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Parental Brain Through Time: function, anatomy, and molecular mechanisms in contexts

Authors

Kumi O. Kuroda[12*], Kansai Fukumitsu[13], Takuma Kurachi[14], Nami Ohmura[15], Yuko Shiraishi[16], Chihiro Yoshihara[12]

Affiliations

[1] RIKEN Center for Brain Science, Saitama, 351-0198, Japan

2 School of Life Sciences and Technologies, Tokyo Institute of Technology, Kanagawa, Japan

3 Department of Physiology, Fujita Health University School of Medicine, Toyoake, Japan

4 Department of Agriculture, Tokyo University of Agriculture and Technology, Tokyo, Japan

5 Center for Brain, Mind and Kansei Sciences Research, Hiroshima University, Hiroshima, Japan

6 Kawamura Gakuen Woman's University, Chiba, Japan

***Corresponding authors**

Kumi O. Kuroda

School of Life Science and Technology, Tokyo Institute of Technology

4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8503, Japan

E-mail: kurodalab@bio. titech.ac.jp; kumi.kuroda@a.riken.jp

Lab website: https://en.kurodalab.net/

Twitter handle: @kumi_kuroda

Keywords:

Parental behavior, the medial preoptic area, social behavior, calcitonin receptor, amylin

Abstract (200)

Mammalian parental care is highly mother-biased, prompting researchers to presume its connection to female reproductive behavior and physiology, not male. However, recent findings in neurobiological studies suggest the opposite. Considering the evolutionary path of mammalian parental care, the ancestral form of vertebrate parental care appears to be male-biased as in living teleosts (bony fish), and originated from egg guarding as an extension of territorial behavior. Phylogenetic analyses suggest that in basal tetrapods, the harsh reproductive environments have facilitated terrestrial adaptation and extensive parental investment in females, and salamander-like basal amniotes exhibited extended egg retention in female bodies. Molecular and fossil evidence indicates that synapsids that have later evolved into mammals have already performed extensive maternal care including egg/offspring hydration in the Carboniferous period. Then the nocturnal adaptation in Jurassic mammaliaforms promoted endothermy and prolonged maternal care for thermal control and lactation. This situation may have added nutritional gate control to the offspring care circuit to balance parental provisioning with maternal homeostatic needs. Combining these paleontological, comparative ecological, and neuromolecular findings, we propose that the mammalian parenting circuit may be derived from MPOA neurons controlling reproductive behaviors during the terrestrial adaptation in anamniotes, either by divergent or parallel evolution. Next, we discuss another long-postulated hypothesis that complex affiliative sociality among adults, including group living, cooperative infant care, empathy, and altruism, may have emerged primarily for extended support of the offspring growth, utilizing the established maternal care circuit in mammals. These evolution-informed working hypotheses may also help dissect the neural basis of the complex cognitive functions in mammals.

Graphic abstract

This review discusses the ancestors and descendants of mammalian parental care. The core neural circuit of mammalian parental care may possibly be derived from the preoptic neurons for territory and egg guarding in male vertebrates. Reproduction in harsh environments selected tetrapods for terrestrial reproduction, and amniotes for maternal lactation and endothermy. The established maternal care circuit should have served as a foundation for group living, cooperation and altruism in therian mammals.

1. Parental care in vertebrates

1-1 An overview

Parental care is critical for infant survival and mental well-being in humans. Inappropriate infant care due to an unstable early environment or child maltreatment affects mental and physical health and social attitude in later life; thus understanding the neural mechanisms of parental care is of great clinical relevance too [1, 2]. Biologically, parental care is the behavioral component of parental provisioning and can be roughly defined as "any parental trait that is likely to enhance the fitness of the offspring, often at a cost to the parents' fitness" [3, 4]. In the majority of animals, parents do not care for the offspring. However, parental care has evolved numerous times in invertebrates and vertebrates, and among vertebrates, approximately 30 % of teleosts, 25 % of amphibians, 10 % of reptiles, and 97 % of birds provide at least some care. In mammals, infants of all species rely on maternal milk provisioning for survival, indicating the single origin (monophyletic) of mammalian maternal care.

Recent neuroscientific studies unveil the anatomical and molecular features of its core neurocircuit at the medial preoptic area (MPOA), and paleontology and comparative behavioral ecology have gained substantial insights into the evolutionary path of the mammalian lineage. Yet, the integration of these findings from different research disciplines to illustrate the overall perspective of mammalian parental care requires more attention. This article aims to fill this gap and summarize the recent findings relevant to parental brains through time, following the fascinating recent work of "Brains through Time" [5]. As the scope of this review is broad, we mark the key terms in each section with underlines below.

When parental care occurs in sexually-reproducing animals, caregiving is often biased to mothers than fathers except for teleosts and amphibians (Chapter 3) because paternity is often more uncertain than maternity and sexual selection acts more strongly on males to increase their mating rate [6]. In mammals, 100 % of mothers provide care while less than 10 % of fathers do, and in about 90% of cases, mothers are the sole caregiver. Still, non-maternal animals (fathers, older siblings, and other group members) may also provide extensive infant care in several mammalian species such as mice, prairie voles, meerkats, marmoset and tamarin monkeys, and humans [7-11].

Neurobiological researchers may call these behaviors collectively "*parental* behavior", even if the actors are not necessarily biological parents of the young. This is confusing from the evolutionary biological perspective. Still, the proximate neural mechanisms of behaviors are shared among parental

and alloparental behaviors (Chapter 2), and the behaviors *per se* are often qualitatively similar. Moreover, animal parents do not intend to reproduce their genome or precisely recognize their biological relationship when they care for young; instead, parental care is driven via the parents' motivational state that their brain produces upon the sensory cues from distressed small conspecifics. As such, "misplaced parental care" is pervasive among the same or even cross-species [8].

1-2 Parental care behaviors in rodents

Maternal care in mammals includes multiple behavioral components, including providing maternal milk, thermoregulation, helping with locomotion, protection from predators, parasites, and environmental hazards, and providing opportunities to learn hunting/foraging skills [4, 12, 13]. The extent of maternal care varies among species, from minimal interaction of 3-min / day nursing and prepartum nest-building in rabbits to 6-year continuous interaction with nursing in orangutans [14].

The repertoires of (allo)parental care behaviors in the well-studied species of laboratory rats and mice are summarized (Table 1). Among these, pup retrieval behavior, carrying a pup into their own nest from outside, has been widely used as a representative index of nurturing motivation in mice and rats because pup retrieval behavior is easily and unambiguously measurable and can be performed well by fathers and non-parents [15, 16]. Moreover, experienced caregivers first retrieve pups before engaging in other pup-directed care behaviors such as licking/grooming or crouching over, as an adaptive serial order of maternal behaviors [17]. Another component of well-studied maternal care is licking / grooming and nursing posture [18, 19]. In laboratory mice, however, licking / grooming behaviors are less precisely dissociated from self-grooming or sniffing than in rats, which may cause some variabilities as discussed below. Please refer to previous literature [20-22] for references and assessment protocols for each component of parental nurturing behaviors and [23] for additional experimental designs of postpartum maternal motivations.

It should be stressed that parental care behaviors are easily disturbed by any perturbation of animals' general fitness or environmental stress [2], possibly because they are not essential for the performer's life, unlike freezing or feeding. Moreover, many other deficits, such as olfactory disturbances and hyper/hypoactivity, can secondarily affect the performance of the pup retrieval irrespective of parental motivation *per se*. Therefore substantial care should be taken upon measurements to avoid unnecessary stress induced by handling or novel arena/room for testing and to

include the indices reflecting general wellness, sensorimotor agility such as first sniffing latency and general locomotor activity in the retrieval assay [20, 24].

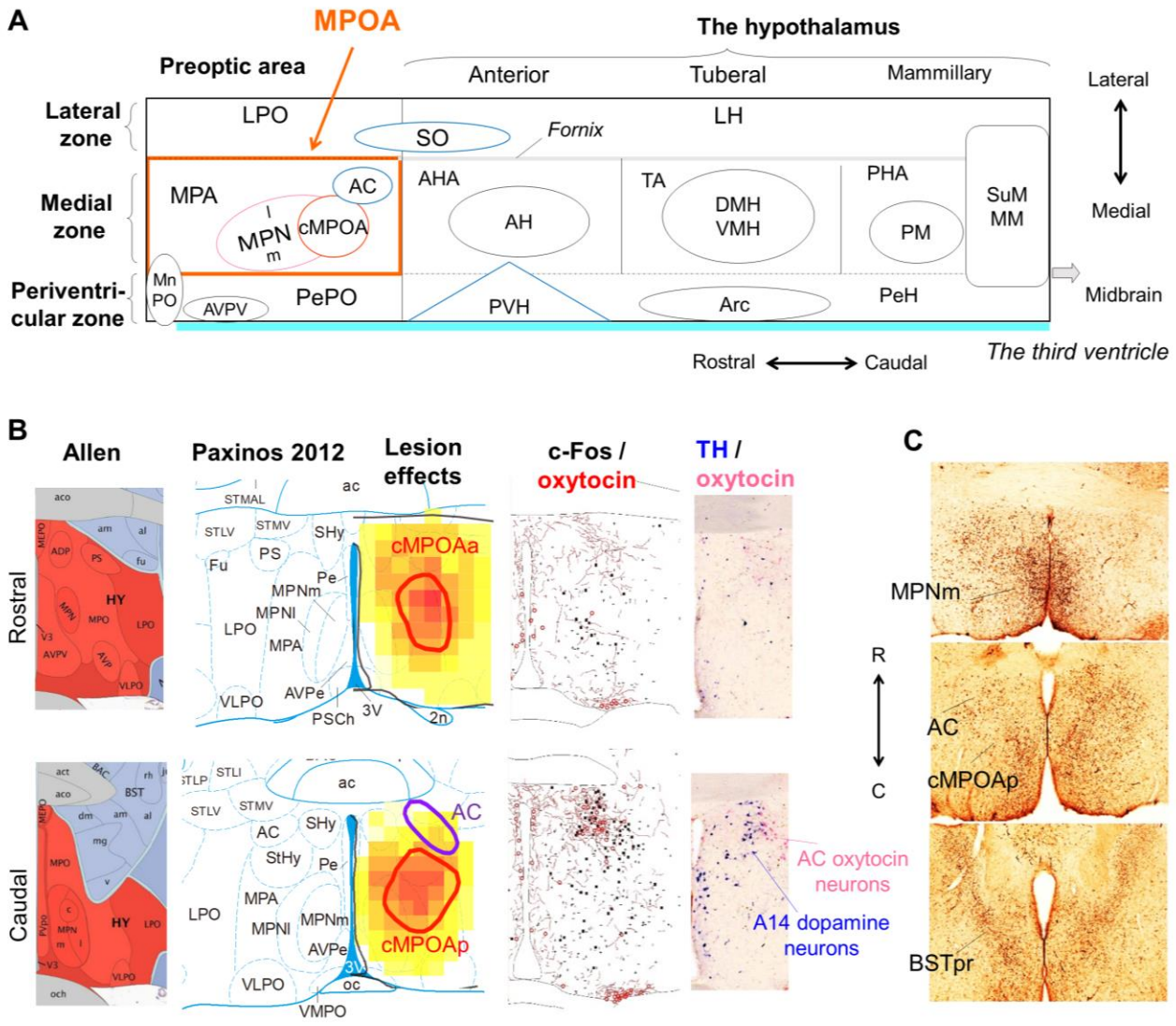

Figure 1. The neuroanatomy of the MPOA and its parenting-relevant subregions

(A) Schematic representation of the preoptic-hypothalamic continuum, sagittal view with the mediolateral axis. Note that the dorsoventral axis is compressed. Modified based on Fig. 1 of [27]. The POA-hypothalamic continuum can be segmented into 4 parts along the rostrocaudal axis and 3 pieces along the mediolateral axis. One of the resultant 12 segments is the MPOA, shown in the orange rectangle. Nuclei with oxytocin neurons are colored blue.

Periventricular zone: Median preoptic n. (MnPO)

Anteroventral periventricular n. (AVPV)
Paraventricular n. of hypothalamus (PVH)
Periventricular n. of hypothalamus (PeH)
Arcuate n. (Arc)
Media1 zone
Medial preoptic area (MPA)
Medial preoptic n. (MPO)
Anterior hypothalamic n. (AH)
Anterior hypothalamic area (AHA)
Tuberal area of the hypothalamus (TA)
Ventromedia1 n. (VMH)
Dorsomedial n. (DMH)
Premammillary n. (PM)
Mammi1lary complex
medial mammillary n. (MM)
lateral mammillary n. (LM)
supramammillary n. (SuM)
Posterior hypothalamic area (PHA)
Lateral zone
Lateral preoptic area (LPO)
Lateral Hypothalamic area (LH)
Supraoptic n. (SO)

(B) Two coronal sections depicting the anterior and posterior part of the cMPOA, illustrating: from the left, the Allen mouse brain atlas [40], Franklin and Paxinos' stereotaxic atlas [270], the location of the cMPOA (anterior and posterior) and AC with Spearman's correlation coefficients (red is smaller *p*-value) of voxel-based lesion-behavior mapping [43]; the oxytocin neurons and fibers (red) and c-Fos induced by parental care in virgin females; oxytocin (pink) and tyrosine-hydroxylase (purple) expressing neurons. Note that the Allen atlas is dorsolaterally elongated than the stereotaxic atlas, due to the production procedure [271]. ac: anterior commissure. oc: optic chiasm. 3V: third ventricle. Note that the highest density of Fos expression (in the AC) does not coincide with the lesion effects (in the cMPOA).

(C) The inverted V shape formed by the estrogen receptor alpha-containing neurons, starting from the PePO/MPNm to the BSTpr. Three coronal sections of the female brain at postpartum day 0, the top two are roughly the same level as (B). Black: estrogen receptor alpha-immunoreactivity.

Box 1. The MPOA in the preoptic-hypothalamus continuum

While developmental neuroscience dissociates the hypothalamus and the preoptic area (POA) [25, 26], there are practical benefits to dealing with them together as a continuum (Fig. 1A); first, the POA and hypothalamus are spatially adjacent and connected heavily through the longitudinal fiber system; second, both of them contain multiple subregions that regulate autonomic, endocrine and innately motivated behaviors.

According to Simerly, the MPOA is one of the twelve (3 x 4, in mediolateral and rostrocaudal) divisions of the preoptic-hypothalamic continuum (Fig. 1A) [27]. The MPOA contains multiple subnuclei

segregated by distinct cellular morphologies, molecular expressions, connectivity, and biological functions [27-31], such as sleep at the ventrolateral preoptic nucleus (VLPO) [32, 33], thermo- and osmoregulation at the median preoptic nucleus (MnPO) [34, 35], puberty onset and fertility through GnRH neurons located at ventral part of the MPOA [36], male and female sexual behaviors [37-39].

It should be noted that the map of the POA varies widely among different versions of Paxinos's stereotaxic atlases [28] and the Allen brain atlas [40] (Fig. 1B). For example, the large portion of the dorsoposterior MPOA in the Paxinos atlas (based on [41]) is regarded as the ventral part of the bed nuclei of stria terminalis (BST) in the Allen atlas (based on [42]). We suggest that identifying the anterior commissural nucleus (AC, Fig. 1B) by its oxytocin neurons as shown in the Paxinos atlas will help to determine the border between the MPOA and the BST. The AC is also remarkable as the most densely and selectively expresses c-Fos, the marker for transcriptional activation of neurons, during parental behaviors (Fig. 1B) [43-45].

As another relevant anatomical structure in the MPOA, an inverted V-shape expression of estrogen receptor alpha (Fig. 1C), from the MPNm to BSTpr, is commonly observed in mu-opioid receptor mRNA [46], prolactin receptor mRNA [47], and aromatase immunoreactivity [48](see also the migration of BST neurons into the MPN, [49]). A similar inverted V-shape of expression is reported for male-biased Sytl4 (synaptotagmin-like 4), slightly more posteriorly [50]. Note that these V shapes are slightly tilted (the ventral is more anterior than in the coronal plane). The anterior and posterior parts of the AC also tilt in the same direction, suggesting the stereotaxic coronal plane is oblique to the natural brain axis.

2. The neural mechanisms of mammalian parental care

2-1 Classical studies

Initial studies focused on neuroendocrine regulation of maternal behavior in mammals, revealing that hormonal milieu during pregnancy and parturition is critical for maternal behavior induction [51]. Among peripartum endocrine factors, estrogen is reported to be important for the onset of rat maternal behavior [52]. Genetic targeting studies showed facilitatory but not indispensable effects of estrogen receptor alpha on pup retrieval in mice and rats [53-55], consistent with the previous findings showing that neither ovariectomy nor hypophysectomy grossly disrupts allomaternal behaviors [16, 56, 57]. For the

sensory modalities required for maternal behavior, many species (e.g., rats and humans) utilize "multisensory control" and do not depend on any single sensory modality [58-60], while some species heavily rely on a specific sensory input (e.g., olfaction in mice, audition in bats) for maternal care.

Then Michael Numan presented a seminal series of studies, demonstrating that the medial preoptic area (MPOA, Fig. 1) is responsible for rat maternal care, possibly through its dorsolateral connections with the brain stem such as the ventral tegmental area (VTA) [61-65]. Since then, the MPOA has been established as the brain hub for maternal, paternal, and alloparental nurturing behaviors, with evidence in laboratory rats [61, 66, 67], hamsters [68], biparental California mice (Peromyscus californicus) [69], laboratory mice [43], rabbits [70], sheep [71], common marmoset monkeys [72], and with supportive observations in humans [73 74] (See [4, 14] for a comprehensive review). Furthermore, the POA has been implicated in parental care in non-mammalian vertebrates, such as in ring doves [75] turkey hens [76], poison frogs [77, 78], and in teleosts [79]. Because parental care is supposed to emerge numerous times independently among vertebrates, this consistent involvement of the MPOA is impressive.

So far, no other brain area is known to be as selectively and critically required for parental care as the MPOA is. For example, the medial amygdala (MeA) lesions or severing of the stria terminalis do not inhibit or may even facilitate pup retrieval [80-83]. Chen et al. [84] showed that optogenetic inhibition of posterodorsal MeA (MeApd) VGAT-Cre (GABAergic) neurons suppresses pup grooming but not pup retrieval or crouching (for activation, see Fig. 1K2 of [84]) ["pup grooming" includes any contact with a pup by mouth, and holding a pup by the forelimbs in this study], while they showed significant effects of MeApd GABA neuron activation/inhibition on male infanticide. These data collectively suggest that the role of MeApd in pup retrieval is relatively small compared with its well-established importance for male sexual behavior, intermale aggression, or infanticide. Similarly, bilateral lesions or pharmacological suppression of various regions of the midbrain periaqueductal gray (PAG) do not inhibit pup retrieval while affecting other parental behavior components such as arched-back nursing (kyphosis) or maternal aggression [85-88]. Lesions or functional inhibition of oxytocin neurons and /or other neurons in the paraventricular nucleus of the hypothalamus (PVH) may disturb pup retrieval, especially the initial acquisition phase in non-maternal animals in several studies [89-92]. Yet, in several cases, these results can be derived from the general anxiolytic effects of oxytocin [93, 94], and the PVH may not be critically involved in ongoing maternal care except for milk ejection [95] (for the role of oxytocin, refer to Section 4-1). For the role of the cingulate and other cerebral cortex, septum, basolateral amygdala, and ventral pallidum, please refer to [4, 20, 96].

The major shortfall of the classical studies employing permanent brain lesions is the non-specific deleterious effects caused by brain damage in general and should be accompanied by appropriate control experiments, such as the similar-sized lesions in the other brain area and the inclusion of non-targeted behavioral assessment such as general physiological fitness and locomotion, to prove the specificity of the behavioral alteration [97, 98]. Still, provided these necessary cautions, the voxel-based lesion-behavior mapping has yielded many remarkable findings with anatomical precision, e.g., Broca and Wernicke areas crucial for distinct types of aphasia. Also, an associated negative result (i.e., the lesion did not affect another behavior) is very informative to show the selectivity of the target brain region for a given behavior; for example, the MPOA lesions in rats and mice that disrupt maternal care do not grossly affect female sexual behaviors or parturition of average numbers of litters [43, 61], also suggesting that the maternal care defects are not caused by severely-disturbed general health.

2-2 Parenting-relevant MPOA subregions

Our research group has taken an anatomical approach to narrow down the responsible area for maternal, paternal and alloparental care within the MPOA. Utilizing the voxel-based lesion behavior mapping, we defined the central part of the posterior MPOA (cMPOA, Fig. 1B) [43, 44], a subdivision marked by a cluster of glutamatergic neurons, as the most indispensable MPOA subdivision for (allo)parental care. Bilateral cMPOA lesions completely abolish pup retrieval and induce infanticide regardless of sex, without affecting feeding, locomotion, female mating, pregnancy, and parturition.

The cMPOA partially overlaps with the estrogen receptor alpha-expressing neurons in the medial preoptic nucleus (MPN) and its V-shaped continuum toward the bed nucleus of stria terminalis, principal part (BSTpr) (Fig. 1C, Box1). The MPN-BSTpr has been established to be essential for male sexual behavior in all vertebrates tested [99]. The cMPOA, especially in the posterior part, is significantly activated by male sexual behaviors [44]. In contrast, the MPN is not necessary for lordosis in rats, the consummatory aspect of female sexual behavior. The cMPOA's closer tie with male but not female sexual behaviors is puzzling, as mammalian parental care is heavily biased toward females (see Section 4-1).

The cMPOA is adjacent to the anterior commissural nucleus (AC), the third largest population of the magnocellular oxytocin neurons in rats and mice [100-104]. Oxytocin neurons in the AC, SON and PVH are highly activated during parturition and nursing, though not during pup care *per se* [43]. This spatial positioning of "caregiving" neurons in the intersection of the areas responsible for male sexual behaviors

and parturition/milk ejection may be suited for their function as a post-mating caregiving behavior in both sexes.

2-3 Molecularly-defined neuronal populations involved in various (allo)parental behaviors

As the MPOA comprises heterogenous neuronal populations, it is preferable to specify the cell type(s) required for (allo)parental care. Traditional histological analyses [43, 105, 106] have suggested that several marker molecules, such as estrogen receptor alpha, galanin, and neurotensin, are activated during pup care. Viral vector-mediated genetic techniques have further enabled cell-type specific manipulations of these specific neuronal groups during (allo)parental care.

a) **Estrogen receptor alpha**

Estrogen signaling via the estrogen receptor alpha and beta (encoded by *Esr1* and *Esr2,* respectively) is important for the onset of rat maternal behavior [52]. Genetic targeting studies showed facilitatory effects on the onset of heightened maternal care in mice and rats, though not essential, especially for non-maternal animals [53-55]. Ribeiro et al. reported that short-interference RNA-based *Esr1* knockdown in the MPOA using the adeno-associated viral vector (AAV) altered a wide array of female social behaviors, including postpartum retrieval, licking, and nursing behaviors [107], while pup survival was intact (Personal communication with Prof. Ana Ribeiro).

Fang et al. [108] reported that hM4Di-mediated chemogenetic inhibition of MPOA Esr1+ neurons using an Esr1-Cre knockin line inhibits pup retrieval in virgin females and lactating mothers without affecting pup sniffing, grooming, or crouching over (cf. Fig. 1D-F of [108]). GCaMP6 signal of MPOA Esr1+ (but not Esr1-) neurons starts to rise as the females approach the pup and peak at the onset of pup retrieval, larger in mothers than in virgin females, but not at pup grooming or crouching. In vivo single-unit recording suggested that the subset of MPOA neurons responding to nest building or sniffing of males are separate from those responding to pup sniffing, approach, and retrieval. Furthermore, MPOA Esr1+ neurons (>70% are GABAergic, and slightly less than 20% are glutamatergic) project to the ventral tegmental area (VTA) and preferentially inhibit non-dopaminergic VTA neurons. VTA dopaminergic neurons are activated at the onset of pup retrieval [108, 109] (plausibly reflecting the reward prediction error rather than the retrieval *per se* [110]). Finally, virgin females' pup retrieval in a novel arena was facilitated by optogenetic activation of MPOA Esr1+ projection to the VTA and inhibited by a sodium channel blocker bupivacaine infusion and blocking neuronal spiking in the VTA. This fascinating study elucidated the detailed features of pup-retrieval responsible Esr1+ neurons in the

MPOA, in contrast to Esr1+ neurons in the ventromedial nucleus of the hypothalamus, ventrolateral part (VMHvl), of which modulation does not affect pup retrieval [111].

Xu and colleagues reported that Caspase 3-based ablation of either GABAergic or glutamatergic MPOA neurons significantly inhibits pup retrieval [112] and that optogenetic activation of VGat+ MPOA neurons induces, and optogenetic inhibition reduces, pup retrieval and nest building, while Esr1+ MPOA neurons affect only pup retrieval [113]. It should be noted, however, that the definition of "pup retrieval" in their study is pup-carrying and does not mean pup-placing into the nest. Moreover, fake pups (rubber blocks) were also "retrieved and grouped" by optogenetic stimulation of MPOA neurons [112], leaving the possibility that this pup-carrying can be performed as a hunting-like object carrying, mediated by CamKII+ MPOA neurons (but not by Vglut2+ or Vgat+ MPOA neurons, surprisingly) [114]. In addition, Xu and colleagues made an inspiring argument on competition between feeding and maternal behavior in line with the previous report [115], based on their findings that the presence of pups inhibits feeding stimulated by 10hr fasting or chemogenetic activation of arcuate Agrp neurons [116] and optogenetic stimulation of AGRP neurons inhibits maternal nest building without affecting pup retrieval [113].

Overall, these studies demonstrate the critical role of MPOA Esr1+ neurons in pup retrieval behaviors. However, Esr1+ neurons consist of heterogenous populations that represent one-third of the total MPOA neurons, and are distributed widely in the whole MPOA [30, 108], leaving room for further specification.

b) Galanin

Galanin is a brain-gut peptide concentrated in the hypothalamus and promotes feeding, mating, and sleep [117]. The seminal study of Dulac and colleagues in 2014 reported that galanin+ MPOA neurons govern parental behavior, especially pup grooming (includes pup sniffing and licking in this paper) [118]. Ablation of MPOA gal+ neurons using AAV-borne diphtheria toxin disturbed pup retrieval behavior, pup grooming in fathers and male mating behavior, without affecting locomotion or inter-male aggression. Optogenetic activation of MPOA gal+ neurons stimulated pup grooming in fathers and decreased crouching and total paternal care (Fig. 5, [118]), decreased intermale aggression and increased locomotion.

Next, Kohl et al. [119] identified that MPOA gal+ neurons receive pup-activated inputs from the BST and medial amygdala (MeA) in virgin females and fathers, substantia nigra pars compacta and anteroventral periventricular nucleus (AVPV) in mothers and fathers, and PVH vasopressin neurons, but

not from PVH oxytocin neurons or AVPV TH+ neurons in fathers. They also identified that MPOA gal+ neurons projects to PVH oxytocin, vasopressin and CRH neurons, AVPV TH+ neurons, and to the periaqueductal gray (PAG), MeA, and the VTA in both males and females. Pup retrieval was not affected by optogenetic inhibition or activation of MPOA galanin neuron projections either to the PAG, VTA, or MeA. In contrast, pup grooming (separate from licking in this study) was decreased or increased by MPOAgal->PAG inhibition or activation, respectively. The number of barrier-crossings inside the cage (i.e., locomotion, see the methods) was reduced or increased by MPOAgal-> VTA inhibition or activation [119]. Because Esr1+ neurons do not appear to be critically involved in pup grooming (see above, [108]), these studies showed that gal+Esr1- neurons (18% of gal+ neurons [120]) projecting to PAG may govern pup grooming behavior.

Then, Moffit et al. [30] utilized single-cell RNA sequencing and uncovered the complex neuronal composition of the POA, comprised of 43 inhibitory, 23 excitatory, and 3 hybrid neuronal clusters. The authors noted that while inhibitory neurons tend to be clustered by the neuromodulators, such as galanin, vasopressin, or Tac1, excitatory neurons are clustered by anatomical structures or nuclei and segregated in distinct anatomical structures within the POA. Then, using multiplexed error-robust FISH (MERFISH) for 155 genes, they achieved spatial details of each neuronal group, including 10 galanin+ MERFISH clusters. Among these, they further identified I-14 neurons as the commonly activated cluster during parenting in virgin females, mothers, and fathers, and modestly during male mating behavior. I-14 is characterized by its expression of calcitonin receptor (Calcr) and bombesin receptor subtype 3 (Brs3) with Vgat, galanin, and Esr1. Calcr and Brs3 are G-protein-coupled seven transmembrane receptors implicated in feeding suppression (see sections 4-2 for the possible reasoning). I-14 neurons are spatially distributed most densely in the StHy (Fig. 6C, 7C of [30]), corresponding with the AC in the present paper Fig. 1 and in MPN/MPA. Of note, Moffitt et al. did not explicitly described oxytocin neurons in the MPOA, but their analysis detected significant oxytocin expression in E-23 cluster, suggesting that AC oxytocin neurons are essentially glutamatergic as in the PVH [121, 122]. The lack of a significant increase of c-Fos expression in E-23 in maternal mice may be due to their pup exposure using a single pup. Overall, this landmark study uncovered Calcr and Brs3-expressing neurons in the AC/MPN/MPA as the most strong candidate for "offspring care" neurons. The remaining question was the functional significance of these neurons and molecules in parental care.

c) Calcitonin receptor (Calcr)

Our research group has manually screened for molecules most highly colocalized with parenting-induced c-Fos within the cMPOA (Section 2-2) and identified Calcr and Brs3 [123]. The independent identifications of these two molecules with Moffit et al. [30] suggest the robustness of the results. We focused on Calcr hereafter, as we could produce Cre-transgenic lines with faithful Cre expression for Calcr but not for Brs3. Neurons endogenously expressing Calcr (Calcr+) are confined to the cMPOA and AC in the whole POA. Calcr+ neurons are mostly Esr1+ and represent a small fraction of Esr1+ neurons (ca. 5 % in virgin females, 12 % in PPD 4 mothers) [123]. Calcr+ neurons comprise at least two subpopulations; one is GABAergic, mostly gal+ and expressed in both cMPOA and AC, resembling the I-14 described above [30]. The second population is Vglut2+ (glutamatergic), 18% gal+ in mothers, and mostly confined to the cMPOA [123], appearing to be a separate population from I-14.

Cre-dependent tetanustoxin silencing of cMPOA Calcr+ neurons severely disturbed pup retrieval in virgin females and postpartum mothers and brood-nest building, leading the pup survival of less than 20 % for Calcr+-silenced mothers, without affecting normal mating, pregnancy, delivery, litter size, placentophagia, or pup sniffing latency. Moreover, while most virgin male C57BL/6 mice are infanticidal, chemogenetic activation of cMPOA Calcr+ neurons (but not cMPOA VGAT+ neurons) reversibly abolished infanticide in the majority of subject males. These data collectively suggest the importance of cMPOA glutamatergic Calcr+ neurons in basal parental motivation.

In peripartum mothers, Calcr expression in cMPOA/AC GABAergic neurons becomes 8 times higher than in virgin females. Knockdown of endogenous MPOA Calcr to about 60% in mothers by RNA interference reduced maternal-specific heightened motivation to rescue pups from the open arms of the elevated plus maze, suggesting that peripartum upregulation of Calcr+GABA+ neurons in the cMPOA enhances maternal motivation.

In primates, a parenting-responsible brain region has not been previously identified. We next examined the MPOA of common marmosets, a New World monkey species that utilizes family cooperation with vocal communication for infant care like humans. We found a Calcr+ neuron cluster in the small subregion of the marmoset posterior MPOA, which colocalizes with c-Fos after alloparental care [72]. Voxel-based lesion-behavior mapping identified that the Calcr+ MPOA subregion is responsible for infant carrying tolerance (the ability to endure infant carrying without physically rejecting the infants) without affecting general health, locomotion, and other social behaviors with family members. Furthermore, the amylin administration at the marmoset cMPOA facilitated infant carrying [124]. These

data collectively suggest that the Calcr-expressing MPOA subregion is responsible for infant caregiving behaviors across mammals. (Of note, the spatial distributions of Calcr+ neurons vary among species, thus, we propose to switch the acronym of the cMPOA from central to Calcr-expressing MPOA subregion, to better define the counterpart brain region across species.)

2-4 Summary and remaining questions in the circuit mechanisms

The above data shows that Calcr+Esr1+ cMPOA neurons are most relevant for basal pup retrieval behaviors, Esr1-Gal+ MPOA neurons for pup grooming, and Gal+Calcr+Esr1+VGAT+ AC/cMPOA neurons for heightened maternal care. However, Esr1+, gal+, and Calcr+ parenting-relevant neurons contain both excitatory and inhibitory subpopulations [30, 123], complicating the working model of neural circuity for parental care. In particular, More selective manipulations of each specific neuronal group, especially for glutamatergic and GABAergic subpopulations, among each cell type,.

Zhang et al. [125] reported that activation of glutamatergic MPOA neurons induces "anxiety-like" behaviors (including a pup-directed attack in their study), hyperlocomotion, and pupil dilation. Hyperlocomotion was reported by stimulating MPOA gal+ [118] or all neurons [112] (may also for neurotensin+ [126]), while we never observed hyperlocomotion by stimulating specifically cMPOA neurons optogenetically or chemogenetically, or Calcr+ neurons chemogenetically [44, 123]. These differences may be caused by the size and/or location of the targeted area (see Fig. 1A, B). If the target area is too large, it may affect the "preoptic locomotor region" that initiates locomotion by electrical stimulation via their projection to the mesencephalic locomotor region [127], induce hyperlocomotion which disturbs many naturalistic behaviors, especially crouching over pups.

It is also notable that the importance of prolactin signaling in the MPOA for maternal nursing and [128] paternal behaviors [129, 130](see [9, 131]). Outside of the MPOA, dopaminergic neurons in the AVPV for female-specific pup retrieval [132], oxytocin neurons in the PVH for the onset of allomaternal [133] and paternal behaviors [92], the locus coeruleus [134], lateral habenula [135], amygdala and cerebral cortex [136, 137 138, 139]. Also, there are many advances in the mechanism of infanticide [140-145], many of which have been discussed extensively elsewhere [9, 146](Inada &Miyamichi, 2023).

3. Evolutionary origin of mammalian parental care

To better understand the neuromolecular features of mammalian parental care described above, this chapter outlines the evolutionary path of mammalian parental care (Fig. 2, orange line), mentioning parental care patterns in the extant vertebrate groups. We skip detailed descriptions about birds for the space limitation, although avians share significant similarities of parental care and endothermy with mammals [147].

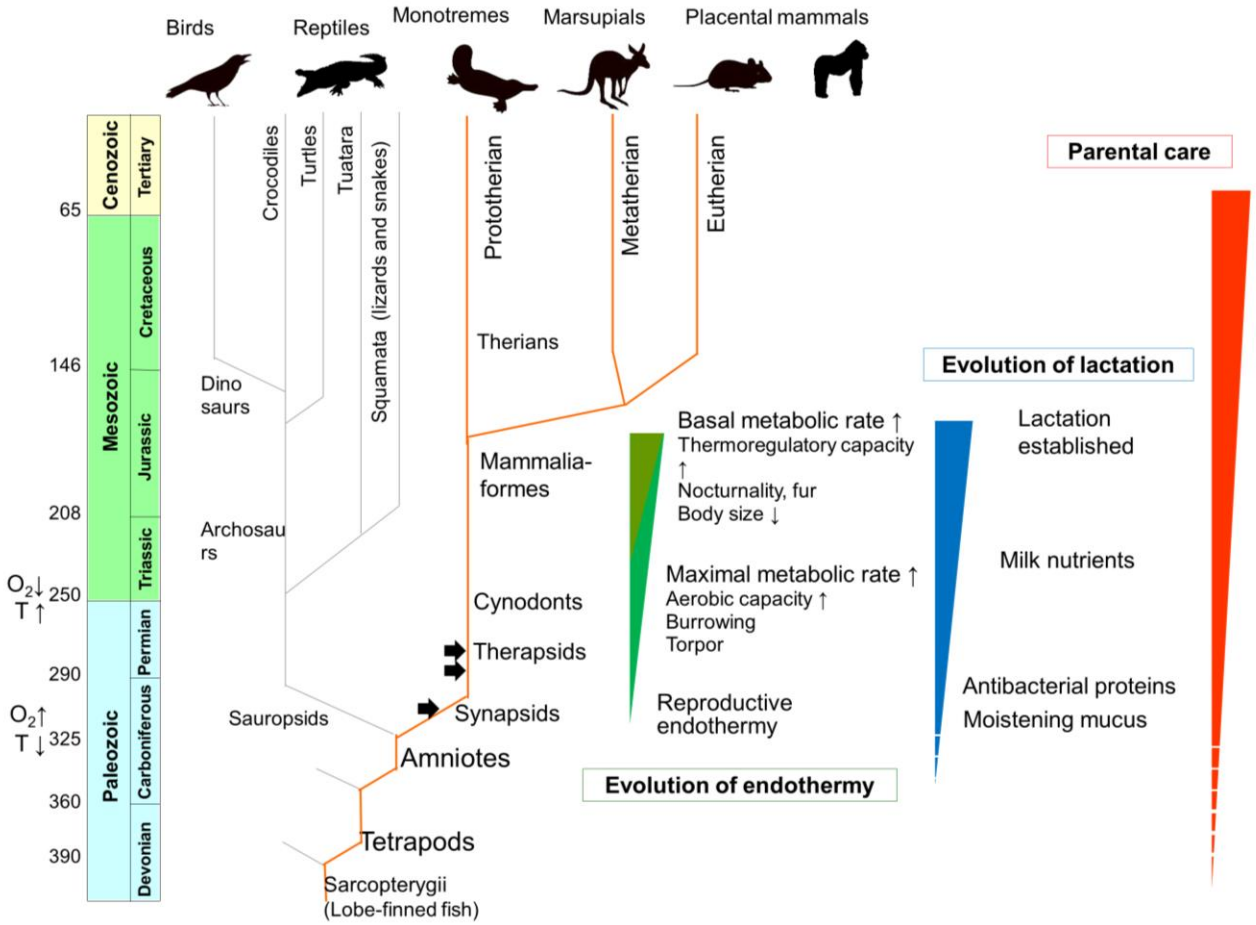

Figure 2. The evolution of mammals, lactation and endothermy

Schematic of mammalian evolution, based on [167] [190]. Synapsids: amniotes having a single temporal fenestra in the scull. Therapsids: synapsids having incisors, canines, and molars. Black arrows indicate the fossil evidence of parental care in Paleocene. The silhouettes of example species are from http://phylopic.org.

3-1 Parental care in extant fish and ancestral vertebrates of the mammalian lineage

Parental care in extant fish exhibits remarkable paternal bias than maternal, unlike most animals. Among about 30% of living teleost families that show some parental care, male care (50-84%) is more common than female care, and male-only care occurs in 9 times as many genera as female-only care [3]. The primary form of this male-only care is egg guarding and is explained as the byproduct of male territoriality: male-only care is exclusively performed by the species engaged in external fertilization, and with eggs frequently deposited directly within the male's territory, thus egg guarding does not constrain the male's additional mating [148]. In some species, females prefer to mate with males already caring for eggs or with larger broods, increasing the benefits to males of providing care and thus maintaining the male-only care system [148-150]. In contrast, most female-only care occurs in species exhibiting internal fertilization, because internal fertilization increases uncertainty of paternity and thus hampers the evolution of paternal care in many cases [3, 151].

It should be noted that parental care patterns in fish are incredibly diverse and sometimes liable or opportunistic within the same species. Comparative analyses in ray-finned fish have proposed that paternal, maternal and biparental care developed independently from no care with the frequency in this order, and the loss of any parental care can occur in all cases but less frequently than its occurrence [152]. As an example of extensive biparental care [153], Amazonian pirarucu *Arapaima gigas* parents build a nest in the 1-1.5cm shallow flooded area for 3-5 days, fertilize externally, and continuously guard the nest together for 9 days. After the hatching, the male guides the shoaling fry above its darkened head for up to 3 months, while the female swims around the male and offspring for 1 month. During this reproductive period, parents secrete a whitish fluid from their head, plausibly to provide nutrition and/or passive immunity. Constituents of similar provisioning have been examined in epidermal mucus in cichlids [154] and pouch fluid in male seahorses [155].

Among teleosts, lobe-finned fish (Sarcopterygians), including lungfish are closer than ray-finned fish (Actinopterygians) to the direct ancestor of mammals. Like amphibians, most lungfish adults reduce gills and breathe air obligatory. In five out of 6 extant lungfish species, males guard the eggs in the nest [156]. For example, *Lepidosiren* males guard and aerate eggs and larvae within nests. During this period, the males develop vascular filaments on the paired fins, probably for gas exchange either for offspring or for themselves to reduce nest leaves for respiration [157], indicating the substantial morphological adaptation for paternal care. These data from extant teleosts suggest that early vertebrate parental care may be derived from mating-related behaviors in males. In support of this idea, the MPOA has been

reported to be a key brain site for male sexual behaviors in all vertebrate groups tested, including teleosts [99, 158]. The neural mechanism of parental care is still understudied; it was reported that MPOA gal+ neurons are activated during parental mouthbrooding care in maternal cichlids [79] and during courtship but not paternal care in male midshipman [159].

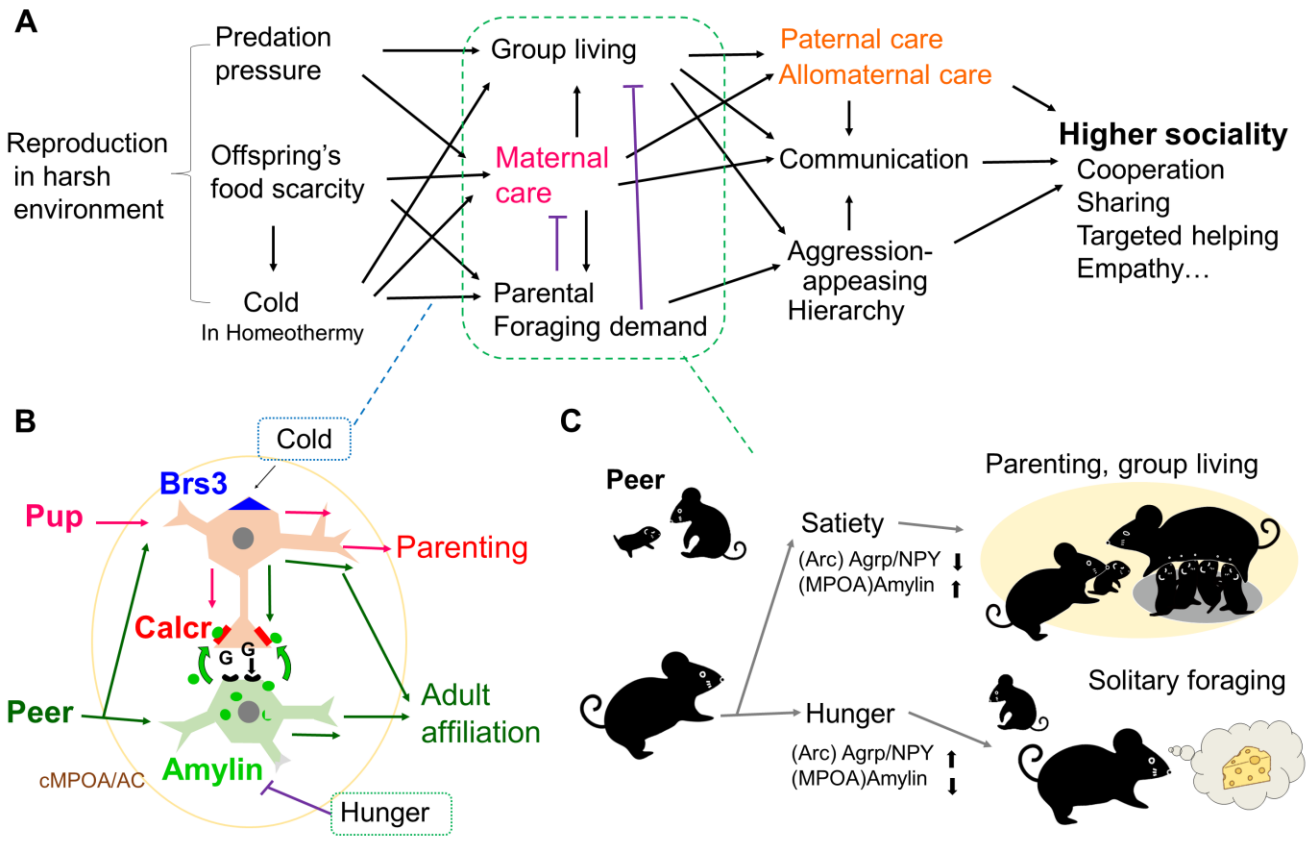

Figure 3. The mammalian maternal care circuity in the evolutionary and ecological contexts

(A) The working hypothesis of the evolution of mammalian maternal care and extended sociality. Group living includes pair bonds.

(B) The working model of Calcr-amylin neurons in the cMPOA/AC. Pup-derived sensory cues activate Calcr neurons (orange) and drive parental behaviors. Peer-derived sensory signals activate both Calcr and amylin neurons (green). Calcr neurons either GABAergic or glutamatergic project to amylin neurons, and amylin may retrogradely activate Calcr neurons via Calcr molecules distributed throughout the plasma membrane of soma and fibers. This signaling is required for contact-seeking behaviors among adults. See [123, 224] for details.

(C) Possible titration of maternal care and adult group housing by food availability via Calcr-amylin and Agrp/NPY systems.

3-2 Parental care in living amphibians and tetrapod mammalian ancestors

Tetrapod ancestors have developed legs along with lungs to live on land in the middle Devonian (Fig. 2). The terrestrial transition also moved the offspring's habitat toward land, which is beneficial for protection from aquatic predators but increases the risk of desiccation and the temperature variability (Fig. 3A). While most living amphibians spawn in aquatic environments and provide no care, 25% care for the egg, tadpole, and/or juvenile stage of offspring. Male-only and female-only care are equally common, although offspring feeding and viviparity are performed only by females [160]. Among all 3 living amphibian lineages (Caudata/Urodale (salamanders), Anura (frogs and toads), and Gymnophiona (caecilians)), a terrestrial system of egg development and has evolved, and in such species, parental care is nearly universal [161, 162].

Nearly all members of Aromobatidae and Dendrobatidae poison frogs have some form of parental care, typically egg attendance and transport of the tadpoles to a terrestrial pool of water such as phytotelma or a stream [163]. Both male and female care occurs with or without pair bonding. Utilizing such diversity, Fisher et al. [78] compared the neural activation patterns of tadpole transport care in three Dendrobatidae species with male uniparental, female uniparental and biparental care patterns. They identified that the medial pallium and the POA are consistently activated during tadpole transport, independent of sex. In the male-uniparental *D. tinctorius*, galanin expression increase is associated with tadpole transport in the POA and medial pallium. Activation of POA galanin neurons during tadpole transport is observed in biparental *R. imitator*, but not in the other two. The same group [77] also demonstrated that maternal tadpole feeding induces neuronal activation in the MPOA and lateral septum commonly in two distant species *Oophaga Sylvatica* and *Mantella laevigata*. The activity of POA oxytocin neurons is oppositely associated with maternal feeding in the two species.

89 % of Caudata (inc. salamanders) species fertilize internally, except for the most ancient families [164]. Among internal fertilizers, females provide care in 58 %, no care in 42 %, and male care does not occur. And terrestrial egg-laying occurs almost exclusively within species engaging in internal fertilization and is facilitated by maternal care [164] (Fig. 3A). Seymouria, one of the extinct closest relatives of stem amniote, exhibited salamander-like development [165]. Furthermore, recent studies suggest that the ancestral amniotes retained the embryo in the female's body (extended egg retention, EER) and maybe even viviparous like 20 % of squamates and most mammals [166]. The authors propose

that oviparity without EER in turtles, crocodiles and birds was derived from EER. Thus, the stem amniotes may have evolved from salamander-like tetrapods with EER.

The terrestrial transition of early tetrapods was also accompanied by increased dermal protection by developing skin collagen and elaborate skin glands that secreted mucous compounds and antimicrobial proteins to facilitate gas exchange and to protect against desiccation and infection, as do the multicellular glands of living amphibians [162]. Such skin secretion may provide moisture and disinfection to attending offspring, as some salamanders curl around their eggs to keep them moist with their skin gland secretion. Molecular evidence suggests that the antimicrobial peptides involved in the innate immune system evolved into multiple milk constituents in the amniote ancestors of mammals in the late Carboniferous period (see below) [167-169].

3-3 Parental care and endothermy in living reptiles and amniotic mammalian ancestors

An amnion is a membrane covering the amniote embryo and amniotic fluid. With amnion, chorion, and allantois, the basal amniotes protect the embryo in the water- and yolk-filled sac and can reproduce on land. This reproduction mode should have significantly reduced the need for parental effort to prevent the eggs from aquatic predators and desiccation, leading to a relatively low (10%) prevalence of parental care among extant reptiles. It also imposed the strong female bias of amniote parental care when it occurs; male-only care is not observed among living reptiles and mammals, and only in 1 % of avians [147].

Living reptiles have long been considered primarily nonsocial and non-parental, but this view is outdated [170]. All crocodilians and tuataras (see Fig. 2 gray lines for the reptile lineage) engage in maternal care, such as egg attendance and nest defense. Some crocodilian mothers excavate the nest, carry hatchlings to the nest, and feed, and may also biparental care [171, 172]. They may cooperatively care for the young, taking turns guarding their offspring utilizing vocal communications. Most turtle species vocalize when they mate or as a pre-hatchling to communicate with their mother and littermates [171, 173]. Male turtles are often larger than females, fight for mating opportunities, and perform complex courtship behaviors in aquatic species. Most turtle females create nests on land and cover the nest after laying, and some species guard their nests for weeks. Eighteen Squamata (lizards and snakes) species are found to form stable-membered groups in the long term, some up to 20 years [174]. A tropidurid lizard *Liolamemus huacahuasicus* is a viviparous species that lives at high altitudes in the pre-Andes mountains. The

gestation period lasted nearly 10 months, and females lost almost half their body weight at parturition. Although direct maternal attendance such as neonate grooming was not found, mothers defended the territory where their offspring resided and had access to food and burrows for up to two years. Paternal care is also suspected since an observed mating pair defended overlapping territories [175]. Thus, here again the indirect form of parental care manifests as an extension of territorial behaviors, possibly with some kind of recognition of their offspring, in order not to mistakenly attack them.

Amniotes then diverged into synapsids (including living mammals) and sauropsids (including living reptiles and birds) in the Carboniferous period (Fig. 2). The oldest fossil evidence of tetrapod parental care is the plausible mother-infant pair of a valanopid synapsid at 306-309 million years ago (mya) [176]. The small one is found encircled by the tail of the large individual, resembling a parent denning with an offspring. During the evolutionary path from synapsids to mammaliaforms, several key features of extant mammals have developed, including lactation and endothermy, as described below.

a) Lactation as hydration, disinfection, and feeding of the offspring

Although amnionic membranes enabled terrestrial egg development, early synapsids' eggs did not have been fully calcified and were vulnerable to desiccation, like those of monotremes and most squamates [162, 166]. Thus, early synapsids may have buried their eggs into moisture-laden soil, hydrated them with contact with the moist skin, or carried them in a moist pouch, similar to extant monotremes [177]. Sticky secretions from the skin patch may attach the eggs to the maternal skin, thus promoting heat transfer during incubation.

Granular glands of living amphibians secrete at least 500 peptides, and several of these molecules in the basal amniotes should have evolved into milk constituents in mammals; lysozyme to alpha-lactalbumin [which is involved in the synthesis of lactose], secretory calcium-binding phosphoproteins to caseins, lipocalins to beta-lactoglobulin, and xanthine oxidoreductase as the necessary component of milk fat globule [167, 168]. Such an apocrine-like glandular skin secretion in early synapsids in the late Carboniferous period is believed to function for nutrient transfer to offspring, starting in cynodonts and established in mammaliaformes during the Jurassic period, supported by the fossil evidence of delayed tooth development and "milk teeth" (diphyodont) in these species (Fig. 2) (however, see [178]).

b) Endothermy for parental care and the evolution from synapsids to mammals

Another important invention of this period is endothermy. The transition from aquatic to terrestrial habitats increases temperature fluctuations, which cause inappropriate embryonic development. Farmer [179] proposed the "parental care hypothesis" of endothermy evolution that high stable body temperature has been driven to facilitate offspring growth, in contrast to the traditional view that endothermy evolved first and parental care second. In support of this hypothesis, extant reptiles, all pythons brood, and some control egg temperature by shivering [180]. Viviparity in Squamata is associated with cold climates, possibly for thermal protection of embryos [181, 182]. In addition, Tattersall et al.[183] identified endothermy in tegu lizards selectively in their reproductive period. After laying, the females remain with the eggs for up to 75 days with little or no foraging activity. During this period, females' body temperatures were sustained up to 10°C higher above ambient, independently from activity or feeding, resulting in a 5°C increase in the nest temperature. This observation strongly supports the hypothesis that the primary driving force of non-shivering heat generation is its benefit for parental care [181, 184].

Therapsids that appeared in early Permian had intermittently fibrolamellar bones (well-vascularized and rapidly grown), suggesting that they started to increase the metabolic rate [185]. Their increasingly erect gait enabled them to raise their bodies above the ground. A mid-Permian therapsid Diictodon specially excavated burrows as brood chambers with specialized limbs for digging [186]. They showed sexual dimorphism of the presence/absence of formidable tusks, suggesting aspects of their social behavior, such as polygyny [187], and in Triassic, formed a herd with more than 23 young individuals [188, 189].

At the end of the Permian (P-T boundary, 252 Ma), the largest extinction in Earth's history occurred because of massive volcanic eruptions in Siberia. Ambient temperature decreased, along with the oxygen level drop from 30% to 10 %, leading most of the synapsids to die except for burrowing species. During Triassic, sauropsids surpassed synapsids due to their effective respiratory system with air sacs. Synapsids reduced their body size and became predominantly nocturnal throughout the Mesozoic era, also for a dietary niche with insects at low-light periods.

Cynotonds appeared in the late Permian and diversified into nocturnal niches after the great extinction at the end of the Permian period [190]. In the early Triassic, they had a bony secondary palate, which enabled respiration while feeding, increased basal metabolic rate, and later neonatal suckling. The most derived cynodonts, the Probainognathia, have developed enlarged brain size suggestive of sensory

vibrissae (whiskers), maxillary turbinates and reduced lumbar ribs, enabling high respiratory rate and increased maximal metabolic rate. A fossil of a mammaliamorpha tritylodontid *Kayentatherium wellesi* demonstrates 38 near-hatching young in one clutch, suggesting the still relatively simple maternal care [191].

In the late Triassic, mammaliaforms (stem mammals) developed from Probainognathia and increased their ability to control body temperature by increasing basal metabolic rate and body insulation by fur. This should also facilitate offspring's energy demand and may coevolve with the establishment of lactation through the mid-Jurassic. Milk lipid signaling might also co-evolve with thermogenic adipose tissue [192]. The cynodont-mammaliaform transition is also marked by the mammalian jaw joint and inner ear complex, which enables advanced hearing [191]. Together with increased olfactory and tactile sensitivity, these features may have pushed the development of relevant cortical areas further [190, 193].

In the late Jurassic, all mammals possessed mammary glands, fur, external ears, endothermy, and a large ratio of brain volume to body mass. Egg-laying monotremes diverged from marsupials and placentals (therians) at ca. 166 mya. Juramaia is the earliest fossil therian [194].

4. Parental brain circuit: the neuromolecular features in contexts

4-1 Anamniote mating-associated behaviors as the possible origin of mammalian parental care

The solid molecular evidence supports that egg-moistening (or offspring-hydrating, in case of viviparity) care by skin gland secretion as early as 310 mya was a primordial form of lactation [195 168]. The oldest fossil evidence of synapsid parental care is in 309-306 mya [176]. Considering the viviparity and matrotrophy (lactation) have evolved only once in mammals {Blackburn, 2015 #3943}, these data indicate that the origin of mammalian parental care existed at the latest in early synapsids. Furthermore, recent studies suggest that in ancestral stem amniotes, amniotic membranes appeared in the maternal oviducts as specializations to control fetal–maternal interaction in association with EER (see Section 3-2) [166]. Both lactation and viviparity require significant maternal morphological changes to evolve and induce the co-adaptation of offspring physiology, and thus should have been lost at low rates if at all, as suggested by amphibian phylogenic studies [160], unless another invention such as fully-calcified egg shells as in crocodilians and birds enabled the loss of EEA [166]. Thus it is plausible that stem synapsids already performed substantial maternal care.

Then what about pre-synapsids? Two pioneering researchers, Oftedal and Farmer both emphasized the close tie of parental care with terrestrial adaptation throughout anamniotes and suggested the possible pre-amniotic origin of lactation and reproductive endothermy, respectively [162, 181]. Our observations that mammalian parental care neurons overlap with neurons involved in male sexual behaviors support their assumption: as described above, ablation of MPOA gal+ neurons in mice or pharmacological suppression of cMPOA in a primate common marmosets disturb pup retrieval as well as male mating behavior [118 124]. In addition, parenting-responsible MPOA neurons are significantly activated during male (but not female) sexual behaviors [30, 44]. These observations are understandable if mammalian parental care shares its mechanism with male parental care in ancestral salamanders and lobe-finned fish.

This assumption does not necessarily imply that mammalian maternal care is monophyletic to paternal care of lobe-finned fish but can be parallel evolution; namely, a subpopulationof the neurons involved in male mating became specialized with mating-associated behaviors, such as female and territory defense, mating site selection and preparation (nesting), egg attendance and guarding. Although such paternal care was opportunistic, whenever the harsh environment provided selection pressure for parental care, the same set of neurons was utilized multiple times independently, including the emergence of maternal care in synapsids. This mechanism can be regarded as parallel rather than convergent evolution [196]. Additionally, if including the subtle nesting behaviors into parental care, it may not be impossible to assume the divergent evolution of parental care neurons since early anamniotes, similar to the evolution of human eyes can be traced back to cordate as the directional photosensing system, while the detailed structures of eyes have evolved convergently [197].

On the other hand, if mammalian parental care is the invention of amniotes, the parental care circuit can be linked more with the neural mechanism of female reproduction, especially oviposition or parturition. This idea leads to the popular presumption that postpartum maternal care should be triggered by oxytocin. Oxytocin is a peptide hormone critical for maternal reproductive physiology, including egg laying and parturition (together with vasopressin-homologs [198]), and indispensable for milk ejection during nursing in mammals [4, 199]. And numerous publications demonstrate the role of oxytocin in mammalian pro-social behaviors (though also in various non-social functions such as stress responses and energy metabolism) [200-202] (see also [203]). However, the genetic ablation of oxytocin leads to surprisingly normal postpartum maternal care in multiple rodent species [23, 45, 204-208] (for other vertebrate species, refer to [209 210]). The oxytocin's facilitatory effects on paternal and allomaternal care appear even

more significant than those on postpartum maternal care (for example, compare [92] and [208] with a similar methodology from the same laboratory) [133].

One possible explanation of this enigma is that the evolutionary pressure for allomaternal care made oxytocin less important for infant care motivation in family-living species such as mice, prairie voles and marmosets, although oxytocin was initially critical and still so in species with maternal-only care, such as sheep and rats [4, 211]. This explanation explains why oxytocin is not necessary for maternal care in multiple mammalian species, but still cannot explain the more significant overlap of maternal care circuit with male than female sexual behaviors:

So far, the working hypothesis of the possible anamniote origin of mammalian parental care neurons can resolve this puzzle most parsimoniously. Still, much more studies are necessary to establish the evolutionary basis of mammalian parental care. It should be noted here that the MPN is unnecessary for lordosis in rats, the consummatory aspect of female sexual behavior, although it is implicated in proceptive/appetitive components of female sexual behaviors [212-214]. Thus, the mammalian parenting circuit might have originated from the circuit stimulating proactive sexual motivation in both sexes. Of relevance, the vertebrate brain is not decisively dichotomized between sexes: many fish change sex during their life; sex determination is environment-dependent in 5 % of living reptile species; and mammalian brain sex is dependent significantly on peripheral ovarian hormones rather than simply determined by genetic sex. These facts may underly why the core circuit of parental care is the same for both sexes. The apparent sexual dimorphism of mammalian parental care may be later derived from the sex-dependent regulatory mechanisms, involving estrogen and oxytocin, to activate/inhibit the common parenting circuit according to the contexts.

4-2 Balancing homostatic needs and maternal care: possible contributions of Calcr and Brs3

Endothermy facilitates offspring growth but increases maternal and offspring's caloric demand and subsequent foraging demand for the mother. Thus, when food resources are scarce, mothers must reduce the amount of care for the sake of foraging or give up caring for offspring (desertion), possibly via neuropeptide-Y+ Arc neurons projecting to the dorsal raphe and the MPOA [113, 215, 216]. In this sense, the benefit of lactation for females is minimizing the energy drain associated with initial vitellogenesis and offering the female an extended period to terminate her reproductive investment upon deteriorating

environmental conditions with minimal energy loss [178]. This may also explain why the parenting-responsible neurons are marked by two Gq-coupled receptors that signal satiety, Calcr and Brs3 (Fig. 3).

While Calcr's peripheral ligand is calcitonin, Calcr in the brain forms a complex with Receptor Activity Modifying Proteins (Ramps) to bind amylin, as calcitonin is absent in the brain (Fig. 3B) [217]. amylin/Iapp (islet amyloid polypeptide) is a brain-gut peptide and is co-secreted with insulin from pancreatic β cells to inhibit food intake through actions on the area postrema [218, 219]. Amylin is also produced in the hindbrain, arcuate nucleus, and the cMPOA/AC subregions in the MPOA [123, 220-224]. Circulating and hypothalamic amylin levels are upregulated by satiety and downregulated by hunger. Morphological evidence suggests that MPOA amylin neurons are innervated by Calcr+ neurons and the local application of amylin activates Calcr+ neurons [224]. Thus, MPOA amylin levels can up/downregulate Calcr+ neurons to facilitate/suppress parental care depending on the food resource condition (Fig. 3C), together with or as a part of the proposed mechanisms involving Agrp/NPY neurons in the Arc [113, 215, 216]. To prove this possibility, it should be determined if the amylin level in the MPOA indeed reflects hunger/satiety and regulates Calcr+ neuronal activity in vivo.

Brs3 is an orphan receptor in placental mammals and is expressed in the MnPO, MPA, PVH, DMH, and parabrachial nucleus [225]. Brs3 knockout mice developed obesity with increased food intake and reduced resting metabolic rate and body temperature. While DMH Brs3+ neurons regulate body temperature, energy expenditure and heart rate, MnPO BRS3+ neurons are activated by cold exposure and induce cold defense responses via the sympathetic nervous system [226, 227]. Brs3 has also been identified for its female-biased expression in the MeA and the principal part of the BST [50, 84]. Brs3 expression in the cMPOA/AC is highly upregulated peripartum along with Calcr (Kuroda, 2022, Gordon Research Conference on Hypothalamus). It is tempting to test whether Calcr/BRS3 neurons in the cMPOA/AC are activated by cold exposure (Fig. 3B). If this is the case, the next test is whether the BRS3 signaling is involved in cold adaptation of maternal care, such as to increase nest building or nest attendance to keep pups warm.

While reproduction with external fertilization is not severely restricted by hunger, the transition from ectothermy to endothermy supported by lactation should have increased the caloric cost for maternal care in early mammals. To balance the maternal investment, survival and infant needs, satiety signals of amylin-Calcr and Brs3 might have been added to the existing parental care circuit as the neural mechanism of the parent-offspring conflict. Although it is generally hard to test the hypothesis on the evolutionary path as stem mammals are extinct, further investigations of the neuromolecular circuit

of maternal care in monotremes may shed light on this issue, as monotremes have proto-endothermic features such as considerable daily variations in body temperature and seasonal hibernation [228]. In addition, the relevance of Calcr in calcium mobilization during pregnancy, eggshell formation and lactation should be examined separately [229].

Like amylin-Calcr and Brs3, oxytocin suppresses food intake and mediates cold defense [230, 231], as oxytocin knockout mice are defective in cold defense physiology and behaviors. Thus the direction of oxytocin functions in metabolic control is in the same direction as Calcr and Brs3. In contrast, galanin and prolactin increase food intake and facilitate heat loss [232, 233], which may counteract Calcr and Brs3. The crosstalk of these molecular signaling may fine-tune the homeostasis during pregnancy and lactation.

5. Beyond maternal care to higher affiliative sociality

So far, we have discussed how stem-mammalian maternal care has evolved through time. Now we shift the focus to the further evolution of maternal care into alloparental care, group living, and complex socialites such as altruism and empathy.

The classical definition of "society" refers to adult animals and excludes parent-offspring groups (termed "subsocial") and [234]. However, for practical benefits in studying neural mechanisms of behaviors, here we define "social behavior" as “any action directed by an individual towards a conspecific" [235] and thus include sexual and parental nurturing behaviors in social behaviors. Social behaviors include i) competitive/agonistic behaviors, such as territorial fighting, threat, and submission; ii) cooperative/affiliative behaviors that possibly result in the attraction of conspecifics for a certain amount of time; and iii) neutral social behaviors, including social recognition and communication (for more discussion on the terminology issues, see the supplementary discussion of [224]).

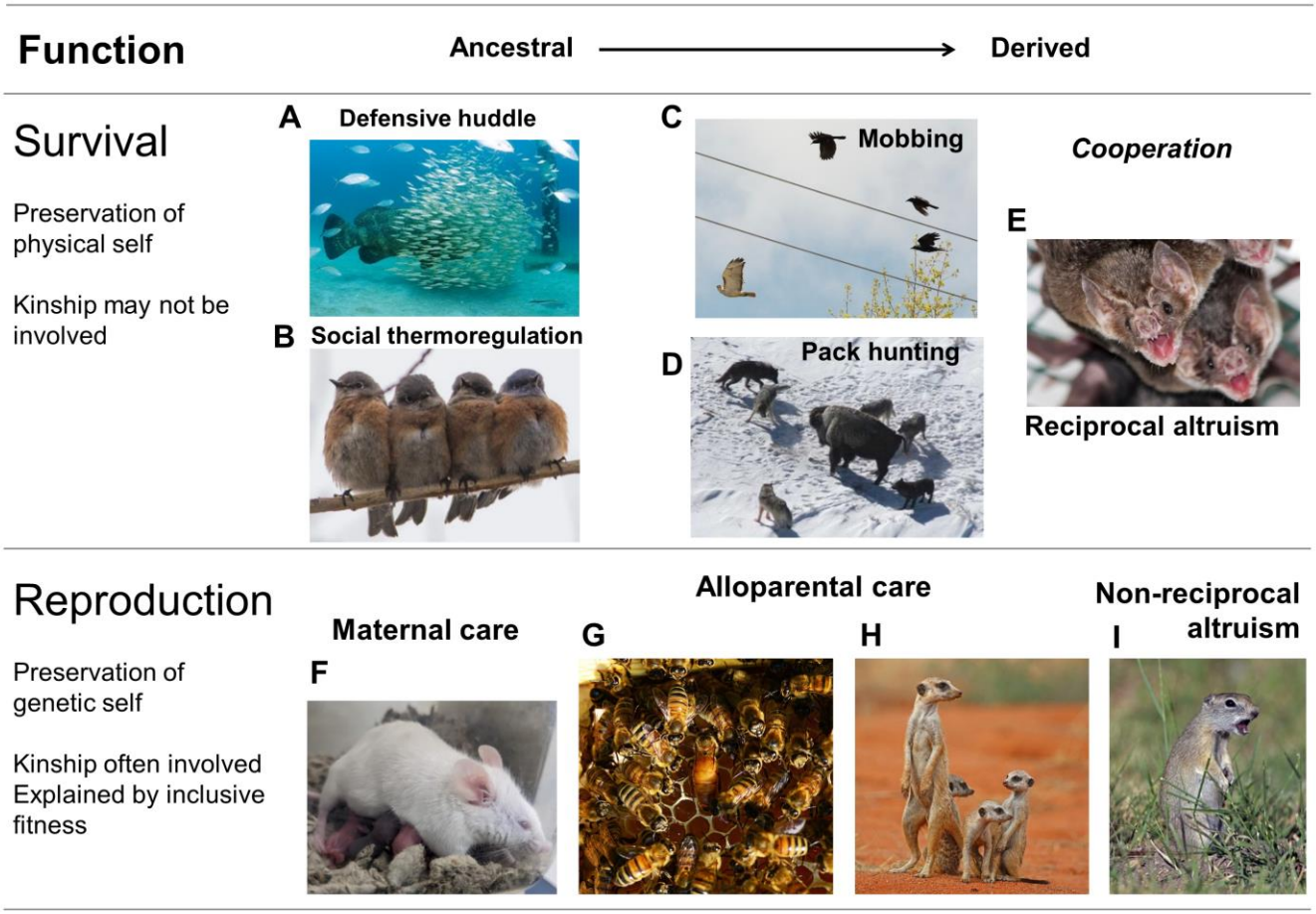

Figure 4. Two lineages of affiliative social behaviors

(A) A tight schooling of prey fish upon the predator (Goliath Grouper) approach. (B) Western bluebirds huddling together during cold weather. (C) American crows mobbing a red-tailed hawk. (D) Canadian Gray Wolves surrounding a bison. (E) Vampire bats, of which blood sharing is explained by reciprocal altruism. (F) Nursing behavior of a laboratory mouse mother. (G) A Honeybee colony. (H) A cooperative breeder meerkat (*Suricata suricatta*) with 3 young. (I) Belding's ground squirrel, showing altruistic alarm call. Sources: Geraldecarroll (A), Balonde (B), Dori (C), Doug Smith (D), Oasalehm (E), Bodhisattwa (G), Charlesjsharp (H), Ron Wolf (I). Wikimedia, CC-BY-SA 3.0 (A), 3.0 us (C), 2.0 (G) or 4.0 (others). D: public. Note that two lineages are not mutually exclusive; for example, carnivore group hunting is more common amongst kin than non-kin [272].

5-1 Two major aims of affiliative sociality: survival and parenting

The fitness consequence of any behavior is determined by its cost vs. values for survival (sustenance of physical self) and reproduction (sustenance of genetic self). Thus, widely-observed affiliative social behaviors should also be derived from survival and/or reproductive benefit. From various ethological evidence, Eibl-Eibesfeldt has proposed two major drives for affiliative sociality (Fig. 4) 229: "bond formation via the flight drive", exemplified by shoaling fish. Its most basic form is a "selfish herd" [236], an open anonymous group formed by cover-seeking within conspecifics, in which each animal moves toward the center to reduce its chance of being caught by a predator (defensive huddle) or exposed to cold (thermoregulatory huddle), risking other group members. This survival-purposed affiliative sociality is not necessarily associated with the kinship of the members. It may have developed into more complex cooperation such as mutualism (e.g., pack hunting) and reciprocal altruism (e.g., food sharing of vampire bats) [237 238 239 240].

As another drive for affiliative sociality, Hamilton has identified the inclusive fitness, or genetic relatedness between the actor and recipient (thus can be regarded as an extended version of reproduction) [241, 242]. Then Eibs-Eibesfeldt pointed out that although sexual drives induce a strong contact-seeking motivation, a lasting bond seems to be rarely established via the sexual drive except for several primate species including humans. In contrast, derivatives of "*parental care* drive" are found pervasively to underlie social bonds (Fig. 3A, 4) [243]. Eibl-Eibesfeldt raised numerous examples of infantile behaviors such as food begging and milk-sucking by adults for subordination signals and solicitation of care or attention during courtship. He also pointed out the diversion of originally-parenting behaviors such as nest-building, mouth-to-mouth feeding, and grooming into courtship, appeasing, and bond-formation between adults in birds and mammals. He agreed with Konrad Lorenz's supposition [244] that the friendship has arisen from the redirection of intra-species aggression, but suggested that such aggression may be originated from joint offspring defense in many cases.

In harmony with Eibes-Eibesfeldt's notion, complex social traits such as stable association with recognition of members, communication, cooperation, and alloparenting, are found only in species that care for offspring extensively, like mammals and Hymenoptera [234]. Halliwell et al. [245] found that the intergenerational social grouping (95 in 1210 species) is significantly preceded by viviparity in squamate reptiles, and the primary selective driver for viviparity seems to be the thermal control of offspring, and associated with cold climates [181]. In mammals, when resource competition is low, females are generally more gregarious, sociable, and vulnerable to isolation stress than males, plausibly for

benefits in maternal care [246]. Female group living often involves matrilineal kinship, thus within-group altruism such as communal nursing or allomaternal care can be facilitated by inclusive fitness. And such female group-living indeed promotes the survival of their young in humans [8, 247], baboons [248], and mice [249, 250] (see also [251]).

On the other hand, when resource competition is high, females live separately from each other. This condition makes social monogamy (pair-bond) profitable for males at least in several mammalian taxonomic groups, and paternal care flows from social monogamy because mate's reproductive fitness is the same as the own reproductive fitness in monogamy [252 253]. Social monogamy then leads to cooperation and altruism within families for high kinship between group members [254].

In addition, as a proximate cause of alloparental and altruistic behaviors among adults, the "misplaced parental care" hypothesis has long been postulated in social insects, birds, and mammals [8 255]. Parental species may misdirect their parental altruistic behaviors toward suffering adults, regardless of kinship. Furthermore, empathy and non-reciprocal altruism are supposed to be derived from parental care as well; indeed, understanding others' needs and providing necessary care without reciprocity are the features of parenting [4, 243, 256-258].

Supporting the parenting origin of non-reciprocal altruism, Burkart et al. [259] tested 15 primate species including human children (see Section 2-3, c)) for the non-solicited, non-reciprocal "proactive prosociality" (i.e., acting to provide food to group members despite the provider cannot get the food). They found that the level of proactive prosociality is best correlated with the extent of alloparental care of the species rather than with brain size, presence of pair bond, male-male, female-female bond, cooperative hunting or other indicators tested. Alloparental species like humans, golden-headed lion tamarins and titi monkeys act most prosocially, common marmosets modestly, and maternal-only caring species, macaque monkeys and chimpanzees barely behave prosocially, despite their high cognitive abilities.

Huang et al. [260] examined the altruistic rescue behavior of common marmosets. They found that marmoset (allo)parents readily rescue their own and unrelated infants trapped across a 50-cm water pool by jumping over the water and opening the trap box, *provided* that they have an infant less than 1-month-old (mo) in their family *and* that the trapped infant is less than 1 month old. Surprisingly, marmosets rarely rescue other family members (pair-bonded partners or juveniles older than 2 mo). However, parents of 1-mo infants rescue a trapped mate *if* pre-recorded infant calls are played from the other side of the trap box. The authors reasoned that having 0-mo infants in their family should change

their brains to respond selectively to infant calls. They examined the infant call-induced brain activation patterns by functional MRI. While nulliparous pairs did not show any brain activation by infant calls, parents of young infants exhibited significant activation in the auditory, insular and parainsular cortices.

These two studies strongly support the parental-care origin of altruism as proposed [243]. Moreover, Huang et al. reported the strikingly low responsivity to rescue in long-bonded mates or juvenile offspring, compared with the immediate rescue of infants, and the increase in family rescue induced by infant calls. We also observed low non-reciprocal food sharing even among pairs in the paradigm described in [261] (unpublished observation). These observations further suggest that the altruistic helping brain circuit utilizes the infant care circuit and thus depends on infant cues to be activated even in family-living non-human primates.

5-2 The shared neuromolecular circuit of maternal care and sociability

During our study on mouse parental care, we inadvertently noticed that the amylin expression in the cMPOA/AC decreases to less than 3 % by 6 days of social isolation compared to that during group-housing, and recovers by 2 weeks of reunion with peers. Isolation of female mice from free social interactions first induces active contact-seeking, then depressive-like behavior and stress responses. Reunion with peers induces physical contact, and activates both amylin+ and Calcr+ neurons in the cMPOA/AC. Chemogenetic activation of amylin neurons increases, and molecular knockdown of either amylin or Calcr attenuates contact-seeking behavior. Consistent with the discussion in Section 5-1, amylin-Calcr circuity in the cMPOA/AC is female-biased, and females engage in contact-seeking behaviors significantly more than males [262]. Neither Calcr+ nor amylin+ neurons are not activated by defensive huddle (bright-light induced huddling in the dark phase), supporting the two-independent origins of social contacts. Thus it is presumed that amylin-Calcr signaling in the cMPOA/AC mediates affiliative sociality among adult females and parental care.

Amylin system may also be involved in parental care and pair bond formation in birds; in the zebra finch, of which males only sing for courtship, amylin expression is higher in paired males than in unpaired males or females in song-learning related brain areas such as HVC (high vocal center) and area X, as well as in the MPOA [263]. Together with the pioneering reports in rats [222, 223], amylin in the MPOA appears involved in parental care and reproduction-relevant affiliative sociality, even though its regulation is species-specific.

Furthermore, the metabolic control of amylin expression may titrate the affiliative sociability, as well as parental care, depending on the amount of food resource (Fig. 3C). This nutritional gate control is important because the increase of foraging demand is the major drawback of social living, and many social animals become more solitary when the food resource is restricted. In the case of house mice *Mus musculus*, they are aggressive and solitary in non-commensal habitats (e.g., fields, sand dunes), while they become amicable and form high-density multimale/multifemale colonies in commensal habitats with superabundant food supply (e.g., human-settlements) [235, 250]. Further experiments are needed to prove this possibility directly.

Our studies are limited to simple contact-seeking behaviors and have not examined the prosocial behaviors that benefit other individuals. Considering the abundant ethological evidence for the parental-care origin of complex social behaviors among adults (Fig. 3A and 4) discussed in Section 5-1, more attention should be placed on the MPOA for the neural basis of empathy and prosociality, along with the prefrontal cortex, insula or amygdala [264]. Wu et al. [265] reported that the GABAergic projections from MeA to the MPOA mediate consolating allogrooming behavior, to the precisely same extent in male and female mice. In humans, Moll et al. [266] identified that kinship-related social scenarios evocative of affiliative emotion induce septal–preoptic–anterior hypothalamic activity that cannot be explained by positive or negative emotional valence alone. Further analyses on cost/risk-taking altruism in rodents and primates should shed more light on the evolutionary origin and regulatory mechanisms of complex affiliative sociality in mammals.

6 Concluding remarks and future research directions

By integrating the neuromolecular and evolutionary perspectives, we propose that the possible origin of mammalian maternal care is anamniote parental care, which was originally simple and male-biased and gradually elaborated and female-biased via reproductive strife under harsh environments. With evolution of internal fertilization and endothermy, multiple regulatory molecules (inc. female reproductive hormones and metabolism-involved receptors) and their sexual dimorphism may have been added to the core parenting neurocircuitry, to regulate the timing and extent of parental behaviors in a sex-biased manner in the mammalian lineage. In mammals, paternal care has been derived again from maternal care with alloparental care, and in turn facilitates cooperative behaviors among group members. From this view, even the most intricate social system of modern humans appear to be the

result of *K*-strategy in *r/K* selection theory [267], the effort to maximize the survival of small number of offspring. Although these assumptions are all hard to prove, comparative analyses of neural mechanisms of parental care across vertebrates shall shed light on this issue.

This line of research shall also contribute to understanding the synthesis of the mammalian brain; what brain inventions enabled the gradual increase of complexity and flexibility of mammalian parental care and affiliative sociality on the vertebrate brain bauplans [268]. Selection for survival (e.g., agility in nocturnal environments) as well as reproduction (e.g. flexible tactics to hide offspring from predators) under various environmental pressure should have elaborated the brain structures, such as the mesolimbic dopamine pathway in early tetrapods, three-layered dorsal pallium in early amniotes, the "neocortex" and corticostriatal loops in early synapsids, and corpus callosum and distinct motor cortex in eutherian mammals [193]. Furthermore, although we could not discuss it in this paper, the mechanism and evolution of the infant attachment system as the counterpart of the parental care system deserve more research attention [269]. Such efforts to understand the neural basis of the parent-infant relationship will pave the way to resolve various problems in affiliative social behaviors, starting from child abuse and domestic violence in families, bullying and harassment in the community, and crimes and conflicts in our society.

Acknowledgments

We thank Drs. Nobuyuki Kutsukake, Kazunari Miyamichi, Michael Numan, and anonymous reviewers for critical reading and commenting on the manuscript and our lab members for assistance. This research was supported by RIKEN Center for Brain Science (2022-3), JSPS KAKENHI Grant Number 22H02664 and 22K19486 (K.O.K.).

Competing interest statement

The authors declare no competing interests.

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