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REVIEW

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Parental brain through time: The origin and development of the neural circuit of mammalian parenting

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Abstract

This review consolidates current knowledge on mammalian parental care, focusing on its neural mechanisms, evolutionary origins, and derivatives. Neurobiological studies have identified specific neurons in the medial preoptic area as crucial for parental care. Unexpectedly, these neurons are characterized by the expression of molecules signaling satiety, such as calcitonin receptor and BRS3, and overlap with neurons involved in the reproductive behaviors of males but not females. A synthesis of comparative ecology and paleontology suggests an evolutionary scenario for mammalian parental care, possibly stemming from male-biased guarding of offspring in basal vertebrates. The terrestrial transition of tetrapods led to prolonged egg retention in females and the emergence of amniotes, skewing care toward females. The nocturnal adaptation of Mesozoic mammalian ancestors reinforced maternal care for lactation and thermal regulation via endothermy, potentially introducing metabolic gate control in parenting neurons. The established maternal care may have served as the precursor for paternal and cooperative care in mammals and also fostered the development of group living, which may have further contributed to the emergence of empathy and altruism. These evolution-informed working hypotheses require empirical validation, yet they offer promising avenues to investigate the neural underpinnings of mammalian social behaviors.

KEYWORDS
amylin, calcitonin receptor, medial preoptic area, parental behavior, social behavior

INTRODUCTION

Parental care in vertebrates

Recent neuroscientific studies on parental behaviors unveil its core neuromolecular circuit centered on the medial preoptic area (MPOA). In addition, progress in paleontology and comparative behavioral ecology have provided substantial insights into the evolutionary path of mammalian parental behaviors. Yet, these findings from different research disciplines should be integrated to illustrate the overall perspective of mammalian parental care. This article aims to fill this gap and summarize the recent findings relevant to parental brains through time, which follows the fascinating recent work of Striedter and Northcutt.[1]

We first provide an overview of parental behaviors and their neurobiological mechanisms, focusing on laboratory mice. Second, we seek

TABLE 1 Components of maternal behaviors in laboratory mice and rats.

Behavior	Description
Pup-directed behaviors	
Nursing	Crouching over the pups to provide the opportunity to suckle in various nursing postures
Retrieval	Picking up the pup gently by a part of the body (most commonly, the dorsal skin) with the incisors and carrying it to the nest site
Grouping	Gathering the pups together into one quadrant so that they touch one another
Anogenital licking	Contacting the pup by the tongue and licking the anogenital region of the pup to stimulate excretion
Body licking	Contacting the pup by the tongue and licking the pup's body generically except for the anogenital region
Tactile stimulation	Any contact with pups, such as stepping on pups or resting in contact with pups
Non-pup-directed behaviors	
Placentophagia	Removal (and ingestion) of the placenta, umbilical cord, amniotic membrane, and fluids from the pup's body
Nest building	Transporting the nesting materials toward the nest or manipulating the material to shape the enclosed nest edge
Defense of the young	Protection of the pups from intruders, predators, and environmental hazards. It is called "maternal aggression" if the target of maternal defense is an unfamiliar conspecific.

the roots of mammalian parental care through vertebrate evolution. We then attempt to synthesize a working hypothesis of the possible anamniote origin of mammalian parenting neurons and move on to the affiliative social behaviors that should have evolved from parental care and conclude with some future directions.

It should be noted in the beginning that neurobiology researchers, including us, may call infant–nurturing behaviors collectively as *parental behavior*, even when the caregivers are not the biological parents of the young.[2,3] This practice may be confusing for evolutionary biologists. This is because the proximate neural mechanisms of infant care behaviors are shared among parental and alloparental behaviors. Animal caregivers may not precisely recognize their biological relationship with the young; instead, parental care may often be solicited simply by the distress signals from the young, sometimes even toward adult conspecifics or animals of different species, termed "misplaced parental care."[4] Thus, in the neurobiological context, please recognize the term "parental" as "parent-like," including alloparental care.

An overview of parental care in vertebrates

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 psychological and physical health as well as social attitudes later in life; thus, understanding the neural mechanisms of parental care is of great clinical relevance.[5,6] 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.[2,7]

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.

When parental care occurs in sexually reproducing animals, caregiving is often biased to mothers compared to fathers—except for teleosts and amphibians—because paternity is more uncertain than maternity, especially when the eggs are fertilized in the female's body (internal fertilization), imposing negative selection pressure for paternal investment.[8] In mammals, 100% of mothers provide care, while less than 10% of fathers do. In about 90% of cases, mothers are the sole caregivers. Still, nonmaternal animals (fathers, older siblings, and other group members) may also provide extensive infant care in several mammalian species, such as California mice (*Peromyscus californicus*), prairie voles (*Microtus ochrogaster*), meerkats (*Suricata suricatta*), marmoset and tamarin monkeys (Callitrichids), titi monkeys (Callicebus), and humans, as discussed in Refs. 4, 9–12, and 13.

Parental care behaviors in rodents

Maternal care in mammals includes multiple behavioral components including: milk provisioning; thermoregulation; helping with locomotion; protection from predators, parasites, and environmental hazards; and providing opportunities to learn hunting/foraging skills.[2,14,15] 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 suckling in orangutans[16] and lifelong relations in bonobos and humans.[17,18]

The repertoires of parental care behaviors in the well-studied species of laboratory rats and mice are summarized in 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 nonparents.[19,20] 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 parental behaviors.[21] Another component of well-studied maternal care is licking/grooming and nursing posture.[22,23] 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 for references and assessment protocols for each component of parental nurturing behaviors[24–26] and for additional experimental designs of postpartum maternal motivations.[27]

It should be stressed that parental care behaviors are easily disturbed by any perturbation of animals' general fitness or environmental stress,[6] 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 attention should be given to avoid unnecessary stress induced by handling or novel arena/room for testing and to simultaneously measure the indices reflecting general wellness; sensorimotor agility, such as first sniffing latency; and general locomotor activity in a retrieval assay.[24,28]

THE NEURAL MECHANISMS OF MAMMALIAN PARENTAL CARE

Classical studies

Initial studies focused on neuroendocrine regulation of maternal behavior in mammals, revealing that the hormonal milieu during pregnancy and parturition is critical for maternal behavior induction.[63] Among the multiple peripartum endocrine factors, estrogen is reported to be important for the onset of rat maternal behavior.[64] Genetic targeting studies showed faciliatory but not indispensable effects of estrogen receptor alpha on pup retrieval in mice and rats,[65–67] consistent with the previous findings showing that neither ovariectomy nor hypophysectomy grossly disrupts allomaternal behaviors.[20,68,69] As 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.[70–72] In contrast, some species heavily rely on a specific sensory input (e.g., olfaction in mice and sheep, audition in bats[25 73 74 75]) for maternal care.

Michael Numan presented a seminal series of studies demonstrating that the MPOA (Figure 1) is responsible for rat maternal care, possibly through its dorsolateral connections with the brain stem, such as the ventral tegmental area (VTA).[76–80] Since then, the MPOA has been established as the brain hub for maternal, paternal, and alloparental nurturing behaviors, with evidence in laboratory rats,[76,81,82] hamsters,[83] biparental California mice,[84] laboratory mice,[55] rabbits,[85] sheep,[86] common marmoset monkeys (*Callithrix jacchus*),[87] and with supporting observations in humans[88,89] (see Refs. 2 and 16 for comprehensive reviews). Furthermore, the POA has been implicated in parental care in nonmammalian vertebrates, such as ring doves (*Strep-*

BOX 1 The MPOA in the preoptic–hypothalamus continuum

Recent findings in developmental neuroscience dissociate the mouse preoptic area (POA) from the hypothalamus based on the developmental expression of transcription factors.[29,30] Still, there are practical benefits of the classical practice that deals with them together as a continuum (Figure 1A).[31] First, the POA and hypothalamus are spatially adjacent and extensively connected 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 12 (3 × 4, in mediolateral and rostrocaudal) divisions of the preoptic–hypothalamic continuum (Figure 1A).[31] The MPOA contains multiple subnuclei segregated by distinct cellular morphologies, molecular expression patterns, connectivity, and biological functions,[31–35] such as sleep at the ventrolateral preoptic nucleus (VLPO),[36,37] thermo- and osmoregulation at the median preoptic nucleus (MnPO),[38,39] puberty onset and fertility through kisspeptin and gonadotropin-releasing hormone (GnRH) neurons located in the anteroventral preoptic area (AVPV) and ventral part of the MPOA,[40] and male sexual behaviors at the medial preoptic nucleus (MPN).[41–44] The MPN is also implicated in proceptive/appetitive components of female sexual behaviors, though dispensable for the consummatory lordosis component.[45–47]

It should be noted that the map of the POA varies widely among different versions of Paxinos's stereotaxic atlases[48] and the Allen brain atlas[49] (Figure 1B). For example, the large portion of the dorsoposterior MPOA in the Paxinos atlas (based on Ref. 50) is regarded as the ventral part of the bed nucleus of the stria terminalis (BST) in the Allen atlas (based on Ref. 51). We follow the Paxinos atlas because the anterior commissural nucleus (AC, Figure 1B in the Paxinos atlas) marked by its oxytocin neurons has been included in the POA.[52–54] The AC is also remarkable as it selectively expresses c-Fos at incredibly high levels during parental behavior, and c-Fos is a marker for transcriptional activation of neurons when performing parental behaviors (Figure 1B).[55–57] Whether the AC is an overlapping part of the striohypothalamic nucleus (StHy) or a separate entity remains unknown.

Another relevant anatomical structure in the MPOA is a V-shaped expression of estrogen receptor alpha (Figure 1C),[58] from the MPNm to BSTpr. This V-shaped expression is commonly observed with mu-opioid receptor mRNA,[59] prolactin receptor mRNA,[60] and aromatase immunoreactivity[58] (see also the migration of BST neurons into the MPN[61]). A similar V-shape of expression is reported for male-biased Sytl4

(synaptotagmin-like 4), slightly more posteriorly.[62] 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.

topelia risoria),[90] turkey hens,[91] poison frogs,[92,93] and teleosts.[94] Because parental care is supposed to have emerged numerous times independently among vertebrates, this consistent involvement of the MPOA is notable.

So far, no other brain area is known to be as selectively and critically required for parental care as the MPOA is. For example, medial amygdala (MeA) lesions or severing of the stria terminalis do not inhibit or may even facilitate pup retrieval.[95–98] Chen et al.[99] 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 Ref. 99). They also found significant effects of MeApd GABAergic neuron activation/inhibition on male infanticide. These data collectively suggest that the role of the 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.[100–103] Lesions or functional inhibition of oxytocin neurons and/or other neurons in the paraventricular nucleus of the hypothalamus (PVH) may disturb pup retrieval, especially during the initial acquisition phase in nonmaternal animals.[104–107] Yet, in several cases, these results can be derived from the general anxiolytic effects of oxytocin,[108,109] and the PVH may not be critically involved in ongoing maternal care except for milk ejection.[110] For the role of the cingulate and other cerebral cortex areas, septum, basolateral amygdala, and ventral pallidum, please see Refs. 2, 24, and 111.

Lesion–behavior mapping has been useful in determining the brain areas responsible for behavioral disruptions. For example, lesion–behavior mapping has led to the identification of the Broca and Wernicke areas as brain areas responsible for distinct types of aphasia.[112,113] A major shortfall of classical studies employing permanent, experimentally induced brain lesions is the nonspecific deleterious effects caused by brain damage. Thus, to demonstrate the specificity of the behavioral alteration,[114,115] the lesion experiments should be accompanied by appropriate control experiments, such as similar-sized lesions of another brain area and the inclusion of nontargeted behavioral assessments, such as general physiological fitness and locomotion.[76,78,87,116] Also, associated null results (i.e., the lesion did not affect another behavior) are very informative to show the selectivity of the target brain region for a given behavior. For example, MPOA lesions in rats and mice that disrupt maternal care do not grossly affect female sexual behaviors or parturition of average numbers of litters.[55,76] This finding also suggests that maternal care defects are not caused by disturbed general health.

Neuroanatomy of the parenting-relevant MPOA subregion, cMPOA

The below sections describing neurobiological studies of the MPOA and parenting mainly focus on laboratory mice unless otherwise specified. Our research group has taken an anatomical approach to narrow down the area responsible for maternal, paternal, and alloparental care within the mouse MPOA. Utilizing voxel-based lesion–behavior mapping, we defined the central part of the posterior MPOA (cMPOA, Figure 1B),[55,56] a subdivision marked by a cluster of glutamatergic neurons, as the most indispensable MPOA subdivision for parental care. Bilateral cMPOA lesions 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 the stria terminalis, principal part (BSTpr) (Figure 1C and Box 1). The MPN-BSTpr has been established to be essential for male sexual behavior in multiple rodent species.[117] The medial MPN (MPNm) and BSTpr are significantly activated by male sexual behavior together with the cMPOA.[56] In contrast, the MPNm is unnecessary 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 below).

The cMPOA is adjacent to the anterior commissural nucleus (AC), the third largest population of the magnocellular oxytocin neurons in rats and mice.[52–54,118,119] Oxytocin neurons in the AC, supraoptic nucleus (SO), and PVH are highly activated during parturition and nursing, though not during pup care per se.[55] This spatial positioning of "caregiving" neurons (Figure 1A) that are at the intersection of the areas responsible for male sexual behaviors and parturition/milk ejection may be suited for their function in postmating caregiving behaviors in both sexes.

Molecularly defined neuronal populations involved in various parental behaviors

As the MPOA is comprised of a heterogeneous neuronal population, specifying the cell type(s) required for parental care is ideal. Traditional histological analyses[55,120,121] 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 parental care.

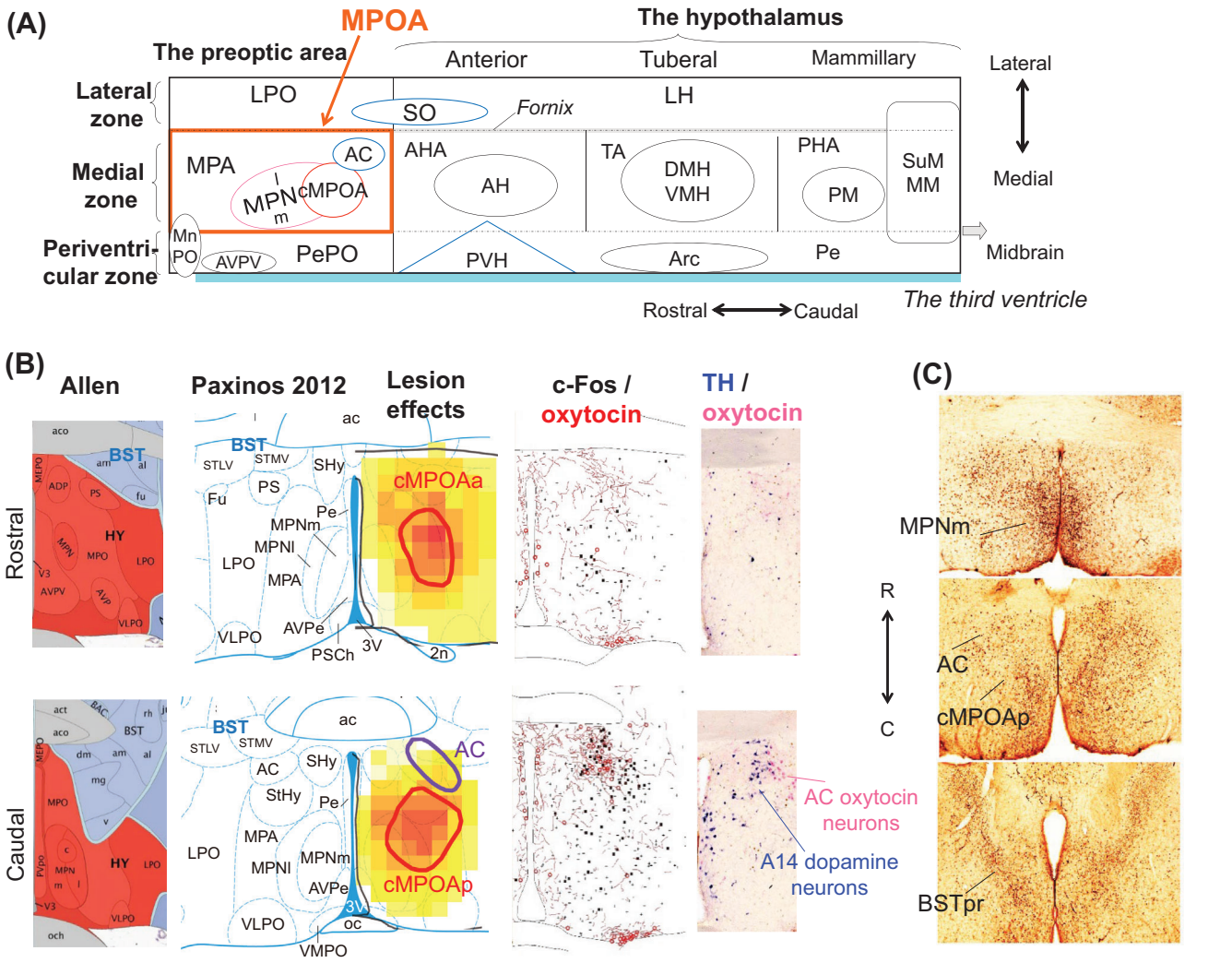

FIGURE 1 The neuroanatomy of the MPOA and its parenting-relevant subregions. (A) Schematic representation of the preoptic-hypothalamic continuum, sagittal view with the mediolateral axis. Note that the dorsoventral axis is compressed. Modified based on Fig. 1 of Ref. 31. The POA–hypothalamic continuum can be segmented into four parts along the rostrocaudal axis and three sections along the mediolateral axis. One of the resultant 12 segments is the MPOA, illustrated by the thick orange rectangle. Nuclei with oxytocin neurons are colored blue. (B) Two coronal sections depicting the anterior and posterior part of the cMPOA, illustrating, from the left, the Allen mouse brain atlas,[49] Franklin and Paxinos' stereotaxic atlas,[48] the location of the cMPOA (anterior and posterior; red outline) and AC (purple outline) with Spearman's correlation coefficients (the darker color indicates smaller *p*-value) of voxel-based lesion–behavior mapping[55]; the oxytocin neurons and fibers (red) and c-Fos induced by parental care in virgin females; oxytocin (pink) and tyrosine-hydroxylase (TH, blue) expressing neurons. The areas with names starting from ST in the Paxinos atlas belong to the BST but not to the preoptic area and are shown in smaller fonts. The Allen atlas is dorsolaterally elongated compared to the Paxinos' stereotaxic atlas due to the production procedure.[268] Of note, the highest density of c-Fos expression (in the AC) does not coincide with the area of the largest lesion effects (in the cMPOA).[55] (C) The V-shape formed by the estrogen receptor alpha-containing neurons, starting from the PePO/MPNm to the BSTpr.[269] Three coronal sections of the female brain at postpartum day 0, the top two are roughly the same level as (B), the bottom one is more dorsal to the others. Black: estrogen receptor alpha-immunoreactivity. Abbreviations: 2n, optic nerve; 3 V, third ventricle; ac, anterior commissure (o, olfactory limb; t, temporal limb); AC, anterior commissural n.; ADP, anterodorsal n. of preoptic area; AHA, anterior hypothalamic area; AH, anterior hypothalamic n.; AVP, anteroventral n. of preoptic area; AVPV or AVPe, anteroventral periventricular n.; Arc, arcuate n.; BAC, bed n. of anterior commissure; BST, bed n. of stria terminalis; BSTpr, BST principal n.; cMPOA, the central part of the medial preoptic area (a, anterior; or p, posterior); DMH, dorsomedial hypothalamic n.; Fu, fusiform n.; HY, hypothalamus; LH, lateral hypothalamic area; LM, lateral mammillary n.; LPO, lateral preoptic area; MM, medial mammillary n.; MPA, medial preoptic area (note that the MPOA means the whole area, and MPA conventionally designates the MPOA area excluding otherwise named nuclei); MPN, medial preoptic n. (m, medial; l, lateral; c, pars compacta); MnPO or MEPO, median preoptic n.; oc or och, optic chiasm; PVH, paraventricular n. of hypothalamus; Pe or PVpo, periventricular n. of hypothalamus; PePO, periventricular n. of preoptic area; PHA, posterior hypothalamic area; PM, premammillary n.; PS, parastrial n.; StHy, striohypothalamic n.; STLV, BST lateral division ventral part; STMAL, BST medial division anterolateral part; STMV, BST medial division ventral part; SuM, supramammillary n.; SO, supraoptic n.; SHy, septohypothalamic n.; TA, tuberal area of the hypothalamus; VLPO, ventrolateral preoptic n.; VMH, ventromedia1 hypothalamic n.; VMPO, ventromedial preoptic n.

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.[64] Genetic targeting studies showed faciliatory effects at the onset of heightened maternal care in mice and rats (although not essential), especially for nonmaternal animals.[65–67] Ribeiro et al. reported that short-interference RNA (siRNA) knockdown of *Esr1* mRNA in the MPOA using an adeno-associated viral vector (AAV) altered a wide array of female social behaviors, including postpartum retrieval, licking, and nursing behaviors,[122] while pup survival was intact (personal communication from Ana Ribeiro).

Fang et al.[123] reported that hM4Di-mediated chemogenetic inhibition of MPOA ESR1$^+$ neurons using an *Esr1*-Cre knock-in line inhibits pup retrieval in virgin females and lactating mothers without affecting pup sniffing, grooming, or crouching (cf. Fig. 1D–F of Ref. 123). GCaMP6 signaling of MPOA ESR1$^+$ (but not ESR1$^-$) neurons starts to increase as the females approach the pup and peaks at the onset of pup retrieval (and is greater 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 VTA and preferentially inhibit nondopaminergic VTA neurons. VTA dopaminergic neurons are activated at the onset of pup retrieval[123,124] (plausibly reflecting reward prediction error rather than the retrieval per se[125]). Finally, virgin females' pup retrieval in a novel arena was facilitated by optogenetic activation of MPOA ESR1$^+$ projections to the VTA and inhibited by an infusion of the sodium channel blocker bupivacaine that blocked neuronal spiking in the VTA. This fascinating study elucidated the detailed features of pup-retrieval driven by 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.[126]

Xu and colleagues reported that Caspase 3-based ablation of either GABAergic or glutamatergic MPOA neurons significantly inhibits pup retrieval.[127] Optogenetic activation of VGAT$^+$ (also known as SLC32A1) MPOA neurons induces (and optogenetic inhibition reduces) pup retrieval and nest building, while ESR1$^+$ MPOA neurons only affect pup retrieval.[128] It should be noted, however, that the definition of "pup retrieval" in their study is pup-carrying and does not mean pup-gathering into the nest. Moreover, fake pups (i.e., rubber blocks) were also "retrieved and grouped" through optogenetic stimulation of MPOA neurons,[127] leaving the possibility that this pup-carrying could be interpreted as a hunting-like object carrying mediated by CAMKII$^+$ MPOA neurons (but not by VGLUT2$^+$ (also known as SLC17A6) or VGAT$^+$ MPOA neurons, surprisingly).[129] Xu and colleagues also made an inspiring argument on competition between feeding and maternal behavior in line with a previous report,[130] based on their findings that the presence of pups inhibits feeding stimulated by 10 h of fasting or chemogenetic activation of arcuate AGRP neurons.[131] Furthermore, optogenetic stimulation of AGRP neurons inhibits maternal nest building without affecting pup retrieval.[128]

Overall, these studies demonstrate the critical role of MPOA ESR1$^+$ neurons in pup retrieval behaviors. However, ESR1$^+$ neurons consist of heterogeneous populations representing one-third of the total MPOA neurons and are distributed widely throughout the MPOA,[34,123] leaving room for further specification.

Galanin

Galanin is a brain–gut peptide concentrated in the hypothalamus and promotes feeding, mating, and sleep.[132] The seminal study by Dulac and colleagues in 2014 reported that MPOA GAL$^+$ neurons govern parental behavior, especially pup grooming (including pup sniffing and licking).[133] 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 intermale aggression. Optogenetic activation of MPOA GAL$^+$ neurons stimulated pup grooming in fathers and decreased crouching and total paternal care (see Fig. 5 in Ref. 133). It also decreased intermale aggression and increased locomotion.

Next, Kohl et al.[134] found that MPOA GAL$^+$ neurons receive pup-activated inputs from the BST and 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 tyrosine-hydroxylase [TH$^+$] neurons) in fathers. They also found that MPOA GAL$^+$ neurons project to PVH oxytocin, vasopressin, and corticotropin-releasing hormone neurons, AVPV TH$^+$ neurons, and to the PAG, MeA, and the VTA in both males and females. Pup retrieval was not altered by optogenetic inhibition or activation of MPOA GAL$^+$ neuron projections to the PAG, VTA, or MeA. In contrast, pup grooming (separate from licking in this study) was decreased or increased by inhibition or activation of the projection from MPOA GAL$^+$ neurons to PAG, respectively. The number of barrier-crossings inside the cage (i.e., locomotion; see the methods) was reduced or increased by the inhibition or activation of the projection from MPOA GAL$^+$ neurons to the VTA, respecivtely.[134] Because ESR1$^+$ neurons do not appear to be critically involved in pup grooming,[123] these studies showed that GAL$^+$ESR1$^-$ neurons (18% of GAL$^+$ neurons[135]) projecting to the PAG may govern pup grooming behavior.

Moffitt et al.[34] utilized single-cell RNA sequencing and uncovered the complex neuronal composition of the POA, which is comprised of 43 inhibitory, 23 excitatory, and three hybrid neuronal clusters. The authors noted that while inhibitory neurons tended to be clustered by neuromodulators, such as galanin, vasopressin, or TAC1, excitatory neurons were clustered by anatomical structures or nuclei and were segregated into distinct anatomical structures within the POA. Then, using multiplexed error-robust FISH (MERFISH) for 155 genes, they described the spatial details of each neuronal group, including 10 GAL$^+$ 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. I-14 neurons are spatially distributed most densely in the striohypothalamic nucleus (Figs. 6C and 7C of Ref. 34), which corresponds with the AC in Figure 1 of this paper. I-14 neurons are also distributed in the MPN/MPA. Of note, Moffitt et al. did not explicitly describe oxytocin neurons in the MPOA, but their analysis detected significant oxytocin expression in an E-23 cluster, suggesting that AC oxytocin neurons are essentially glutamatergic, as in the PVH.[136,137] 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$^+$BRS3$^+$ neurons in the AC/MPN/MPA as the strongest candidates for "offspring care" neurons. The remaining question was the functional significance of these neurons and molecules in parental care.

Calcitonin receptor

Our research group has manually screened for molecules most highly colocalized with parenting-induced c-Fos within the cMPOA and identified CALCR and BRS3,[138] which agreed with Moffitt et al.[34] We focused on CALCR hereafter, as we could produce Cre-transgenic lines with faithful Cre expression for CALCR but not for BRS3. Neurons 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 (~5% in virgin females and ~12% in postpartum day 4 mothers).[138] CALCR$^+$ neurons are comprised of at least two subpopulations; one is GABAergic, mostly GAL$^+$, and expressed in both the cMPOA and AC, resembling the I-14 described above.[34] The second population is VGLUT2$^+$ (glutamatergic), 18% GAL$^+$ in mothers, and mostly confined to the cMPOA,[138] appearing to be a separate population from I-14.

Cre-dependent tetanus toxin silencing of cMPOA CALCR$^+$ neurons severely disturbed pup retrieval and brood-nest building in virgin females and postpartum mothers, leading to a pup survival rate of less than 20% for *Calcr*$^-$silenced mothers. Mating, pregnancy, delivery, litter size, placentophagia, and pup sniffing latency were intact in these mothers. 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 most subject males.[138] 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 is eight 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 an elevated plus maze, suggesting that peripartum increases of CALCR$^+$GABA$^+$ neurons in the cMPOA enhance maternal motivation.[138]

In primates, a parenting-responsible brain region has not been previously identified. We, therefore, 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 a small subregion of the marmoset posterior MPOA that colocalized with c-Fos after alloparental care.[87] 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, amylin administration to the marmoset cMPOA facilitated infant carrying,[139] plausibly by binding and activating CALCR$^+$ neurons, which has also been shown in mice.[140] 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 changing the "c" in cMPOA from "central" to "*Calcr*-expressing" to better define this MPOA subregion across species.

Summary and remaining questions of circuit mechanisms

The above data show that (1) CALCR$^+$ESR1$^+$ cMPOA neurons are relevant for basal pup retrieval behaviors, (2) ESR1$^-$GAL$^+$ MPOA neurons are important for pup grooming, and (3) GAL$^+$CALCR$^+$ESR1$^+$VGAT$^+$ AC/cMPOA neurons heighten maternal care. However, ESR1$^+$, GAL$^+$, and CALCR$^+$ parenting-relevant neurons contain both excitatory and inhibitory subpopulations,[34,138] 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 need to be performed.

Zhang et al.[141] reported that activation of glutamatergic MPOA neurons induces anxiety-like behaviors (including pup-directed attack), hyperlocomotion, and pupil dilation. Hyperlocomotion was reported when stimulating GAL$^+$,[133] neurotensin$^+$,[142] or all neurons[127] in the entire MPOA, but not when manipulating the cMPOA specifically.[56,138] These differences may be due to the size and/or location of the targeted area (see Figure 1A,B). If the target area is too large, it may affect the preoptic locomotor region that initiates locomotion through electrical stimulation via their projection to the mesencephalic locomotor region,[143] (thus inducing hyperlocomotion) which disturbs many naturalistic behaviors, especially crouching over pups.

It is also notable that prolactin signaling in the MPOA is important for maternal nursing[144] and paternal behaviors[145,146] (see Refs. 10 and 147). There are also relevant brain areas and neurons outside of the MPOA, such as oxytocin neurons in the PVH for the onset of allomaternal[148] and paternal behaviors[107]; dopaminergic neurons in the AVPV, VTA,[125,149] locus coeruleus,[150] and lateral habenula[151]; and melanin-concentrating hormone neurons in the lateral hypothalamus,[152] amygdala and, cerebral cortex.[153–156] Also, there are many important studies on the mechanism of infanticide,[157–162] many of which have been discussed extensively elsewhere.[10,163,164]

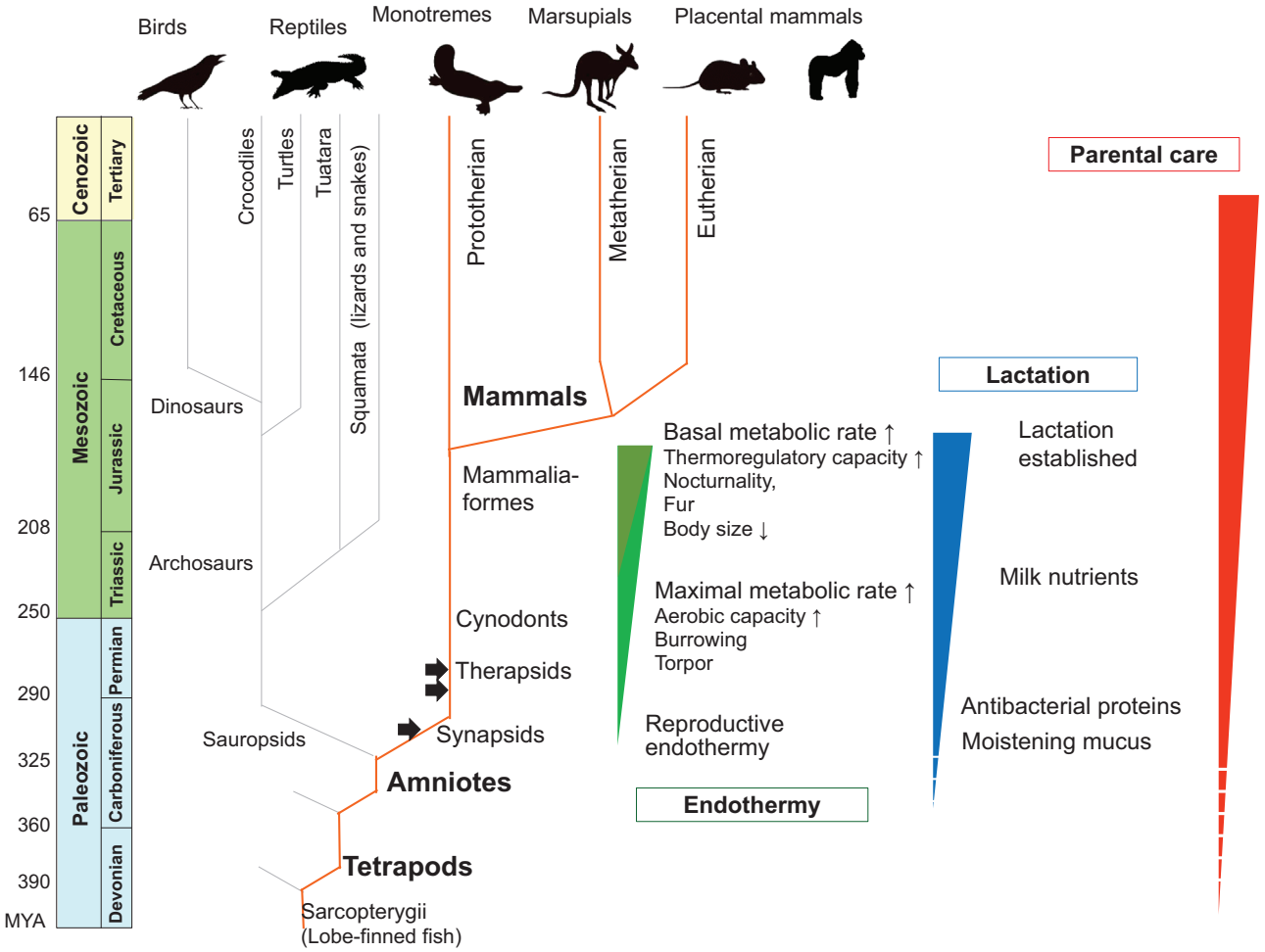

FIGURE 2 The evolution of mammals, lactation, and endothermy. Schematic of mammalian evolution, based on Refs. 181 and 201. Synapsids: amniotes having a single temporal fenestra in the skull. Therapsids: synapsids with incisors, canines, and molars. Black arrows indicate fossil evidence of parental care in the Paleocene. Abbreviation: MYA, million years ago. The silhouettes of example species are from http://phylopic.org.

Of relevance, the vertebrate brain is not decisively dichotomized by genetic sex: many fish change sex during their life; sex determination is environmentally dependent in 5% of living reptile species; and mammalian brain sex is significantly dependent on peripheral ovarian hormones rather and not simply determined by genetic sex. These facts may explain why the core circuitry 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, prolactin, oxytocin, and testosterone to activate/inhibit the core parenting circuit according to the context.

PARENTAL CARE EVOLUTION IN VERTEBRATES: COMPARATIVE BEHAVIORAL ECOLOGY AND PALEONTOLOGY

To better understand the neuromolecular features of mammalian parental care, this section outlines its possible evolutionary path (Figure 2, orange line), discussing parental care patterns in extant vertebrates, excluding avians[165] due to space limitations.

Living fish and ancestral vertebrates

About 30% of living teleost (bony fish) families show parental care, which may be opportunistic. In ray-finned fish, paternal, maternal, and biparental care emerged independently from the lack of care. Any loss of any parental care has likely occurred less frequently than its emergence.[166]

Male care (50–84% of parenting species) is more prevalent than female care in fish, and male-only care occurs in nine times as many genera as female-only care.[7] After external fertilization, eggs are often deposited within the male's territory, thus male egg guarding can be a byproduct of territory defense.[167] In contrast, most female-only care occurs with internal fertilization, which results in an increase of paternity uncertainty and thus suppresses male care.[7,168]

Among teleosts, lobe-finned fish (Sarcopterygians) (including lungfish) have evolved into tetrapods. Like amphibians, most lungfish adults lose their gills and breathe air obligatorily. In five of six extant lungfish species, males guard eggs in nests.[169] *Lepidosiren* males aerate eggs and larvae by developing vascular filaments on their fins during reproductive seasons.[170]

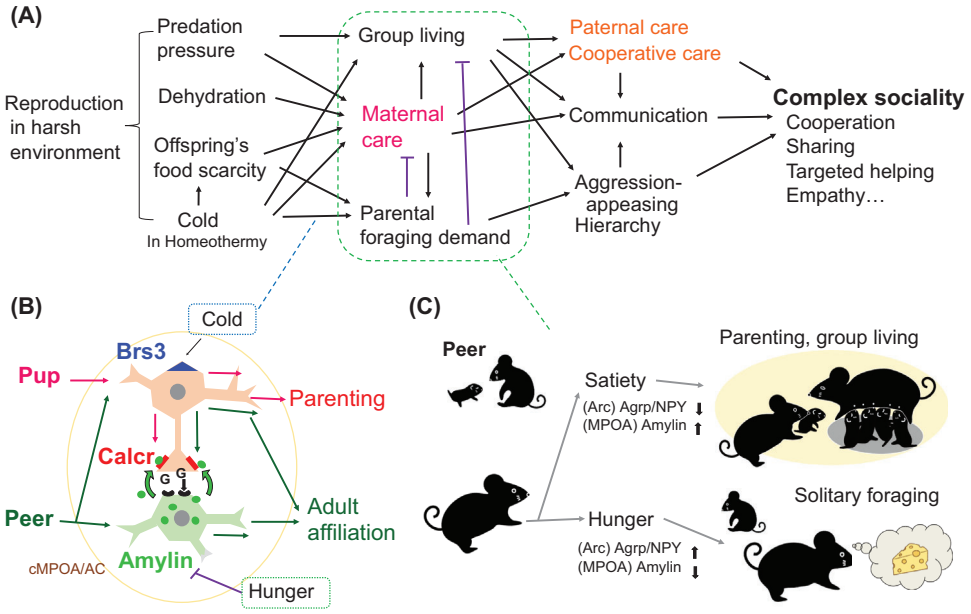

FIGURE 3 The mammalian maternal care circuity in evolutionary and ecological contexts. (A) The working hypothesis of the origin and development of mammalian maternal care. Group living includes pair bonding. (B) The working model of CALCR-amylin neurons in the cMPOA/AC. Pup-derived sensory cues activate CALCR neurons (top) and drive parental behaviors. Peer-derived sensory signals activate both CALCR and amylin neurons (bottom). CALCR neurons 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.[138,140] (C) Possible titration of maternal care and adult group housing by food availability via CALCR-amylin and AGRP/NPY systems. Abbreviations: AC, anterior commissural n.; AGRP, agouti-related protein; Arc, arcuate nucleus; BRS3, bombesin receptor subtype 3; CALCR, calcitonin receptor; cMPOA, the central part of the medial preoptic area; MPOA, medial preoptic area; NPY, neuropeptide Y.

These data on fish suggest that basal vertebrate parental care might have stemmed from male-biased reproductive behaviors, such as nesting and territorial defense. Consistently, the parenting-involved MPOA is a key brain site also for male (but not female) sexual behaviors for all vertebrate groups examined, including teleosts.[117,171,172] For example, during the courtship of electric fish *Brachyhypopomus gauderio*, males emit social electric signals and their nucleus preopticus ventricularis anterior in the POA is transcriptionally activated and expresses more vasotocin.[173] In other studies, POA GAL$^+$ neurons are activated during mouthbrooding in maternal cichlids[94] and during male courtship, but not paternal care in male midshipman (*Porichthys notatus*)[174]—requiring further studies examining GAL$^-$ neurons.

Living amphibians and tetrapod ancestors of mammals

Devonian adult tetrapods developed legs and lungs to live on land (Figure 2). The offspring's habitat was also moved toward land, which is beneficial for protection against aquatic predators but increases the risk of desiccation and temperature instability (Figure 3A). Although most living amphibians provide no parental care after aquatic spawning, 25% of species, including all three amphibian lineages (Caudata/Urodale [salamanders and newts], Anura [frogs and toads], and Gymnophiona [caecilians]), develop eggs on land and provide parental care.[175,176] Male-only and female-only care are equally common, although offspring feeding and viviparity are performed exclusively by females.[177]

Most Aromobatidae and Dendrobatidae poison frogs attend to their eggs and transport tadpoles to a terrestrial pool of water.[178] Both male and female care occurs with or without pair bonding. Utilizing such diversity, Fischer et al.[93] reported the neural activation patterns during tadpole transport in three Dendrobatidae species with male uniparental, female uniparental, and biparental care. The medial pallium and POA are consistently activated during tadpole transport, independent of sex. In the male uniparental *D. tinctorius*, galanin expression in the POA and medial pallium was associated with tadpole transport. Activation of POA galanin neurons during tadpole transport is observed in biparental *R. imitator* but not in *D. tinctorius* or *O. sylvatica*. O'Connell's group[92] also demonstrated that maternal tadpole feeding induces neuronal activation in the POA and lateral septum, although the activity of POA oxytocin neurons was negatively associated with maternal feeding in two distant species.

Among amphibians, Caudata (salamanders) most resemble the extinct stem amniotes.[179] Eighty-nine percent of Caudata species fertilize internally, except for the most ancient families.[180] Fifty-eight percent of internal fertilizers engage in female care, 42% no care, and male care does not occur. Terrestrial egg-laying occurs almost exclusively in internal fertilizers and is accompanied by maternal care[180] (Figure 3A). Thus, the male-to-female shift of parental care probably occurred during terrestrial adaptations including internal fertilization in Caudata.

The early tetrapods adapted to terrestrial life also through increased dermal protection and gas exchange by developing skin collagen and skin glands that secreted mucous compounds and antimicrobial proteins.[176] Such skin secretion may also protect attended offspring, as seen in some salamanders. Molecular evidence indicates that the antimicrobial peptides involved in the innate immune system evolved into milk constituents of mammals (see below).[181–183]

Living reptiles and amniotic ancestors of mammals

With the development of the amnion and chorion (a sac covering the embryo with water and yolk), the basal amniotes (Figure 2) reproduced on land. The early amniotes fertilized internally and retained the embryo in the female's body (extended embryo retention [EER]), and may have even been viviparous like some salamanders and 20% of squamates. Viviparity protects the embryo and neonates from environmental hazards and was sustained throughout amphibian evolution once it emerged.[184] Viviparous amphibians rarely care for their offspring after birth[177]; thus, the emergence of EER/viviparity as a maternal investment strategy may have reduced the need for behavioral care, leading to a low (10%) prevalence of parental behaviors among reptiles. EER after internal fertilization also imposed a strong female bias in parental care when it occurs; male-only care is not found in reptiles and mammals, and only in 1% of avians.[165]

The traditional view that reptiles are nonsocial is outdated.[185] All crocodilians and tuataras (Figure 2) engage in maternal care, such as egg attendance and nest defense.[186,187] Most turtles vocalize when they mate or before hatching for communication.[186,188] At least 18 Squamata species form stable-membered groups, some up to 20 years.[189] In the viviparous lizard, *Liolamemus huacahuasicus*, the mother defends the territory where her offspring reside and provides access to food and burrows for up to 2 years,[190,191] an indirect form of parental care.

Evolution of lactation and endothermy for parental care in mammals

Amniotes diverged into synapsids (including mammals) and sauropsids in the Carboniferous (Figure 2). The oldest fossil evidence of synapsid parental care is 306–309 million years ago (MYA).[192] The fossil is of young encircled by a plausible mother's tail, resembling a denning parent–offspring dyad. Several key mammalian features have developed during the evolutionary path from synapsids to mammaliaforms (stem mammals), including lactation and endothermy.

Lactation as hydration, disinfection, and feeding of the offspring

Early synapsids' eggs lacked fully calcified shells and were still vulnerable to desiccation like the eggs of monotremes and most squamates.[176,184] Thus, early synapsids such as Dimetrodon may have buried their eggs in moisture-laden soil, hydrated them with contact from moist skin, or carried them in a moist pouch—as living monotremes do.[193,194] Apocrine-like skin glands of amphibians secrete ~ 500 peptides, and several of these molecules in basal amniotes have evolved into milk constituents in mammals; lysozyme to alpha-lactalbumin, secretory calcium-binding phosphoproteins to caseins, and lipocalins to beta-lactoglobulin.[181,182] Such skin secretions fed the offspring, starting in cynodonts and established in Jurassic mammaliaformes, as demonstrated by the fossil evidence of delayed tooth development and milk teeth (Figure 2) (see Ref. 195).

Endothermy for parental care and the evolutionary path from synapsids to mammals

Farmer[196] proposed that the primary drive for the evolution of nonshivering heat generation is to facilitate offspring growth in thermally unstable environments.[197,198] Indeed, endothermy in tegu lizards selectively occurs in their reproductive period.[199] After laying, tegu females remain with their eggs for up to 75 days without foraging, with their body temperature 10°C higher than the ambient temperature and maintenance of a 5°C increase in the nest temperature.

Most synapsid species went extinct following the drastic decrease of ambient temperature and oxygen level from 30% to 10 % at the end of the Permian (252 MYA) due to the massive Siberian volcanic eruptions. Surpassed by Sauropsids, Mesozoic synapsids reduced their body size and became nocturnal, with a dietary niche of insects. Cynodonts in the early Triassic had a bony secondary palate that enabled respiration while feeding, increased basal metabolic rate, and later, neonatal suckling. The most derived cynodonts, Probainognathia, developed maxillary turbinates and reduced lumbar ribs, enabling a high respiratory rate and increased maximal metabolic rate. A fossilized example of the mammaliamorpha *Kayentatherium wellesi* was found with 38 near-hatching young in one clutch, suggesting simple maternal care.[200]

In the late Triassic, mammaliaforms maintained body temperature by increasing basal metabolic rate, insulation by fur, and lactation. The cynodont–mammaliaform transition is also marked by the mammalian jaw joint and inner ear complex,[200] and together with increased olfactory and tactile sensitivity (such as with whiskers), these features have increased the relevant cortical areas to yield a large ratio of brain-body mass.[201,202]

EVOLUTIONARY ORIGIN OF MAMMALIAN PARENTAL CARE

Mating-associated behaviors in anamniotes as the possible origin of mammalian parental care

How far can we trace the direct root of mammalian parental care? The oldest fossil evidence of synapsid parental care is from 309 to 306 MYA.[192] Solid molecular evidence suggests that

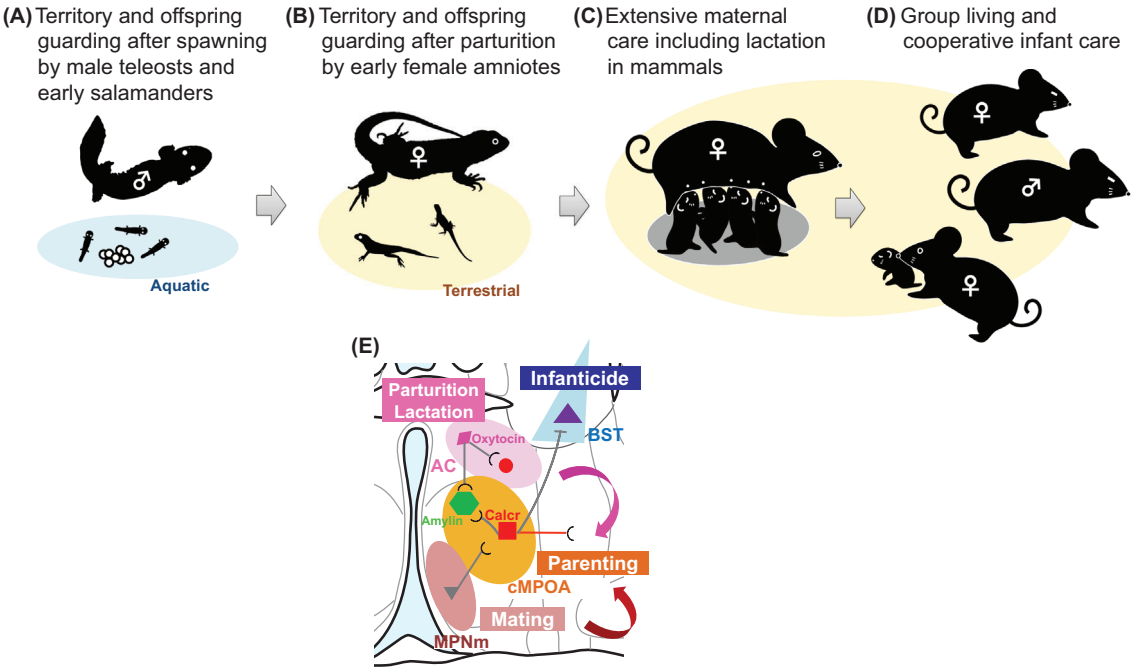

FIGURE 4 Summary of the working hypothesis on the evolution of mammalian parental care. (A) In early Sarcopterigii and Caudata, males may defend offspring along with their territory after aquatic spawning. POA neurons mediate courtship and copulation and may simultaneously activate surrounding neurons, which eventually become involved in mating-associated behaviors, such as nest attendance and offspring defense. (B) In early amniotes, in which females invest in their offspring by extended embryo retention, these territory/offspring defense neurons in the POA may be triggered by estrogen and oxytocin at parturition, while the mechanism of sustained defense is not known. (C) In mammals, extensive maternal care is mandatory and may add CALCR expression in cMPOA-parenting neurons for metabolic gate control. Some BST neurons have evolved to induce infanticide as a reproductive strategy, possibly through neurons involved in predation. (D) cMPOA parenting neurons start functioning in paternal care, cooperative care, and group living in some mammals. (E) Spatial organization of groups of MPOA neurons. Abbreviations: AC, anterior commissural n.; BST, bed n. of stria terminalis; CALCR, calcitonin receptor; cMPOA, the central part of the medial preoptic area; MPNm, medial preoptic n. medial part. The silhouettes of example species are from http://phylopic.org.

offspring-moistening care via skin gland secretion was established as early as 310 MYA.[203,182] Care behavior such as egg/offspring moistening requires significant maternal morphological changes and should induce the coadaptation of offspring physiology; thus, it should have been rarely lost, if at all.[171] These data indicate that the direct origin of mammalian parental care already existed in the Carboniferous synapsids.

Going further back in evolution, it is generally thought that maternal care in the synapsid lineage evolved independently (as convergent evolution) from preamniotic parental care, given the scarcity of parental care in living reptiles. However, Oftedal and Farmer independently suggested the possible preamniotic origin of lactation and thermoregulation of offspring, respectively.[176,198] Oftedal argues that the secretory skin glands and some milk constituents exist in the ancestral form of amphibians. Farmer points out the strong association between parental investment (especially thermoregulation of offspring by viviparity and parental behaviors) and terrestrial reproduction in anamniotes.

Following these pioneers, we here summarize a third line of evidence supporting the preamniote origin of mammalian parental care from a neurobiological perspective (Figure 4). As discussed above, the primary form of anamniote parental care is egg attendance and guarding that immediately follow external fertilization (Figure 4A, B). The MPOA or POA is a key brain site for male sexual behaviors in all vertebrate groups that have been tested, including teleosts, amphibians, and reptiles (Figure 4E).[117,171,172,204,205–206] The existing evidence, though limited, also suggests the role of the MPOA in basal vertebrate parental care as seen in mammals.[94] In mammals, the studies by Dulac and colleagues, followed by ours, have demonstrated that the MPOA neuronal populations activated during male mating and paternal care overlap significantly (Fig. 1g of Ref. 133; Fig. 8D of Ref. 34; and Fig. 2 of Ref. 56). The male mating and parenting neurons also overlap functionally, as ablation of MPOA GAL$^+$ neurons in mice or pharmacological suppression of the cMPOA in common marmosets disturbs infant retrieval as well as male mating behavior (Extended Data Fig. 5 of Ref. 133).[207] Furthermore, the conditional knockout of the transcription factor PTF1A from the POA and tuberal hypothalamus by crossing *Ptf1a*$^{flox/del}$ with *Nkx2.1-Cre* abolishes brain masculinization, including male sexual behaviors, together with severe disturbances of female parental behaviors.[208]

Supposing that mammalian parental care was a new invention of amniotes, the parental care circuit could have been linked more with female reproduction, especially oviposition or parturition, than male reproduction, because internal fertilization and EER have a strong maternal bias in amniote parental care. This idea leads to the widespread presumption that maternal care should depend on

oxytocin. Oxytocin is a peptide hormone critical for egg laying and parturition and indispensable for milk ejection in mammals (together with vasopressin homologs[209]).[2,210,211] However, the genetic ablation of oxytocin leads to surprisingly normal postpartum maternal care in multiple rodent species[27,57,212–216] (for other vertebrates, see Refs. 217 and 218). Oxytocin does facilitate the initiation of parental care, especially for paternal and allomaternal care, but is surprisingly less critical for postpartum maternal care (e.g., Miyamichi and colleagues[107,216]).[148] Moreover, the overlap of MPOA parenting neurons with female-mating neurons is much less pronounced than that with male-mating neurons,[34,208] and MPOA lesions or the silencing of cMPOA CALCR$^+$ neurons abolishes parental care without affecting female mating and parturition.[138]

These findings can be parsimoniously synthesized if mammalian parental care stems from male-biased, mating-related behaviors in anamniotes (Figure 4). This working hypothesis assumes that, first, a subpopulation of the MPOA neurons involved in male-biased proceptive mating behaviors (see Box 1) became specialized for mating-associated behaviors, such as territory defense (which is regulated by MPOA androgen receptors[219]) and the selection and preparation of a spawning site (nesting), which eventually extended to egg guarding in teleosts or basal tetrapods. Then, during the female shift of offspring care in tetrapods and early amniotes, the same population of MPOA neurons might have then been involved in egg/offspring guarding by mothers, and finally become selectively responsible for intensive maternal care in synapsids.

It should be noted that this assumption does not necessarily mean that mammalian maternal care is orthologous to paternal care of lobe-finned fish. As parental behaviors are opportunistic in many anamniotes and have appeared and disappeared multiple times, similar forms of parental care might have emerged repeatedly whenever a harsh environment exerted a selection pressure for it (e.g., indirect offspring guarding as an extension of territorial behavior in male lungfish and female lizards). And if the mating-involved MPOA neurons have been utilized repeatedly in multiple independent evolutions of parental care, such an evolutionary process would be that of *parallel* evolution, which is distinct from *convergent* evolution.[220] Alternatively, it may be similar to the evolution of eyes in humans and squids, which used to be a textbook example of convergent evolution. However, it has turned out that the gene *Pax6* is commonly responsible for the development of human eyes, squid eyes, and the directional photosensing system of chordates. Thus, their core photosensing system may be orthologous, while the lens structures of eyes have evolved convergently in humans and squids.[221] In any case, many more studies on the neural mechanisms of mating and parental behaviors in nonmammalian vertebrates are necessary to test the present working hypothesis and establish the evolutionary basis of vertebrate parental care.

Balancing homeostatic needs and maternal care: Possible contributions of CALCR and BRS3

Endothermy facilitates offspring growth but increases mother and offspring caloric demand and subsequent foraging demand for the mother. Thus, when food resources are scarce, mothers must reduce the amount of care for more foraging or give up caring for offspring (desertion). Such a hunger-induced restriction of maternal motivation may be conveyed via neuropeptide-Y$^+$ Arc neurons projecting to the dorsal raphe and the MPOA, as suggested.[128,222,223] In this sense, lactation may benefit females by minimizing the energy drain associated with initial vitellogenesis thus offering the female an extended period to terminate her reproductive investment upon deteriorating environmental conditions with minimal energy loss.[195] This may also explain why the parenting-responsible neurons are marked by two G_q-coupled receptors that signal satiety, CALCR and BRS3 (Figure 3).

While CALCR's peripheral ligand is calcitonin, which is absent in the brain, CALCR in the brain forms a complex with receptor activity modifying proteins (RAMPs) to bind amylin (Figure 3B).[224] Amylin/IAPP (islet amyloid polypeptide) is a brain–gut peptide that is cosecreted with insulin from pancreatic β cells to inhibit food intake through actions on the area postrema.[225,226] Amylin is also produced in the hindbrain, arcuate nucleus, and the cMPOA/AC subregions in the MPOA.[138,140,227–230] 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.[140] Thus, MPOA amylin levels can up/downregulate CALCR$^+$ neurons to facilitate/suppress parental care depending on the food resource condition (Figure 3C), together with or as a part of the proposed mechanisms involving AGRP/NPY neurons in the Arc.[128,222,223] To prove this possibility, however, future studies should determine if the amylin level in the MPOA reflects hunger/satiety as well as regulates CALCR$^+$ neuronal activity in vivo.

BRS3 is an orphan receptor in placental mammals that is expressed in the median preoptic nucleus (MnPO), MPA, PVH, dorsomedial hypothalamus (DMH), and parabrachial nucleus.[231–233] *Brs3* knockout mice develop obesity with increased food intake and have a reduction in resting metabolic rate and body temperature. While DMH BRS3$^+$ neurons regulate body temperature, energy expenditure, and heart rate, BRS3$^+$ MnPO neurons are activated by cold exposure and induce cold defense responses via the sympathetic nervous system.[231,234] BRS3 has also been identified for its female-biased expression in the MeA and the principal part of the bed nucleus of the stria terminalis (BST).[62,99] BRS3 expression in the cMPOA/AC is highly upregulated peripartum along with CALCR,[235] and the next step would be to test whether CALCR/BRS3 neurons in the cMPOA/AC are activated by cold exposure (Figure 3B). If they are, then BRS3 signaling may be involved in cold adaptation of maternal care, such as increased 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 maternal investment, survival, and infant needs, the satiety signals of amylin–CALCR and BRS3 might have been added to the existing parental care circuitry as a neural mechanism to mediate parent–offspring conflict. However, it is generally hard to test any hypothesis about this evolutionary path since stem mammals are extinct. Investigations of the neuromolecular

circuits of maternal care in monotremes may shed light on this issue, as monotremes have protoendothermic features, such as considerable daily variations in body temperature and seasonal hibernation.[236] In addition, the relevance of CALCR in calcium mobilization during pregnancy, eggshell formation, and lactation should be examined separately.[237]

Like amylin–CALCR and BRS3, oxytocin suppresses food intake and mediates cold defense,[238,239] since oxytocin knockout mice are defective in cold defense physiology and behaviors. Thus, the function and direction of oxytocin in metabolic control are the same as CALCR and BRS3. In contrast, galanin and prolactin increase food intake and facilitate heat loss,[240,241] which may counteract CALCR and BRS3. The crosstalk of these molecular signals may fine tune the homeostasis during pregnancy and lactation.

BEYOND MATERNAL CARE TOWARD COMPLEX AFFILIATIVE SOCIALITY

Now, we shift the focus to the diversification of mammalian maternal care into alloparental care, group living, and complex sociality, such as altruism and empathy.

The definition of *society* in classic sociobiology refers to adult animals and excludes parent–offspring groups (termed *subsocial*).[242] However, for practical purposes in behavioral neuroscience, here we define social behavior as any action directed toward a conspecific,[243] and affiliative social behaviors as those that possibly result in the stable association of conspecifics, including parental care (refer to supplementary discussion of Ref. 140).

Parental behavior as the evolutionary basis of affiliative sociality, empathy, and altruism

Eibl-Eibesfeldt pointed out parental care and flight as the two principal drives for long-lasting social bonding in terrestrial vertebrates.[244] Consistently, female mammals are generally more sociable than males and tend to live in groups, possibly for cooperative maternal care (Figure 3A).[245] When resource competition is too high for females in a group, female–male pair living becomes profitable for males[246] (see also Ref. 247). Either type of group-living among adults promotes the emergence of cooperative offspring care (allomaternal and paternal) and facilitates offspring survival in many mammals, including humans.[4,248,249,250]

Within kin groups, altruistic behaviors among members are selected for inclusive fitness.[251,252] Moreover, neural mechanisms for understanding others' needs and providing care without reciprocity may have first emerged for parenting and then directed toward other conspecifics, as suggested.[2,244,253–255] Thus, parental care may foster complex sociality, empathy, and altruistic behaviors among adults from ultimate and proximate causations (Figure 3A).

Supporting this idea, Burkart et al.[256] tested 15 primate species, including human children, for nonsolicited, nonreciprocal proactive prosociality (i.e., acting to provide food to group members despite the provider not getting food). They found that the level of proactive prosociality is best correlated with the extent of alloparental care of the species than with other variables including the brain size, presence of a pair-, intermale-, interfemale bond, and cooperative hunting. Chimpanzees, in which the mother is the sole caretaker of offspring, barely behave prosocially in this task despite their high cognitive abilities. Another impressive study[257] showed that marmoset parents rescue 1-month-old infants but no other family members by jumping 50 cm across water. Parents rescue a trapped mate or juveniles only when prerecorded infant vocalizations are replayed. These observations further suggest that the group living is driven by parental motivation and that the brain circuitry of altruistic helping utilizes the infant care circuitry in primates.

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 of group-housed female mice decreases to less than 3% at day 6 of social isolation and recovers by week 2 of reunion with peers.[140] Isolation of female mice from social interactions first induces active contact-seeking, then depressive-like behavior and stress responses. Reunion with peers leads to 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. Amylin-CALCR circuitry in the cMPOA/AC is female-biased, and females engage in contact-seeking behaviors significantly more than males.[258] Neither CALCR$^+$ nor amylin$^+$ neurons are activated by social contact for defensive huddles induced by bright light,[140] supporting the two independent origins of social contacts proposed by Eibl-Eibesfeldt.

Amylin may also be involved in parental care and pair-bond formation in birds; in 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 the HVC (high vocal center) and area X, as well as in the MPOA.[259] Together with the pioneering reports in rats,[229,230] amylin in the MPOA appears to be involved in parental care and reproduction-associated affiliative sociality, even though its regulation is species-specific.

Furthermore, the metabolic control of amylin expression may titrate affiliative sociability and parental care depending on food resources (Figure 3C). Such a nutritional gate control for social behaviors is essential because food competition is a major drawback of social living, and many social animals become more solitary when food is limited. In the house mice *Mus musculus*, individuals are aggressive and solitary in noncommensal habitats (e.g., fields and sand dunes), while they become amicable and form high-density multimale/multifemale colonies in commensal habitats with superabundant food supply (e.g., human settlements).[243,260] Further experiments are needed to directly demonstrate this possibility.

Studies on amylin and social contact[140,258,261] 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,[2,244,253–255] more attention should be placed on the MPOA for the neural basis of empathy and prosociality, along with the prefrontal cortex, insula, and amygdala.[262] Wu et al.[263] reported that the GABAergic projections from the MeA to the MPOA mediate consolatory allogrooming behavior, to the same extent in male and female mice. In humans, Moll et al.[264] identified that kinship-related social scenarios evocative of affiliative emotions induce septal–preoptic–anterior hypothalamic activity that cannot be explained by positive or negative emotional valence alone. Further analyses on cost-taking altruism in rodents and primates should shed more light on the evolutionary origin and regulatory mechanisms of complex affiliative sociality in mammals.

CONCLUDING REMARKS AND FUTURE RESEARCH DIRECTIONS

By integrating neuromolecular and evolutionary perspectives, we propose that mammalian maternal care may be derived from anamniote parental care, which was initially simple and male-biased, and then became elaborated and female-biased via reproductive strife under harsh environments. Along with the evolution of amnion and endothermy, multiple regulatory molecules (especially female reproductive hormones, which have been extensively studied and reviewed[2,16]) and metabolism-involved receptors may have been added to the core parenting neurocircuitry to regulate the timing and extent of maternal behaviors in the mammalian lineage. Then in mammals, paternal and alloparental care have evolved from maternal care, thus facilitating complex cooperative behaviors, empathy, and altruism among group members. From this viewpoint, even the most intricate social systems of modern humans can be the result of *K*-strategy in *r/K* selection theory[265]—the effort to maximize the survival of a small number of offspring. Although any evolutionary assumptions are hard to prove, comparative analyses of neural mechanisms of parental care across vertebrates should shed light on this issue.

This line of research will also contribute to understanding the evolution of the mammalian brain; what brain traits enabled the gradual increase of complexity and flexibility of mammalian parental care and affiliative sociality on the vertebrate brain bauplans.[266] Selection for survival (e.g., agility in nocturnal environments) and reproduction (e.g., flexible tactics to protect offspring from predators) under various environmental pressures may have elaborated neural circuitry, 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 the corpus callosum and distinct motor cortex in eutherian mammals.[202] Furthermore, although we did 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.[267] 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 with child abuse and domestic violence in families, bullying and harassment in the community, and crimes and conflicts in our society.

AUTHOR CONTRIBUTIONS

Based on the data obtained from the work of all the authors, K.O.K. wrote the manuscript with discussion and contributions from all the other authors.

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COMPETING INTERESTS

The authors declare no competing interests.

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