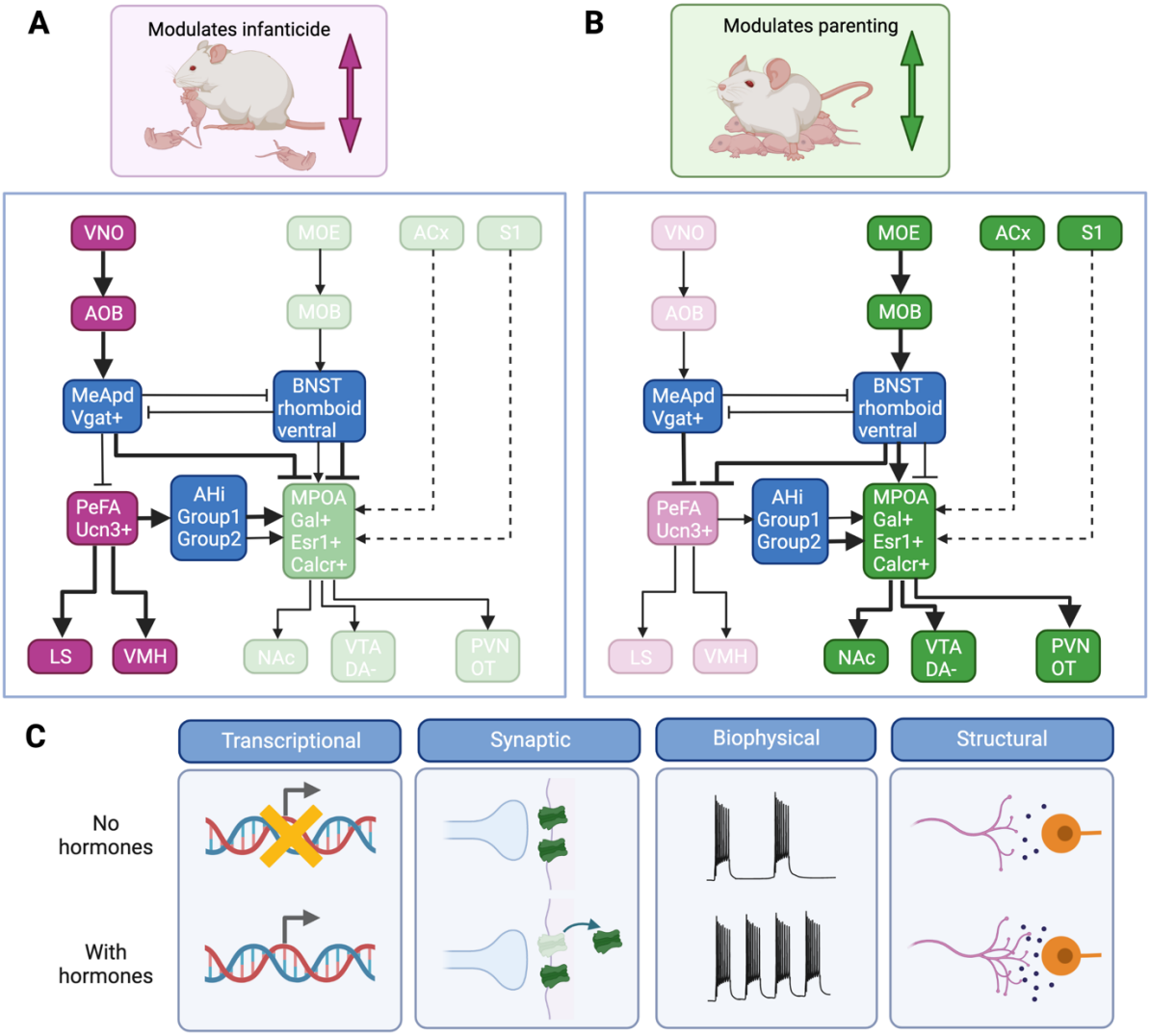

Figure 3. Plasticity in parental and nonparental circuits imposed by hormones. (A) Wiring diagram showing neural loci involved in parental and nonparental behaviours. During infanticidal state, shared nodes (blue) in circuitry enhance activity of nonparental nodes (pink) and suppress parental nodes (green). (B) During parental states, shared nodes in circuitry enhance activity of parental nodes and suppress nonparental nodes. Shared nodes confer significant flexibility in the network, by redirecting neuronal activity between mutually exclusive pathways. (C) Schematic showing plasticity induced by hormonal signalling, including changes in transcription, receptor internalisation, neuronal excitability and dendritic growth.

As hormone signalling plays an essential role in the modulation of circuit activities at transcriptional, synaptic, biophysical, and circuit levels, the core circuitry underlying parental and non-parental behaviours are likely impacted by these neuromodulators. The trigger and temporal dynamics of precisely timed hormonal release in the brain and sensory organs, particularly in virgin males, remains a crucial outstanding question. Such answers would provide compelling evidence for the role of hormonal neuromodulation in behavioural flexibility more broadly.

Unsolved questions

Finally, there are at least three important questions we believe require more evidence to address. First, behavioural switches in parental responses can develop over extended but precise timescales. What process regulates this time frame? Second, what are the specific triggers for the switching of infanticidal state to parenting especially in males? Third, the studies of innate behaviours have long addressed the hierarchical organization of behaviours [10,11,69] but this framework does not address the dynamics of behavioural transitions and therefore needs an update. Given all the behavioural and neural elements so far identified experimentally, what is a theoretical framework that could explain the cyclical nature of this behavioural switching? Resolving these unknowns will undoubtedly advance our basic understanding of the neural mechanisms underlying experience-dependent behavioural switching.

Declaration of interest

None

Acknowledgement

Authors thanks Mathew Edwards, Risa Sueda, and Daniel Regester for critical reading of the manuscript. Figures are generated using Biorender. SB and YI are supported by Gatsby Charitable Foundation (GAT3361) and Wellcome Trust (090843/F/09/Z).

Highlighted references of interest

* special interest

** outstanding interest

8. Carcea I, Caraballo NL, Marlin BJ, Ooyama R, Riceberg JS, Mendoza Navarro JM, Opendak M, Diaz VE, Schuster L, Alvarado Torres MI, et al.: **Oxytocin neurons enable social transmission of maternal behaviour. *Nature* 2021, **596**:553–557.

In this thorough study, long-term behavioural recordings of female virgin mice cohoused with a dam and litter revealed that the mother performs shepherding, to enocurage alloparental caregiving. Neuronal recordings showed oxytocinergic PVN neuron activation in female co-carers paired with USV-induced firing in the left auditory cortex to facilitate retrieval.

*26. Ladyman S, Carter K, Gillet M, Aung ZK, Grattan D: **A reduction in voluntary physical activity during pregnancy in mice is mediated by prolactin**. *Elife* 2021, **10e66260**:1–25.

Ladyman et al. observe that running wheel activity is rapidly reduced during early pregnancy, and persisted through to the first few days of lactation. Conditional deletion of prolactin receptors in the forebrain showed that this behavioural alteration is mediated by prolactin signalling, likely as an adaptive mechanism to conserve energy for parenting.

42. Yoshihara C, Tokita K, Maruyama T, Kaneko M, Tsuneoka Y, Fukumitsu K, Miyazawa E, Shinozuka K, Huang AJ, Nishimori K, et al.: **Calcitonin receptor signaling in the medial preoptic area enables risk-taking maternal care. *Cell Rep* 2021, **35**:109204.

Using Cre-depdendent silencing, Yoshihara et al. demonstrate that Calcr+ neurons in cMPOA are essential for maternal nurturing. Behaviours such as placentophagia, nursing, pup grouping, pup retrieval and nest building were all scored to measure parental actions. Rabies virus tracing showed increased afferents from nucleus accumbens to cMPOA in mothers relative to virgin females.

31. Autry AE, Wu Z, Kapoor V, Kohl J, Bambah-Mukku D, Rubinstein ND, Marin-Rodriguez B, Carta I, Sedwick V, Tang M, et al.: **Urocortin-3 neurons in the mouse perifornical area promote infant-directed neglect and aggression. *Elife* 2021, **10**:1–30.

This study demonstrates that Ucn3-expressing neurons in the PeFA are strongly activated in infanticidal virgin males following pup exposure relative to females and fathers. Differential activation of $Ucn3^+$ neuron terminals revealed modular organisation of nonparental behaviours (neglect, avoidance, aggression) into separate populations.

*37. Smiley KO, Brown RSE, Grattan DR: **Prolactin action is necessary for parental behavior in male mice.** *bioRxiv*, 2021.

Conditional deletion of prolactin receptors from CaMKIIα-expressing forebrain neurons impaired pup retrieval in fathers. Pharmacological suppression of prolactin release during mating had no significant impact on paternal care, but disrupted pup retrieval when bromocriptine administered during pup exposure.

53. Chen PB, Hu RK, Wu YE, Pan L, Huang S, Micevych PE, Hong W: **Sexually Dimorphic Control of Parenting Behavior by the Medial Amygdala. *Cell* 2019, **176**:1206-1221.e18.

Optogenetic activation showed that GABAergic MeApd neurons are implicated in both pup grooming and pup-directed attack depending on stimulation intensity in male mice. Activation of this population in female mice consistently promoted parental behaviour.

*57. Sato K, Hamasaki Y, Fukui K, Ito K, Miyamichi K, Minami M, Amano T: **Amygdalohippocampal area neurons that project to the preoptic area mediate infant-directed attack in male mice**. *J Neurosci* 2020, **40**:3981–3994.

Excitatory MPOA-projecting AHi neurons, were activated during pup-directed attack. Optogenetic excitation of this population is sufficient to disrupt caregiving in previously parental animals. Electrophysiology and histological results suggest that this population is targeted by oxytocin receptor expressing interneurons. Interestingly a subset of AHi neurons are also activated during parenting episodes.

*58. Inada K, Hagihara M, Tsujimoto K, Abe T, Konno A: **Plasticity of Neural Connections Underlying Oxytocin-mediated Parental Behaviors of Male Mice**. *bioRXiv,* 2021.

This study shows chemogenetic activation of oxytocin-expressing PVN neurons enhance pup retrieval and suppress infant-directed attack in virgin male mice. Activity mapping also showed c-fos expression of $Calcr^+$ neurons in the MPOA (identified in [39]) to be elevated whilst expression in $Ucn3^+$ neurons (identified in [31]) were depressed. Furthemore, excitatory connections from the lateral hypothalamus to the PVN were strengthened in fathers compared to virgin males.

*68. Inoue S, Yang R, Tantry A, Davis C ha, Yang T, Knoedler JR, Wei Y, Adams EL, Thombare S, Golf SR, et al.: **Periodic Remodeling in a Neural Circuit Governs Timing of Female Sexual Behavior**. *Cell* 2019, **179**:1393-1408.e16.

This study demonstrates striking morphogenesis of progesterone-expressing VMHvl neuron projections to anteroventral periventricular nucleus mediated by estrogen. This cyclic circuit reconfiguration improved functional connectivity between the two regions and converted females to and from sexually receptive states.

Bibliography

1. Dulac C, O'Connell LA, Wu Z: **Neural control of maternal and paternal behaviors**. *Science (80-)* 2014, **345**:765–770.

2. Kohl J: **Parenting — a paradigm for investigating the neural circuit basis of behavior**. *Curr Opin Neurobiol* 2020, **60**:84–91.

3. Bridges RS: **Neuroendocrine Regulation of Maternal Behavior**. *Front Neuroendocrinol* 2015, **0**:178-196

4. Marsteller FA, Lynch CB: **Reproductive responses to variation in temperature and food supply by house mice: II. Lactation.** *Biol Reprod* 1987, **37**:844–850.

5. Tachikawa KS, Yoshihara Y, Kuroda KO: **Behavioral transition from attack to parenting in male mice: A crucial role of the vomeronasal system**. *Ann Intern Med* 2013, **158**:5120–5126.

6. Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, Dulac CG: **Galanin neurons in the medial preoptic area govern parental behaviour**. *Nature* 2014, **509**:325–330.

7. Vom Saal FS: **Time-contingent change in infanticide and parental behavior induced by ejaculation in male mice**. *Physiol Behav* 1985, **34**:7–15.

8. Carcea I, Caraballo NL, Marlin BJ, Ooyama R, Riceberg JS, Mendoza Navarro JM, Opendak M, Diaz VE, Schuster L, Alvarado Torres MI: **Oxytocin neurons enable social transmission of maternal behaviour**. *Nature* 2021, **596**:553–557.

9. Numan M, Insel TR: *The Neurobiology of parental behaviour.* NY: Springer; 2003.

10. Baerends GP: **The functional organization of behaviour**. *Anim Behav* 1976, **24**:726–738.

11. Tinbergen N: *The study of instinct.* Clarendon Press/Oxford University Press; 1951.

12. Noirot E: **Serial order of maternal responses in mice**. *Anim Behav* 1962.

13. Carola V, Mirabeau O, Gross CT: **Hidden Markov model analysis of maternal behavior patterns in inbred and reciprocal hybrid mice**. *PLoS One* 2011, **6**.

14. Dewsbury DA: **Paternal Behavior in Rodents: The mere presence of a male can be important both pre- and post-natally .** 1985, **852**:841–852.

15. Stolzenberg DS, Numan M: **Hypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in rats**. *Neurosci Biobehav Rev* 2011, **35**:826–847.

16. Marlin BJ, Mitre M, D'Amour JA, Chao M V., Froemke RC: **Oxytocin enables maternal behaviour by balancing cortical inhibition**. *Nature* 2015, **520**.

17. Spruijt BM, Van Hooff JARAM, Gispen WH: **Ethology and neurobiology of grooming behavior**. *Physiol Rev* 1992, **72**:825–852.

18. Gubernick DJ, Alberts JR: **"Resource" exchange in the biparental California mouse (Peromyscus californicus): Water transfer from pups to parents**. *J Comp Psychol* 1987, **101**:328–334.

19. Koller G: **Der nestbau der weisser Maus und seine hormonale Auslosung**. *Verhandlungen Dtsch Zool Gesellschaft* 1952, **11**:160–168.

20. Lisk RD, Pretlow RA, Friedman SM: **Hormonal stimulation necessary for elicitation of maternal nest-building in the mouse (Mus musculus)**. *Anim Behav* 1969, **17**:730–737.

21. Ladyman S, Carter K, Gillet M, Aung ZK, Grattan D: **A reduction in voluntary physical activity during pregnancy in mice is mediated by prolactin**. *Elife* 2021, **10e66260**:1–25.

22. Han Y, Li X-L, Wang SR, Wei YC, Xu XH: **Presence of pups suppresses hunger-induced feeding in virgin adult mice of both sexes**. *Neuroscience* 2017, **362**:228–238.

23. Kimchi T, Xu J, Dulac C: **A functional circuit underlying male sexual behaviour in the female mouse brain**. *Nature* 2007, **448**:1009–1014.

24. König B: **Components of lifetime reproductive success in communally and solitarily nursing house mice - a laboratory study**. *Behav Ecol Sociobiol* 1994, **34**:275–283.

25. Liu HX, Lopatina O, Higashida C, Fujimoto H, Akther S, Inzhutova A, Liang M, Zhong J, Tsuji T, Yoshihara T, et al.: **Displays of paternal mouse pup retrieval following communicative interaction with maternal mates**. *Nat Commun* 2013, **4**:1346–1348.

26. König B, Lindholm AK, Lopes PC, Dobay A, Steinert S, Buschmann FJU: **A system for automatic recording of social behavior in a free-living wild house mouse population**. *Anim Biotelemetry* 2015, **3**.

27. Lauer J, Zhou M, Ye S, Menegas W, Nath T, Rahman MM, Santo V Di, Soberanes D,

Feng G, Murthy VN, et al.: **Multi-animal pose estimation and tracking with DeepLabCut**. *bioRxiv* 2021.

28. Segalin C, Williams J, Karigo T, Hui M, Zeliokowsky M, Sun J, Perona P, Anderson DJ, Kennedy A: **The Mouse Action Recognition System (MARS): a software pipeline for automated analysis of social behaviors in mice**. *bioRxiv* 2021.

29. Parmigiani S, Vom Saal FS: *Infanticide and Parental Care.* Routledge; 1994.

30. Isogai Y, Wu Z, Love MI, Ahn MHY, Bambah-Mukku D, Hua V, Farrell K, Dulac C: **Multisensory Logic of Infant-Directed Aggression by Males**. *Cell* 2018, **175**:1827-1841.e17.

31. Autry AE, Wu Z, Kapoor V, Kohl J, Bambah-Mukku D, Rubinstein ND, Marin-Rodriguez B, Carta I, Sedwick V, Tang M, et al.: **Urocortin-3 neurons in the mouse perifornical area promote infant-directed neglect and aggression**. *Elife* 2021, **10**:1–30.

32. Vom Saal FS, Howard LS: **The regulation of infanticide and parental behavior: Implications for reproductive success in male mice**. *Science (80-)* 1982, **215**:1270–1272.

33. Lukas D, Huchard E: **The evolution of infanticide by females in mammals**. *Philos Trans R Soc B Biol Sci* 2019, **374**.

34. William Huck U, Soltis RL, Coopersmith CB: **Infanticide in male laboratory mice: Effects of social status, prior sexual experience, and basis for discrimination between related and unrelated young**. *Anim Behav* 1982, **30**:1158–1165.

35. Valente S, Marques T, Lima SQ: **No evidence for prolactin's involvement in the post-ejaculatory refractory period**. *Commun Biol* 2021, **4**:2–11.

36. Jirikowski GF, Caldwell JD, Häussler HU, Pedersen CA: **Mating alters topography and content of oxytocin immunoreactivity in male mouse brain**. *Cell Tissue Res* 1991, **266**:399–403.

37. Smiley KO, Brown RSE, Grattan DR: **Prolactin action is necessary for parental behavior in male mice.** *bioRxiv,* 2021.

38. Schiavo JK, Valtcheva S, Bair-marshall CJ, Song SC, Martin KA, Froemke RC: **Innate and plastic mechanisms for maternal behaviour in auditory cortex**. *Nature* 2020, **587**.

39. Sedlak AJ, Broadhurst DD: *Third national incidence study of child abuse and neglect*. 1996.

40. Rosenblatt J: **Psychobiology of maternal behavior: contribution to the clinical understanding of maternal behavior among humans**. *Acta Pædiatrica* 1994, **83**:3–8.

41. Gammie SC, Edelmann MN, Mandel-Brehm C, D'Anna KL, Auger AP, Stevenson SA: **Altered dopamine signaling in naturally occurring maternal neglect**. *PLoS One* 2008, **3**.

42. Yoshihara C, Tokita K, Maruyama T, Kaneko M, Tsuneoka Y, Fukumitsu K, Miyazawa E, Shinozuka K, Huang AJ, Nishimori K, et al.: **Calcitonin receptor signaling in the medial preoptic area enables risk-taking maternal care**. *Cell Rep* 2021, **35**:109204.

43. Sairenji TJ, Ikezawa J, Kaneko R, Masuda S, Uchida K, Takanashi Y, Masuda H, Sairenji

T, Amano I, Takatsuru Y, et al.: **Maternal prolactin during late pregnancy is important in generating nurturing behavior in the offspring**. *Proc Natl Acad Sci U S A* 2017, **114**:13042–13047.

44. Brown RSE, Aoki M, Ladyman SR, Phillipps HR, Wyatt A, Boehm U, Grattan DR: **Prolactin action in the medial preoptic area is necessary for postpartum maternal nursing behavior**. *Proc Natl Acad Sci U S A* 2017, **114**:10779–10784.

45. Hauser H, Gandelman R: **Lever pressing for pups: Evidence for hormonal influence upon maternal behavior of mice**. *Horm Behav* 1985, **19**:454–468.

46. Kohl J, Babayan BM, Rubinstein ND, Autry AE, Marin-Rodriguez B, Kapoor V, Miyamishi K, Zweifel LS, Luo L, Uchida N: **Functional circuit architecture underlying parental behaviour**. *Nature* 2018, **556**:326–331.

47. Renier N, Adams EL, Kirst C, Wu Z, Azevedo R, Kohl J, Autry AE, Kadiri L, Umadevi Venkataraju K, Zhou Y, et al.: **Mapping of Brain Activity by Automated Volume Analysis of Immediate Early Genes**. *Cell* 2016, **165**:1789–1802.

48. Fang YY, Yamaguchi T, Song SC, Tritsch NX, Lin D: **A Hypothalamic Midbrain Pathway Essential for Driving Maternal Behaviors**. *Neuron* 2018, **98**:192-207.e10.

49. Trouillet AC, Keller M, Weiss J, Leinders-Zufall T, Birnbaumer L, Zufall F, Chamero P: **Central role of G protein Gαi2 and Gαi2 + vomeronasal neurons in balancing territorial and infant-directed aggression of male mice**. *Proc Natl Acad Sci U S A* 2019, **116**:5135–5143.

50. Lin D, Boyle MP, Dollar P, Lee H, Lein ES, Perona P, Anderson DJ: **Functional identification of an aggression locus in the mouse hypothalamus**. *Nature* 2011, **470**:221–227.

51. Gandelman R, Zarrow MX, Denenberg VH, Myers M: **Olfactory bulb removal eliminates maternal behavior in the mouse**. *Science (80-)* 1971, **171**:210–211.

52. Fraser EJ, Shah NM: **Complex chemosensory control of female reproductive behaviors**. *PLoS One* 2014, **9**:5–10.

53. Chen PB, Hu RK, Wu YE, Pan L, Huang S, Micevych PE, Hong W: **Sexually Dimorphic Control of Parenting Behavior by the Medial Amygdala**. *Cell* 2019, **176**:1206-1221.e18.

54. Li Y, Mathis A, Grewe BF, Osterhout JA, Ahanonu B, Schnitzer MJ, Murthy VN, Dulac C: **Neuronal Representation of Social Information in the Medial Amygdala of Awake Behaving Mice**. *Cell* 2017, **171**:1176-1190.e17.

55. Tsuneoka Y, Tokita K, Yoshihara C, Amano T, Esposito G, Huang AJ, Yu LM, Odaka Y, Shinozuka K, McHugh TJ, et al.: **Distinct preoptic- BST nuclei dissociate paternal and infanticidal behavior in mice** . *EMBO J* 2015, **34**:2652–2670.

56. McHenry JA, Rubinow DR, Stuber GD: **Maternally responsive neurons in the bed nucleus of the stria terminalis and medial preoptic area: Putative circuits for regulating anxiety and reward**. *Front Neuroendocrinol* 2015, **38**:65–72.

57. Sato K, Hamasaki Y, Fukui K, Ito K, Miyamichi K, Minami M, Amano T:

Amygdalohippocampal area neurons that project to the preoptic area mediate infant-directed attack in male mice. *J Neurosci* 2020, **40**:3981–3994.

58. Inada K, Hagihara M, Tsujimoto K, Abe T, Konno A: **Plasticity of Neural Connections Underlying Oxytocin-mediated Parental Behaviors of Male Mice**. *bioRxiv* 2021.

59. Nakahara TS, Camargo AP, Magalhães PHM, Souza MAA, Ribeiro PG, Martins-Netto PH, Carvalho VMA, José J, Papes F: **Peripheral oxytocin injection modulates vomeronasal sensory activity and reduces pup-directed aggression in male mice**. *Sci Rep* 2020, **10**:1–13.

60. Pekarek BT, Hunt PJ, Arenkiel BR: **Oxytocin and Sensory Network Plasticity**. *Front Neurosci* 2020, **14**.

61. Brown RSE, Piet R, Herbison AE, Grattan DR: **Differential actions of prolactin on electrical activity and intracellular signal transduction in hypothalamic neurons**. *Endocrinology* 2012, **153**:2375–2384.

62. Stagkourakis S, Smiley KO, Williams P, Kakadellis S, Ziegler K, Bakker J, Brown RSE, Harkany T, Grattan DR, Broberger C: **A Neuro-hormonal Circuit for Paternal Behavior Controlled by a Hypothalamic Network Oscillation**. *Cell* 2020, **182**:960-975.

63. Mitre M, Marlin BJ, Schiavo JK, Morina E, Norden SE, Hackett TA, Aoki CJ, Chao M V., Froemke RC: **A distributed network for social cognition enriched for oxytocin receptors**. *J Neurosci* 2016, **36**:2517–2535.

64. Valtcheva S, Issa HA, Martin KA, Jung K, Kwon H-B, Froemke RC: **Neural circuitry**

for maternal oxytocin release induced by infant cries. *bioRxiv* 2021.

65. Liu M, Kim D-W, Zeng H, Anderson DJ: **Make war not love: The neural substrate underlying a state-dependent switch in female social behavior**. *Neuron* 2022, **110**:1–16.

66. Stagkourakis S, Spigolon G, Liu G, Anderson DJ: **Experience-dependent plasticity in an innate social behavior is mediated by hypothalamic LTP**. *Proc Natl Acad Sci U S A* 2020, **117**:25789–25799.

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

68. Inoue S, Yang R, Tantry A, Davis C ha, Yang T, Knoedler JR, Wei Y, Adams EL, Thombare S, Golf SR, et al.: **Periodic Remodeling in a Neural Circuit Governs Timing of Female Sexual Behavior**. *Cell* 2019, **179**:1393-1408.

69. Anderson DJ: **Optogenetics, sex, and violence in the brain: Implications for psychiatry**. *Biol Psychiatry* 2012, **71**:1081–1089.