UC Davis
UC Davis Previously Published Works

Title

Flipping the parental switch: from killing to caring in male mammals.

Permalink
https://escholarship.org/uc/item/9bm049nb

Authors

Elwood, Robert
Stolzenberg, Danielle

Publication Date

2020-07-01

DOI
10.1016/j.anbehav.2020.05.001

Peer reviewed

eScholarship.org
Powered by the California Digital Library
University of California

HHS Public Access
Author manuscript
Anim Behav. Author manuscript; available in PMC 2023 October 26.

Published in final edited form as:
Anim Behav. 2020 July ; 165: 133–142. doi:10.1016/j.anbehav.2020.05.001.

Flipping the parental switch: from killing to caring in male mammals

Robert W. Elwood[a,*], **Danielle S. Stolzenberg**[b]

[a]Queen's University Belfast, School of Biological Sciences, Belfast, U.K.

[b]University of California, Davis, Department of Psychology, Davis, CA, U.S.A.

Abstract

Killing of unrelated young by sexually naïve male mammals is taxonomically widespread, but in many species, males subsequently show paternal care or at least do not harm their own young. This dramatic and important change is due to a shift in paternal state rather than to recognition of young, the mother or the location in which mating occurred. This transition from infanticidal to paternal behaviour is timed so that the inhibition of infanticide is synchronized with the birth of their own young. Ejaculation followed by cohabitation with the pregnant female causes this transition, but the precise stimuli from the female remain elusive. However, changes in social status also cause changes in infanticide. The switch from infanticide is accompanied by physiological change in the male that can be detected by both females and pups. Hormonal changes have been implicated in the switch but establishing causal links has been difficult. Recent neuroanatomical studies show that pup odours activate the vomeronasal organ and its efferent projections to induce infanticide. The emergence of paternal care depends on the inability of the vomeronasal organ to detect pup odours. In the absence of vomeronasal input, pup odours activate a conserved parental circuit and induce caregiving behaviour. An emerging picture is of complex, antagonistic circuits competing for behavioural expression, which allow for males to commit infanticide when they may benefit from such activity but ensure that they do not damage their fitness by killing their own young. However, we stress the need for more work on the neural mechanisms that mediate this process.

Keywords

cohabitation; copulation; hormones; infanticide; mammals; neural mechanisms; paternal care

About 5–10% of mammal species show paternal care, often including carrying, cleaning, bringing food and protecting the young from low temperatures (West & Capellini, 2016), which are all activities that benefit the young in a direct manner (Elwood & Broom, 1978). In other species males may interact with the young without providing direct care, but instead provide indirect benefits such as deterring predators (Lukas & Huchard, 2014). However, infanticide by males is also widespread among the mammals (Lukas & Huchard, 2014). Remarkably, both traits may be shown by individual males because males tend to kill

---

[*] Correspondence: R.W. Elwood, School of Biological Sciences, Queen's University Belfast, 19 Chlorine Gardens, Belfast, BT9 5AJ, U.K. r.elwood@qub.ac.uk (R. W. Elwood).

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

unrelated young, but care for their own young (Elwood, 1977; Hrdy, 1979). Infanticide typically occurs before mating, but the males switch from killing to caring once they can expect to encounter their own offspring (Elwood, 1977). In male mammals infanticide is more widespread than paternal care (Lukas & Huchard, 2014; West & Capellini, 2016) but even species that do not provide direct care of the young stop killing infants. This switch from infanticide is a key determinant of fitness and robust mechanisms are required to ensure the survival of their own young yet enable infanticide when killing conspecific young might benefit the male. The main aim of this review is to examine the complex mechanisms that mediate this marked change. These involve various social stimuli, hormonal changes and changes in specific neural centres that mediate infanticide and paternal care.

LANGUR MONKEYS AND LIONS

Initially, it was not clear how infanticidal behaviour of males affected fitness. For example, Calhoun (1962) hypothesized that infanticide could be either pathological, because the killing of conspecifics was thought to be bad for the species, or advantageous, because it might function to maintain the population at an optimum level. However, those views changed following observations of infanticide when male langur monkeys, *Semnopithecus entellus* (Hrdy, 1974) and male lions, *Panthera leo* (Bertram, 1975) took over groups of females from other males. The females that lost their young came into oestrus and mated with the new males. Thus, infanticide was viewed as being beneficial to the perpetrators because by killing they could advance their own reproduction (Hrdy, 1979). However, when the males' own young were born, they were not harmed and, instead, the males often interacted with the young in an amicable manner. The assumption was that the males somehow 'recognized' the young as being their own (Walters, 1987). This could be due to the male recognizing the mother of the infants as being one with which they had mated, recognizing the location as one in which mating had taken place or, indeed, by direct recognition of some phenotypic marker on the young. All might reasonably correlate with relatedness (Walters, 1987). However, it is doubtful whether such recognition affects infanticide by males (Elwood & Kennedy, 1991).

RODENTS

The observations of monkeys and lions were ground breaking and influenced ideas about individual fitness but did not elucidate how males avoided harming their own young. Species amenable to experimentation were required for this and there followed many studies on rodents, the first using laboratory-reared Mongolian gerbils, *Meriones unguiculatus*, which are biparental (Elwood, 1977). During the female's first parturition the male typically vacates or is ousted from the nest. However, he visits the nest to take pups as they are born, which he then licks, lies over and keeps warm in a newly created temporary nest. After the female has delivered all the litter, she retrieves those taken by the male back to the main nest and there appears to be a high motivation of both parents to care for the young as soon as they are born (Elwood, 1975).

Chance observations, however, suggested that males change from being infanticidal to being paternal during their mate's first pregnancy. To test this idea, adult pairs of gerbils that had

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

yet to produce litters were used. After removal of the female the male was presented with a newborn pup from another pair (Elwood, 1977). Males that had previously reared a litter but currently did not have young in the cage were also tested. Because this species does not have a copulatory plug the time of mating was determined retrospectively.

Sixty per cent of adult naïve males, housed with nonpregnant females, harmed the pups by attempting to eat them (experimenter intervention prevented this), whereas those with females in late pregnancy never harmed pups (Elwood, 1977). Additional observations from other experiments confirmed that attempted cannibalism declined during the female’s pregnancy, and no male with a female in the last 6 days of pregnancy harmed pups (Fig. 1) (Elwood & Ostermeyer, 1984b). By contrast, males that had previously bred never harmed the test pup regardless of the reproductive state of the female at the time of the test (Elwood, 1977). Similar changes in responsiveness to pups prior to the birth of the first litter have since been described for a variety of male rodents, including inbred laboratory strains of mice, wild mice and a variety of species studied in the laboratory but recently derived from wild-caught animals (Lonstein & De Vries, 2000; Rymer & Pillay, 2018; Saltzman, Harris, De Jong, Perea-Rodriguez, Horrell, Zhao, & Andrew., 2017). For ethical considerations about such studies in which some pups may be harmed see Elwood (1991). For statistical considerations regarding potential pseudoreplication that might arise from treating pups rather than males as datum points see Labov, Huck, Elwood, and Brooks (1985).

The observations of inexperienced male gerbils transitioning from infanticide to a paternal responsiveness prompted the question of the role of the female in this switch. Whether she had to be present was tested by removing the late pregnant female from the cage and subsequently testing the male. In keeping with previous observations (Elwood, 1977), no male tested immediately after the female was removed harmed the test pup; however, if the female was out for 1e3 days 50% of males harmed the offered pup (Fig. 2; Elwood, 1980). Thus, without the presence of their pregnant mate, males reverted to infanticide. By contrast, males that had reared a previous litter failed to revert to infanticide when their pregnant mates were removed for 1–3 days (Elwood, 1980). The conclusion was that males breeding for the first time were brought into a temporary state through which they avoided harming pups. This temporary inhibition was dependent upon the presence of the female and, without the female, there was a return to infanticide. However, the experience of being brought into a paternal state and then rearing a litter resulted in a permanent inhibition of infanticide that was then independent of the presence of the female (Elwood, 1980).

Since these early observations on gerbils there has been much research, using various species, on the social stimuli responsible for the onset of paternal care, the hormones that might mediate this change and, more recently, the neural basis of the change. Given the diverse techniques and recent advances the present review aims to provide an integrated overview of this remarkable switch in behaviour.

EFFECTS OF COPULATION VERSUS COHABITATION

At least for gerbils, being with a pregnant female clearly plays a role in males switching from killing to caring. Relevant questions, however, concern the extent to which this

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

transition is conserved across rodent species and whether other factors might be involved. One possibility is that the experience of copulation might have a direct effect. Initially this was considered unlikely because infanticide decreased to zero only some weeks after copulation and the maintenance of the inhibition in gerbils was due to the pregnant female, not the preceding copulation (Elwood, 1977, 1980). Nevertheless, subsequent studies on other rodents demonstrated an effect of copulation. For example, CF-1 male mice, *Mus musculus*, that copulated showed an increase in infanticide over the next few days but then a reduction in infanticide about 18 days later, i.e. about the time the litter would be born. This occurred even if the female was removed from the male when copulation was confirmed (vom Saal, 1985). Males that intromitted their penis but without ejaculation did not show the reduction whereas males that ejaculated did (vom Saal, 1985). Thus, the reduction in infanticide was specific to ejaculation and timed with gestation but did not require subsequent cohabitation with the female. The timing of this reduction in infanticide was shown to be dependent on the number of lightedark cycles following copulation and males maintained in short or long cycles showed shorter or longer absolute times until the reduction of infanticide occurred (Perrigo, Bryant, & vom Saal, 1990). These findings led Perrigo, Belvin and vom Saal (1991) to claim that ejaculation in mice induces a ‘fail-safe neural mechanism’ that inhibits infanticide at the time the male could expect to encounter his offspring even though some males continued to commit infanticide at the time their young would be born.

Other experiments, however, found complete inhibition of infanticide in mice if copulation was followed by cohabitation with the female (Elwood, 1985; Elwood & Ostermeyer, 1984a). Without cohabitation the percentage of previously infanticidal males that showed infanticide 18 days after copulation was about 20% in one experimental group and about 60% in a slight variant (Elwood, 1985). However, there are strain differences in mice with respect to inhibition after copulation and removal of the female. With CS1 mice about 30% of screened infanticidal males still showed infanticide compared to about 60% for CBA males (Kennedy & Elwood, 1988). Note that in these experiments only previously infanticidal males were used whereas in those by Perrigo et al. (1990, 1991) the test animals comprised roughly equal numbers of previously infanticidal and noninfanticidal males. When this difference in subject selection is accounted for, the results from the two laboratories are remarkably similar. However, Perrigo & vom Saal (1994) focused on ejaculation as the key causal factor to eliminate infanticide whereas Elwood (1985) concluded that copulation followed by cohabitation was required. The latter conclusion was also reached by Palanza and Parmigiani (1991) who found that 100% of previously infanticidal male mice did not kill pups following copulation and then cohabitation. A similar transition to paternal responsiveness occurs in wild mice (Soroker & Terkel, 1988). This indicates that selection for a reduction of infanticide in laboratory strains has not produced a new mechanism for the inhibition of infanticide in males. A more recent report indicates that about 30% of C57BL6J male mice still killed pups even after 15–18 days of cohabitation (Tachikawa, Yoshihara, & Kuroda, 2013). However, Tachikawa et al. (2013) isolated the males from gestating females for 2–5 days prior to testing with pups and thus the method and results are like those found in male gerbils separated from the pregnant female (Elwood, 1980).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

In Long-Evans rats, *Rattus norvegicus*, copulation followed by cohabitation significantly reduced infanticide compared to copulation without cohabitation (Brown, 1986), although effects of both copulation and cohabitation have also been noted (Mennella & Moltz, 1988a). In California mice, *Peromyscus californicus*, copulation followed by cohabitation reduced but did not eliminate infanticide (Gubernick, Schneider, & Jeannotte, 1994). Further, in prairie voles, *Microtus ochrogaster* (Terleph, Jean-Baptiste, & Bamshad, 2004) and mandarin voles, *Microtus mandarinus* (Song Tai, Yu, Wu, Zhang, Broders, He, & Guo, 2010) paternal responsiveness was enhanced by this treatment. In white-footed mice, *Peromyscus leucopus*, copulation and cohabitation were not individually manipulated, but male aggression towards alien pups continued when the female did not produce pups, whereas those that successfully mated and cohabited with the pregnant female showed a marked reduction in infanticide (Cicirello & Wolff, 1990). Further, copulation per se in male bank voles, *Myodes glareolus*, did not reduce infanticide (Vihervaara, Sundell, & Ylönen, 2010) but it did in meadow voles, *Microtus pennsylvanicus* (Webster, Gartshore, & Brooks, 1981). Thus, although there is some variability in the proportion of males that continue to attack pups following copulation, most studies agree that copulation followed by cohabitation dramatically reduces infanticide and enhances paternal behaviour.

However, virgin male laboratory mice, housed with pregnant females, failed to show a reduction in infanticide (e.g., Swiss Webster mice, Palanza & Parmigiani, 1991; CF-1 mice, Perrigo & vom Saal, 1994), suggesting that copulation is required to predispose or prime male mice to be influenced by the pregnant female for the elimination of infanticide. However, wild virgin mice housed with a pregnant female did show a reduction in infanticide (Soroker & Terkel, 1988), and cohabitation with either a female or a male enhanced paternal responsiveness in male virgin prairie voles (Terleph et al., 2004).

MECHANISMS MEDIATING THE EFFECTS OF COHABITATION

Olfaction

A series of experiments on gerbils asked which features of the pregnant female influenced the switch from infanticide in males. First, mated male gerbils were separated from their mates with either a wire-mesh screen to allow easy access to odours or a clear plastic screen to reduce access to odours while maintaining visual cues; however, there was no difference in the behaviour of the males when tested with pups (Elwood & Ostermeyer, 1984b). Further, mated male gerbils that had their pregnant mates housed above them so that urine dripped into the males' cages did not maintain their inhibition (Elwood & Ostermeyer, 1984b). Soiled bedding from the pregnant mates' cages transferred to solitary but previously mated males also had no effect on the maintenance of the inhibition (Elwood & Ostermeyer, 1984b). The role of the female's mid-ventral gland (which increases markedly in size and activity in pregnancy) was also investigated, but no relationship was found between gland size/activity and the infanticidal state of the male (Elwood & Ostermeyer, 1984b). Thus, odours were not effective in maintaining the inhibition of infanticide in gerbils.

Airborne pheromones from pregnant females did not affect the switch to a noninfanticidal state after mating in mated CS1 mice (Elwood, 1985) but did in mated Swiss Webster mice (Palanza & Parmigiani, 1991). Further, a chemosignal of low volatility emitted by

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

female rats during pregnancy reduced infanticide in males, but the sample size was small and the result was not significant (Mennella & Moltz, 1988a). In California mice paternal responsiveness seen after the birth of the litter was subsequently maintained by odours of the mother's urine (Gubernick, 1980; Gubernick & Alberts, 1989; Gubernick et al., 1994). Distal cues, including olfactory stimuli, were also effective in maintaining paternal responsiveness in prairie voles (Simoncelli, Delevan, Al-Naimi, & Bamshad, 2010). Thus, there appears to be a role of maternal odours in some rodent species, in some aspects of the regulation of the inhibition of infanticide but it is not conserved.

Social Status (Dominance/Subordination Effects)

Because physical contact between the male and the pregnant female is a key feature in the inhibition of infanticide it was hypothesized that shifts in dominance/subordinate relationships might mediate the inhibition. Subordinate male mice were less likely to commit infanticide than dominant males (Huck, Soltis, & Coopersmith, 1982; vom Saal & Howard, 1982). To test whether changes in status altered infanticide, male CS1 mice were screened for their infanticidal tendencies and then paired for 10 min per day for 5 days (Elwood, 1986). Males that were initially noninfanticidal and were subordinate in the pairings never killed a pup on a second test, whereas significantly more males that became dominant switched to infanticide. Further, males that were initially infanticidal but then became subordinate in the pairings were significantly less likely to harm the test pup in the subsequent test compared to those that became dominant (Elwood, 1986). These results indicate that males shift infanticidal tendencies after specific outcomes of social interactions. Further, if pregnant females can subordinate males, then particularly large females should more easily inhibit the male's infanticide. This appears to be the case because males that were noninfanticidal 13 days after copulation were significantly smaller relative to their mates than were those that were infanticidal (Elwood, 1986).

Like mice, unmated male gerbils subordinate to other males in repeated aggression tests were less likely to be infanticidal than were dominant males (Elwood & Ostermeyer, 1984c). Further, when male gerbils are maintained in single-sex groups most will be subordinate (Williamson, Romeo, & Curley, 2017). When isolated they ceased to be subordinate and the proportion of males showing infanticide increased as the period of isolation increased (Elwood & Ostermeyer, 1984c). Note the similarity with the result of males being isolated from their pregnant mate switching to infanticide (Elwood, 1980). Thus, there is a link between changes in social status and changes in infanticide.

PHYSIOLOGICAL DIFFERENCES BETWEEN INFANTICIDAL AND NONINFANTICIDAL MALES

The paternal state during the mate's pregnancy presumably has a physiological basis (see below for a discussion of hormonal changes) and this might alter circulating metabolites. Infant mice detect odour differences, and produce more ultrasonic calls when presented with the odour of urine from infanticidal males than with the urine of noninfanticidal males (Elwood, Kennedy, & Blakely, 1990; Santucci, Masterson, & Elwood, 1994). Additionally, young mice moved away from the urine of infanticidal males more than from the urine of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

noninfanticidal males (Elwood et al., 1990). Further, newly pregnant females were more likely to abort by failing to implant the blastocysts when exposed to infanticidal males than to noninfanticidal males (Elwood & Kennedy, 1990) and pregnancy block is mediated by olfaction (Bruce & Parrott, 1960). Female mice with newborn litters were also more likely to attack infanticidal than noninfanticidal males (Elwood & Kennedy, 1990) and this discrimination is probably due to olfactory differences. Thus, physiological differences between infanticidal and noninfanticidal males are perceived by both adults and pups.

HORMONES AND THE INHIBITION OF INFANTICIDE

Females alter their responsiveness to pups during pregnancy (Elwood, 1977) and these changes are mediated largely by hormonal changes (Rosenblatt & Ceus, 1998). Although males do not get pregnant, their hormones might change for other reasons and might affect the onset of paternal care (Elwood & Ostermeyer, 1984b; Wynne-Edwards & Timonin, 2007).

Hormones vary with the sex of adjacent embryos in the intrauterine environment: male mice reared between two female embryos have lower testosterone but higher oestrogen during early development and show increased infanticide and reduced paternal responsiveness in adulthood (vom Saal, 1989). With Mongolian gerbil males, however, those gestated between two female embryos acted more paternally (Clark, Vonk, & Galef, 1998) and had lower adult testosterone levels than did males gestated between two male embryos (Clark & Galef, 2000). Further, experimental manipulation of testosterone levels in newborn rat pups indicated that early exposure to testosterone was required for rats to respond to testosterone in adulthood and thus for a high incidence of pup killing (Rosenberg & Sherman 1975) but the opposite result was found for mice (Gandelman & vom Saal, 1977; Samuels, Jason, Mann, & Svare, 1981). Thus, the effect of early testosterone differs between species.

Ejaculation in mice results in a surge of both luteinizing hormone and testosterone, which return to baseline within 45 min (Coquelin & Bronson, 1980) and increased infanticide for a few days after copulation followed by a decrease in infanticide 19 days later (about the time pups would be born; Perrigo, Bryant, Belvin, & vom Saal, 1989). However, hypophysectomized and castrated mice that were given testosterone replacement still showed a mating-influenced reduction in infanticide despite there being no surge in luteinizing hormone or testosterone after ejaculation (Perrigo et al., 1989). However, administration of testosterone, oestradiol and dihydrotestosterone to levels above normal, following castration, eliminated pup killing in gerbils 10–12 days later (Martínez et al., 2015). High testosterone was also shown to inhibit infanticide in Mexican volcano mice, *Neotomodon alstoni*, some days after treatment (Luis et al., 2017). Thus, we have conflicting results for adults regarding the effects of a surge in testosterone. Further contradictory results concern the effect of castration in adulthood, which swiftly reduces the level of testosterone. This treatment increased the paternal responsiveness in mice (Perrigo et al., 1989) and gerbils (Clark & Galef, 2000) but not in another study on gerbils (Martínez et al., 2015), and decreased paternal responsiveness in California mice (Trainor & Marler, 2001).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

As described above, social subordination inhibits infanticide (Elwood, 1986; Elwood & Ostermeyer, 1984c) and social status has been repeatedly linked to testosterone levels. For example, in male mice testosterone is higher in dominants than in subordinates (Machida, Yonezawa, & Noumura, 1981) and removal of testosterone results in a loss of dominance status in male rats (Albert, Walsh, Gorzalka, Siemens, & Louie, 1986). Thus, it is possible that subordination by the female (Elwood, 1986; Elwood & Ostermeyer, 1984c) could reduce the testosterone level in males and this might act to inhibit infanticide. Further, removal of a dominant male mouse from an all-male group allowed other males to increase in rank, which increased testosterone and, within an hour, elevated gonadotropin-releasing hormone mRNA levels in the medial preoptic area (MPOA) of the hypothalamus, an area closely linked to the expression of infanticide and paternal care (Williamson et al., 2017). However, one factor that inhibits infanticide is copulation, which increases testosterone, whereas subordination also inhibits infanticide but causes a reduction in testosterone. The two apparently contradictory results might be explained by an initial increase in testosterone after copulation followed by a dramatic drop (possibly due to subordination) being required for the behavioural switch.

A problem in studying testosterone is that it might be converted to oestrogen so the effects on paternal behaviour/inhibition of infanticide might be due to the oestrogen or the balance of testosterone to oestrogen (Trainor & Marler, 2001). Oestrogen has been implicated in the onset of paternal care in several species, for example dwarf hamsters, *Phodopus campbelli*, and Mongolian gerbils, and oestrogen receptors increase in the MPOA when males become paternal (Romero-Morales et al., 2020).

Prolactin has been frequently implicated in the onset of maternal and paternal care in a range of animals, including rodents (Schradin & Anzenberger, 1999). For example, it is higher in fathers than virgins in California mice (Gubernick, Sengelaub, & Kurz, 1993) but whether it has a causal effect on paternal care has yet to be demonstrated (Rymer & Pillay, 2018). Vasopressin and oxytocin have also been implicated in the onset of paternal care in rodents (Rilling & Mascaro, 2017; Saltzman et al., 2017). For example, infusion of vasopressin in specific brain areas enhances paternal behaviour and receptor antagonists inhibit paternal responses both in male prairie voles (Wang, Ferris, & De Vries, 1994) and in meadow voles (Parker & Lee, 2001). Further, vasopressin immunoreactive staining in the bed nucleus of the stria terminalis (BNST) terminals predicts paternal behaviour in California mice and white-footed mice (Bester-Meredith & Marler, 2003). Oxytocin levels in brain areas associated with paternal care also correlate with the onset of paternal responsiveness, particularly during cohabitation with the pregnant female (Bales & Saltzman, 2016). Finally, high progesterone is linked to infanticide and low paternal care in mice. If progesterone is chemically blocked or progesterone receptors are genetically knocked out, paternal care is increased and infanticide reduced (Schneider et al., 2003). Whether or not this is linked to the normal onset of paternal care seen in males housed with their pregnant mates has yet to be shown.

Despite many studies implicating hormones in the onset of paternal care in various mammalian species, demonstration of causal relationships has proved difficult, and there is a clear need for more work in the area (Bales & Saltzman, 2016; Wynne-Edwards &

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Timonin, 2007). Steroid and peptide hormones probably exert their effects by interacting with specific neural systems; thus, it may be difficult to discern causal relationships using systemic manipulations that could act on multiple neural regions. Further, given the clear role of social context in the behavioural response to infants, experience-induced alterations in steroid or peptide hormone receptor expression within distinct neural systems may impact the extent to which ligands can produce their effects (Stolzenberg & Champagne, 2016). Finally, steroid hormones often exert effects at the transcriptional level as ligand-activated transcription factors. Ultimately, sex, species or even strain differences in chromatin accessibility can impact the transcriptional response to steroid receptor activation, thereby producing entirely different functional effects (Gegenhuber & Tollkuhn, 2019).

THE NEURAL BASIS OF INFANTICIDE AND PATERNAL CARE

A combination of external stimuli and hormonal changes are likely to influence the neurobiology of both infanticidal behaviour and the onset of paternal care, and investigations of these interactions have expanded in recent years. Several labs have capitalized on the sexually dimorphic nature of infanticide to identify differential neuronal and/or transcriptional responses to pups. For example, immediate early gene (IEG) expression has been used to identify neural regions that are active in response to a stimulus and/or during behaviour because these genes are transcribed de novo in response to a variety of stimuli (neurotransmitters, hormones, growth factors; Sheng & Greenberg, 1990). Further, molecular approaches such as single-cell sequencing have helped identify the transcriptional phenotype of neurons that show an IEG response to pups or pup-related stimuli (Moffitt et al., 2018). Note, however, that female mice (both virgin and postpartum) can also display infanticidal behaviour, and therefore some of what we understand about the neurobiology of infanticide may only apply to the regulation of infanticidal behaviour in male mice. It is unclear whether infanticide in female mice occurs because females temporarily gain access to a conserved neural mechanism regulating infanticide or whether a distinct mechanism mediates infanticide in female mice. Further, as we see below, several neural regions thought to be involved in pup-directed aggression have also been implicated in pup avoidance (without aggression) in nonmaternal female rats. Therefore, it is imperative that future work tease apart neural mechanisms mediating pup avoidance from those that mediate pup-directed aggression.

Sensory Cues that Drive Pup-Directed Aggression

There is good evidence that pup-directed aggression is under multisensory control (Isogai et al., 2018). Presenting virgin male mice with a neutral-scented, artificial silicone pup can elicit attack, albeit less so than an artificial silicone pup swabbed with pup odour. Interestingly, presenting a silicone block swabbed with pup odour had no such effect, whereas a silicone ‘hybrid’ block with limbs and tail elicited aggression that was indistinguishable from a characteristic pup attack. Thus, visual and chemosensory pup cues induce infanticidal responses in virgin male mice, although the neural mechanisms involved in the processing of the physical features of pups are basically unknown. With respect to the effects of chemosensory cues in infanticide, pup odours elicit attack in virgin

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

male mice through the vomeronasal system (Tachikawa et al., 2013; Wu, Autry, Bergan, Watabe-Uchida, & Dulac, 2014).

Mice use both the main olfactory epithelium and vomeronasal organ (VNO) to detect pup odours (Gandelman, Zarrow, Denenberg, & Myers, 1971; Matsuo et al., 2015; Tachikawa et al., 2013). The VNO is encased in bone and opens into the nasal and oral cavities (Halpern, 1987), and primarily detects nonvolatile pheromones through direct snout contact with the odorant (Dulac & Torello, 2003). Sensory transduction occurs in vomeronasal sensory neurons when pheromones are recognized by vomeronasal receptors and generate graded potentials via the activation of Gαi and Gαo proteins, which modulate the activity of the canonical transient receptor potential channel 2 (Trpc2; Liman & Dulac, 2006; Zufall, Ukhanov, Lucas, & Leinders-Zufall, 2005). *Trpc2* gene expression is largely restricted to the VNO where it mediates sensory transduction in response to pheromones (Leypold et al., 2002). Vomeronasal sensory neurons send a single axon to synapse on mitral cells in the accessory olfactory bulb (AOB; Halpern, 1987). The AOB then projects to the BNST and the amygdala. Owing to the dense amygdala projections, medial and cortical nuclei that receive vomeronasal inputs are sometimes referred to as the vomeronasal amygdala. Several studies indicate that infanticide is regulated by the VNO and its efferent projections. Ablation of the VNO blocks infanticide in male mice and rats (Izquierdo, Collado, Segovia, Guillamón, & Del Cerro, 1992; Mennella & Moltz, 1988b; Tachikawa et al., 2013). Functional silencing of vomeronasal sensory neurons through mutation of *Trpc2* or *Gnai2* (the gene that encodes Gαi protein) significantly reduced infanticide, and also promoted caregiving behaviour in male mice (Trouillet et al., 2019; Wu et al., 2014). Finally, note that maternal behaviour in females does not require an intact accessory olfactory system (Fleming, Vaccarino, Tambosso, & Chee, 1979; Lepri, Wysocki, & Vandenbergh, 1985; Marques, 1979).

If experimental silencing of the VNO disinhibits caregiving in infanticidal male mice, then social experiences might alter how vomeronasal sensory neurons respond to pup pheromones. In support of this idea, the VNO of virgin male mice is highly responsive to pup chemosensory signals, whereas 21 days post-mating pup odours are incapable of inducing neuronal activity in the VNO of fathers (Tachikawa et al., 2013). These findings indicate that reproductive experience eliminates VNO response to pups and suggest that mating may promote a transition from killing pups to caring for them by blocking detection of pup odours in the VNO. However, the mechanisms underlying this transition in VNO responsivity are unclear. Several vomeronasal receptors (Vmn2r88, Vmn2r65, V1rc1/V1rc30, V1ri9, Vmn2r122/123) have been found to respond to odours from pups; however, none appear to be specific for pup cues (Isogai et al., 2018). Interestingly, whereas total ablation of VNO function eliminates infanticide and induces parental care in virgin males (Tachikawa et al., 2013), genetic deletion of the two VNO receptors that were most responsive to pup cues (Vmn2r288 and Vmn2r65) was not able to recapitulate the effects of VNO ablation (Isogai et al., 2018). The extent to which genetic ablation of one of the other six receptors would eliminate infanticide is not clear. Alternatively, infanticidal behaviour may be under the control of multiple VNO receptors.

Together, the results described above provide strong support for the idea that the onset of paternal care is caused, at least in part, by the inability of vomeronasal sensory neurons

Author Manuscript

to detect pup odours (Fig. 3). A relevant question then, is whether paternal male mice can smell pups at all? In other words, is olfactory information about pups only capable of inducing pup aversion? Interestingly, elimination of all odour information (olfactory bulbectomy) interferes with caregiving behaviour in mice (Gandelman, 1973; Gandelman et al., 1971; Sato et al., 2010). Thus, one possibility is that the accessory olfactory system regulates infanticide whereas parental care relies on the detection of pup cues by the main olfactory epithelium (Matsuo et al., 2015; Wu et al., 2014). However, the role of the main olfactory system in caregiving behaviour may vary greatly by species (Levy & Keller, 2009). For example, in other rodent species such as hamsters and rats, both the main and accessory olfactory systems play an inhibitory role in caregiving behaviour, and in female rats gestational hormones alter the perception of pup odours from aversive to appetitive at birth (Fleming et al., 1979; Marques, 1979).

Hypothesized Circuits in the Regulation of Infanticide

Together, the findings described above indicate that parental care occurs when the VNO loses its ability to detect pup odours, but elimination of all odour information (olfactory bulbectomy) blocks caregiving behaviour in mice. These findings suggest that the vomeronasal system not only activates infanticide, but probably also interferes with the ability of pup odours processed via the main olfactory system to drive caregiving. Given that both the main and accessory olfactory systems converge in the medial amygdala (meA) (Kang, Baum, & Cherry, 2009), it is certainly possible that VNO inputs to this region control infanticide and caregiving by modulating the activity of meA neurons in response to inputs to the main olfactory bulb (MOB).

The pathways involving the vomeronasal system have been well described, with projections to the ventral part of the medial amygdala (meAv) involved in both reproductive and defensive behaviour, whereas the posterior dorsal part of the medial amygdala (meApd) is involved in the regulation of reproductive behaviour alone (Choi et al., 2005). In support of the idea that VNO output drives pup-directed aggression through the activation of a defensive neural system, pup exposure induces *c-Fos* expression in the posteroventral region of the medial amygdala (meApv) of infanticidal, but not paternal male mice (Tachikawa et al., 2013). Interestingly, *c-Fos* expression is induced in both parental and aggressive males within the posterior dorsal subdivision of MeA (meApd); however, expression was higher in aggressive than parental males. A scalable control of meApd GABAergic neurons might regulate behavioural response selection. Chen et al. (2019) used fibre photometry to image Ca^{2+} influx within meApd GABAergic neurons in response to pup cues. Interestingly, an influx of Ca^{2+} was detected in response to pup cues in both infanticidal and noninfanticidal male mice; however, the Ca^{2+} response to pups was significantly higher during infanticidal behaviour. Note that these results fit nicely with the report that pup-induced *c-Fos* expression in meApd occurs in both paternal and infanticidal males but is much higher in the latter group. Importantly, experimental manipulation of the intensity of meApd neuronal activity in noninfanticidal virgin and sexually experienced paternal males via optogenetic stimulation impacted behavioural responses to pups. For example, high stimulation induced infanticidal behaviour in virgin male mice selected for noninfanticidal responses whereas low stimulation tended to induce pup grooming (Chen et al., 2019). High stimulation

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

was also capable of inducing infanticidal responses in noninfanticidal sexually experienced males. Given that MOB and AOB inputs converge in the meApd, one possibility is that convergent input from MOB and AOB input drives the high activity in meApd neurons that contributes to infanticide, whereas silencing of AOB, which occurs in sexually experienced males, results in a lower level of activation and grooming instead of attack. In support of this idea, meApd neurons send dense projections to the MPOA (Pardo-Bellver et al., 2012), which is the central neural site for the regulation of parental care (Numan, 1974; 2014). A strong inhibition of MPOA is certainly capable of inducing infanticidal behaviour towards pups in female mice (Tsuneoka et al., 2013; see Fig. 3). In contrast, it is presently unclear how a lower level of activation of meApd neurons would promote grooming. One possibility is that this scalable meApd signal carries critical odour information from the MOB to the MPOA. This possibility fits with the requirement of main olfactory inputs for the display of caregiving behaviour in mice (olfactory information reaches the MPOA via the meA). Finally, note that the role of meApd output is likely to vary by sex and species. For example, the transcriptional profile of GABAergic neurons in the meApd was found to vary by sex in mice (Chen et al., 2019) and in species that do not rely on a single sensory cue to elicit caregiving behaviour (i.e. rats), both the main and accessory olfactory systems play an inhibitory role in caregiving behaviour (Fleming et al., 1979). Thus, lesions of the meA facilitate the onset of caregiving behaviour in virgin female rats (Fleming, Vaccarino, & Luebke, 1980).

Projections from the MeA are situated to deliver information not only to the MPOA, but also to sites that directly mediate aggressive and defensive behaviours in mice. Both the anterior hypothalamic nucleus (AHN) and ventrolateral part of the ventromedial nucleus (VMNvl) become unresponsive to pup cues as a result of sexual experience (Tachikawa et al., 2013). Similarly, the AHN and VMN along with the periaqueductal grey (PAG, a node of the central defence circuit), which receives input from these sites, show elevated *c-Fos* expression when infanticidal male gerbils are exposed to pups (Romero-Morales, Martínez-Torres, Cárdenas, Álvarez, Carmona, Cedillo, Loya-Zurita, & Luis, 2018). Although the extent to which lesions of these sites could block infanticide and induce care has not been investigated, note that their inhibitory role in maternal behaviour has been confirmed in pupavoidant female rats (Bridges, Mann, & Coppeta, 1999; Sheehan, Paul, Amaral, Numan, & Numan, 2001).

In addition to its hypothalamic inputs, the meA also provides information to the BNST by way of the amygdala (Dong & Swanson, 2003; Sun, Roberts, & Cassell, 1991). A specific region of the BNST, termed the rhomboid nucleus (rhBNST), has recently been implicated in the regulation of infanticide in male mice (Tsuneoka et al., 2015). For example, virgin male mice are typically aggressive towards pups, but can ignore pups or even spontaneously care for them. Tsuenouka et al. (2015) found that *c-Fos* expression in this region could predict, with over 90% fidelity, pup-directed aggression in virgin males. Further, juvenile male mice are not aggressive towards pups, but become infanticidal as they age and the onset of infanticide is associated with changes in the electrophysiological properties of rhBNST neurons (Amano et al., 2017). However, optogenetic silencing of rhBNST neurons delayed, but did not fully inhibit, pup killing (Tsuneoka et al., 2015).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In summary, the critical central site(s) that VNO inputs stimulate to promote infanticide remain unclear. The findings described above suggest that pup cues activate a central aversion system that elicits infanticide and reproductive experience ultimately renders this system unresponsive to pup odours (Fig. 3). However, a single central site that can be manipulated to fully eliminate infanticide has not yet been identified. Rather, the most dramatic suppression of infanticide in virgin male mice results from an activation of neurons within the MPOA that express the neuropeptide galanin (Wu et al., 2014).

Disinhibiting Parental Care

Recall that VNO ablation not only blocked infanticide but also induced caregiving in male mice. This finding suggests that the neural mechanisms that promote infanticide also function to directly interfere with an otherwise responsive maternal circuit. In other words, in mice the maternal neural circuit does not require priming to be receptive to pup cues and this otherwise receptive circuit is actively blocked in infanticidal male mice (Fig. 4). Further, interference with neural activity in the MPOA in maternal female mice not only blocks maternal care but also induces aggression, suggesting that regions that regulate infanticide and regions that regulate care may have reciprocal inhibitory connections (Numan, 2006; Numan & Sheehan, 1997). The fact that destruction of central MPOA neurons elicits infanticide in otherwise parental mice (Tsuneoka, Maruyama, Yoshida, Nishimori, Kato, Numan, & Kuroda, 2013; Tsuneoka et al., 2015) suggests the MPOA regulates paternal care, in part, via a direct inhibition of infanticide. In further support of this idea, pup attack occurred in fewer than 20% of trials in which virgin male mice received optogenetic activation of MPOA neurons. Thus, MPOA galanin-expressing neurons appear to directly inhibit infanticide; however, optogenetic activation of MPOA galanin-expressing neurons that project to the meA was not capable of reducing pup attacks and, although activation of an MPOA galanin neuron pathway to the PAG reduced pup attacks, this pathway was not capable of eliminating infanticide (Kohl et al., 2018). Although the critical MPOA pathway that suppresses infanticide remains to be elucidated, note that there is good evidence for the conserved role of the MPOA and its efferent projections in parental behaviour (Kuroda & Numan, 2014; Numan, 2014; Numan & Insel, 2003; Stolzenberg & Mayer, 2019). Finally, the discovery of a neural circuit that regulates infanticide represents a major advance in the field; however, it does not provide an answer to the main question posed here of what controls the switch from killing to caring.

CONCLUSIONS AND BROADER PERSPECTIVES

Infanticidal male rodents are clearly brought into a paternal state prior to the birth of their young. There is no need to invoke some form of recognition of pups, the location or the mother. One study, however, has suggested that males recognize their young from others of the same inbred strain (Paul, 1986) but the lack of detail in the method makes that study difficult to evaluate. By contrast, other studies have found no differential killing of alien pups and caring for the male’s own pups even when they came from different inbred strains (Elwood & Kennedy, 1991) or different species (Elwood & Ostermeyer, 1984c). Further, there are very limited findings that suggest different infanticidal responses by males that encounter pups with their former sexual partner or with a strange male (Elwood &

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Kennedy, 1991). There is also very little support for location-based recognition that mediates infanticide (Elwood & Kennedy, 1991). Rather, there is evidence of changes in paternal states in a wide taxonomic spread (isopods, burying beetles, fish, birds, as well as mammals) that mediate the switch from infanticide to acceptance of young or eggs (Elwood, 1994). Changes also appear to occur in humans to enhance the paternal responsiveness of males prior to the arrival of their young (Elwood & Mason, 1994). Nevertheless, several studies of rodents and primates show that females may mate with multiple males and suggest that this is a female strategy to ‘confuse paternity’ (Pain, Koenig, & Borries; Yuan 2013; Waser & De Woody, 2006). The notion of males becoming confused about fatherhood appears to spring from recognition hypotheses. Perhaps it should be dropped to avoid misunderstanding about proposed mechanisms of infanticide avoidance.

How the change in state is brought about has not been fully resolved. While there is strong support for ejaculation followed by cohabitation with the pregnant female being key to the change there is less clarity about the specific cues from the female. This is because of variation between species and between inbred strains of mice in their response to specific cues, for example copulation and cohabitation. This variation might be due to inherited differences in the ability of females to produce specific cues. Alternatively, species might differ in their ability to perceive specific cues or response thresholds may vary that cause only some males to switch from infanticidal to noninfanticidal responses. The link between changes in social status and changes in infanticide may indicate a further role of the female. Hormones have been repeatedly implicated in the suppression of infanticide and onset of paternal care but, again, more research is required to clarify their precise role.

We are, however, beginning to understand the role of neurological change with some circuits being suppressed to inhibit infanticide (Fig. 3) and others activated to enhance parental care (Fig. 4). This is a promising area and one that might provide clues as to the role of the hormonal changes in the male because hormonal effects on specific circuits may be tested (Yuan, He; Hou, Wang, Li, Zhang, Yang, Jia, Qiao, & Tai, 2019). Hopefully, this type of study might be linked with specific stimuli that males obtain from the pregnant female so we may finally elucidate the sequence of external and internal changes that result in paternal care. There can be few more dramatic changes in behaviour that have such clear, important fitness consequences and a full understanding how that is mediated is required.

Acknowledgments

We thank Sue Healy, Angela Turner and two anonymous referees for their excellent suggestions for improving this paper. Stolzenberg is supported by NICHD grant number 1R01HD08770901A1.

References

Albert DJ, Walsh ML, Gorzalka BB, Siemens Y, & Louie H (1986). Testosterone removal in rats results in a decrease in social aggression and a loss of social dominance. Physiology & Behavior, 36(3), 401–407. [PubMed: 3703968]

Amano T, Shindo S, Yoshihara C, Tsuneoka Y, Uki H, Minami M, et al. (2017). Development-dependent behavioral change toward pups and synaptic transmission in the rhomboid nucleus of the bed nucleus of the stria terminalis. Behavioural Brain Research, 325, 131–137. [PubMed: 27793732]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bales KL, & Saltzman W (2016). Fathering in rodents: Neurobiological substrates and consequences for offspring. Hormones and Behavior, 77, 249–259. [PubMed: 26122293]

Bertram BC (1975). Social factors influencing reproduction in wild lions. Journal of Zoology, 177(4), 463–482.

Bester-Meredith JK, & Marler CA (2003). Vasopressin and the transmission of paternal behavior across generations in mated, cross-fostered Peromyscus mice. Behavioral Neuroscience, 117(3), 455. [PubMed: 12802874]

Bridges RS, Mann PE, & Coppeta JS (1999). Hypothalamic involvement in the regulation of maternal behaviour in the rat: Inhibitory roles for the ventromedial hypothalamus and the dorsal/anterior hypothalamic areas. Journal of Neuroendocrinology, 11(4), 259–266. [PubMed: 10223279]

Brown RE (1986). Social and hormonal factors influencing infanticide and its suppression in adult male Long-Evans rats (Rattus norvegicus). Journal of Comparative Psychology, 100(2), 155. [PubMed: 3720284]

Bruce HM, & Parrott DMV (1960). Role of olfactory sense in pregnancy block by strange males. Science, 131(3412), 1526–1526. [PubMed: 13805126]

Calhoun JB (1962). Population density and social pathology. Scientific American, 206, 139–148. [PubMed: 13875732]

Chen PB, Hu RK, Wu YE, Pan L, Huang S, Micevych PE, et al. (2019). Sexually dimorphic control of parenting behavior by the medial amygdala. Cell, 176(5), 1206–1221. e18. [PubMed: 30773317]

Choi GB, Dong H, Murphy AJ, Valenzuela DM, Yancopoulos GD, Swanson LW, et al. (2005). Lhx6 delineates a pathway mediating innate reproductive behaviors from the amygdala to the hypothalamus. Neuron, 46(4), 647–660. [PubMed: 15944132]

Cicirello DM, & Wolff JO (1990). The effects of mating on infanticide and pup discrimination in white-footed mice. Behavioral Ecology and Sociobiology, 26(4), 275–279.

Clark MM, & Galef BG Jr. (2000). Effects of experience on the parental responses of male Mongolian gerbils. Developmental Psychobiology, 36(3), 177–185. [PubMed: 10737863]

Clark MM, Vonk JM, & Galef BG Jr. (1998). Intrauterine position, parenting, and nest-site attachment in male Mongolian gerbils. Developmental Psychobiology, 32(3), 177–181. [PubMed: 9553728]

Coquelin A, & Bronson FH (1980). Secretion of luteinizing hormone in male mice: Factors that influence release during sexual encounters. Endocrinology, 106(4), 1224–1229. [PubMed: 7188900]

Dong H-W, & Swanson LW (2003). Projections from the rhomboid nucleus of the bed nuclei of the stria terminalis: Implications for cerebral hemisphere regulation of ingestive behaviors. Journal of Comparative Neurology, 463(4), 434–472. [PubMed: 12836178]

Dulac C, & Torello AT (2003). Molecular detection of pheromone signals in mammals: From genes to behaviour. Nature Reviews Neuroscience, 4(7), 551. [PubMed: 12838330]

Elwood RW (1975). Paternal and maternal behaviour in the Mongolian gerbil. Animal Behaviour, 23, 766–772.

Elwood RW (1977). Changes in the responses of male and female gerbils (Meriones unguiculatus) towards test pups during the pregnancy of the female. Animal Behaviour, 25, 46–51.

Elwood RW (1980). The development, inhibition and disinhibition of pupcannibalism in the Mongolian gerbil. Animal Behaviour, 28(4), 1188–1194.

Elwood RW (1985). Inhibition of infanticide and onset of paternal care in male mice (Mus musculus). Journal of Comparative Psychology, 99(4), 457.

Elwood RW (1986). What makes male mice paternal? Behavioral and Neural Biology, 46(1), 54–63. [PubMed: 3729896]

Elwood RW (1991). Ethical implications of studies on predation and aggression with particular reference to infanticide. Animal Behaviour, 42, 841–849.

Elwood RW (1994). Temporal-based kinship recognition: A switch in time saves mine. Behavioural Processes, 33(1e2), 15–24. [PubMed: 24925237]

Elwood RW, & Broom DM (1978). The influence of litter size and parental behaviour on the development of Mongolian gerbil pups. Animal Behaviour, 26, 438–454.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Elwood RW, & Kennedy HF (1990). The relationship between infanticide and pregnancy block in mice. Behavioral and Neural Biology, 53(2), 277–283. [PubMed: 2331236]

Elwood RW, & Kennedy HF (1991). Selectivity in paternal and infanticidal responses by male mice: Effects of relatedness, location, and previous sexual partners. Behavioral and Neural Biology, 56(2), 129–147. [PubMed: 1759937]

Elwood RW, Kennedy HF, & Blakely H (1990). Responses of infant mice to urinary odours of infanticidal and non-infanticidal male mice. Developmental Psychobiology, 23, 309–317. [PubMed: 2210047]

Elwood RW, & Mason C (1994). The couvade and the onset of paternal care: A biological perspective. Ethology and Sociobiology, 15(3), 145–156.

Elwood RW, & Ostermeyer MC (1984a). Does copulation inhibit infanticide in male rodents? Animal Behaviour, 32(1), 293–294.

Elwood RW, & Ostermeyer MC (1984b). Infanticide in the Mongolian gerbils: Ontogeny, causation and function. In Hausfater G, & Blaffer Hrdy S (Eds.), Infanticide: comparative and evolutionary perspectives (pp. 367–383). New York, NY: Aldine Press.

Elwood RW, & Ostermeyer MC (1984c). The effects of food deprivation, aggression, and isolation on infanticide in the male Mongolian gerbil. Aggressive Behavior, 10(4), 293–301.

Fadok JP, Markovic M, Tovote P, & Lüthi A (2018). New perspectives on central amygdala function. Current Opinion in Neurobiology, 49, 141–147. [PubMed: 29522976]

Fleming AS, Vaccarino F, & Luebke C (1980). Amygdaloid inhibition of maternal behavior in the nulliparous female rat. Physiology & Behavior, 25(5), 731–743. [PubMed: 7443835]

Fleming AS, Vaccarino F, Tambosso L, & Chee P (1979). Vomeronasal and olfactory system modulation of maternal behavior in the rat. Science, 203(4378), 372–374. [PubMed: 760196]

Gandelman R (1973). The development of cannibalism in male Rockland-Swiss mice and the influence of olfactory bulb removal. Developmental Psychobiology, 6(2), 159–164. [PubMed: 4737555]

Gandelman R, & vom Saal F (1977). Exposure to early androgen attenuates androgen induced pup-killing in male and female mice. Behavioral Biology, 20(2), 252–260. [PubMed: 901357]

Gandelman R, Zarrow MX, Denenberg VH, & Myers M (1971). Olfactory bulb removal eliminates maternal behavior in mouse. Science, 171(3967), 210–211. [PubMed: 5540330]

Gegenhuber B, & Tollkuhn J (2019). Sex differences in the epigenome: A cause or consequence of sexual differentiation of the brain? Genes, 10(6), 432. [PubMed: 31181654]

Gubernick DJ (1980). Maternal ‘imprinting’or maternal ‘labelling’in goats? Animal Behaviour, 28(1), 124–129.

Gubernick DJ, & Alberts JR (1989). Postpartum maintenance of paternal behaviour in the biparental California mouse, Peromyscus californicus. Animal Behaviour, 37, 656–664.

Gubernick DJ, Schneider KA, & Jeannotte LA (1994). Individual differences in the mechanisms underlying the onset and maintenance of paternal behavior and the inhibition of infanticide in the monogamous biparental California mouse, Peromyscus californicus. Behavioral Ecology and Sociobiology, 34(3), 225231.

Gubernick DJ, Sengelaub DR, & Kurz EM (1993). A neuroanatomical correlate of paternal and maternal behavior in the biparental California mouse (Peromyscus californicus). Behavioral Neuroscience, 107(1), 194201.

Halpern M (1987). The organization and function of the vomeronasal system. Annual Review of Neuroscience, 10(1), 325–362.

Hrdy SB (1974). Male-male competition and infanticide among the langurs (Presbytis entellus) of Abu, Rajasthan. Folia Primatologica, 22(1), 19–58.

Hrdy SB (1979). Infanticide among animals: A review, classification, and examination of the implications for the reproductive strategies of females. Ethology and Sociobiology, 1(1), 13–40.

Huck UW, Soltis RL, & Coopersmith CB (1982). Infanticide in male laboratory mice: Effects of social status, prior sexual experience, and basis for discrimination between related and unrelated young. Animal Behaviour, 30(4), 1158–1165.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Isogai Y, Wu Z, Love MI, Ahn MH-Y, Bambah-Mukku D, Hua V, et al. (2018). Multisensory logic of infant-directed aggression by males. Cell, 175(7), 1827–1841. e17. [PubMed: 30550786]

Izquierdo MAP, Collado P, Segovia S, Guillamón A, & Del Cerro MCR (1992). Maternal behavior induced in male rats by bilateral lesions of the bed nucleus of the accessory olfactory tract. Physiology & Behavior, 52(4), 707712.

Kang N, Baum MJ, & Cherry JA (2009). A direct main olfactory bulb projection to the 'vomeronasal' amygdala in female mice selectively responds to volatile pheromones from males. European Journal of Neuroscience, 29(3), 624–634. [PubMed: 19187265]

Kennedy HF, & Elwood RW (1988). Strain differences in the inhibition of infanticide in male mice (Mus musculus). Behavioral and Neural Biology, 50(3), 349–353. [PubMed: 3202817]

Kohl J, Babayan BM, Rubinstein ND, Autry AE, Marin-Rodriguez B, Kapoor V, et al. (2018). Functional circuit architecture underlying parental behaviour. Nature, 556(7701), 326–331. [PubMed: 29643503]

Kuroda KO, & Numan M (2014). The medial preoptic area and the regulation of parental behavior. Neuroscience Bulletin, 30(5), 863–865. [PubMed: 25096498]

Labov JB, Huck UW, Elwood RW, & Brooks RJ (1985). Current problems in the study of infanticidal behaviour of rodents: A review. Quarterly Review of Biology, 60, 1–20.

Lepri JJ, Wysocki CJ, & Vandenbergh JG (1985). Mouse vomeronasal organ: Effects on chemosignal production and maternal behavior. Physiology & Behavior, 35(5), 809–814. [PubMed: 4080845]

Lévy F, & Keller M (2009). Olfactory mediation of maternal behavior in selected mammalian species. Behavioural Brain Research, 200(2), 336–345. [PubMed: 19146885]

Leypold BG, Yu CR, Leinders-Zufall T, Kim MM, Zufall F, & Axel R (2002). Altered sexual and social behaviors in trp2 mutant mice. Proceedings of the National Academy of Sciences, 99(9), 6376–6381.

Liman ER, & Dulac C (2006). TRPC2 and the molecular biology of pheromone detection in mammals. In Liedtke WB, & Heller S (Eds.), TRP ion channel function in sensory transduction and cellular signaling cascades (pp. 61–69). Boca Raton, FL: CRC Press/Taylor & Francis.

Lonstein JS, & De Vries GJ (2000). Sex differences in the parental behavior of rodents. Neuroscience & Biobehavioral Reviews, 24(6), 669–686. [PubMed: 10940441]

Luis J, Ramos G, Martínez-Torres M, Carmona A, Cedillo B, & Delgado J (2017). Testosterone induces paternal behavior in sexually inexperienced males of Neotomodon alstoni (Rodentia: Muridae). Revista de Biología Tropical, 65(4), 1419–1427.

Lukas D, & Huchard E (2014). The evolution of infanticide by males in mammalian societies. Science, 346(6211), 841–844. [PubMed: 25395534]

Machida T, Yonezawa Y, & Noumura T (1981). Age-associated changes in plasma testosterone levels in male mice and their relation to social dominance or subordinance. Hormones and Behavior, 15(3), 238–245. [PubMed: 7298026]

Marques DM (1979). Roles of the main olfactory and vomeronasal systems in the response of the female hamster to young. Behavioral and Neural Biology, 26(3), 311–329. [PubMed: 486028]

Martínez A, Ramos G, Martínez-Torres M, Nicolás L, Carmona A, Cárdenas M, et al. (2015). Paternal behavior in the Mongolian gerbil (Meriones unguiculatus): Estrogenic and androgenic regulation. Hormones and Behavior, 71, 91–95. [PubMed: 25935727]

Matsuo T, Hattori T, Asaba A, Inoue N, Kanomata N, Kikusui T, et al. (2015). Genetic dissection of pheromone processing reveals main olfactory system-mediated social behaviors in mice. Proceedings of the National Academy of Sciences, 112(3), E311–E320.

Mennella JA, & Moltz H (1988a). Infanticide in rats: Male strategy and female counter-strategy. Physiology & Behavior, 42(1), 19–28. [PubMed: 3387474]

Mennella JA, & Moltz H (1988b). Infanticide in the male rat: The role of the vomeronasal organ. Physiology & Behavior, 42(3), 303–306. [PubMed: 3136468]

Moffitt JR, Bambah-Mukku D, Eichhorn SW, Vaughn E, Shekhar K, Perez JD, et al. (2018). Molecular, spatial and functional single-cell profiling of the hypothalamic preoptic region. Science, 362(6416). eaau5324. [PubMed: 30385464]

Numan M (1974). Medial preoptic area and maternal behavior in the female rat. Journal of Comparative and Physiological Psychology, 87(4), 746–759. [PubMed: 4426995]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Numan M (2006). Hypothalamic neural circuits regulating maternal responsiveness toward infants. Behavioral and Cognitive Neuroscience Reviews, 5(4), 163–190. [PubMed: 17099111]

Numan M (2014). Neurobiology of social behavior: toward an understanding of the prosocial and antisocial brain. London, U.K.: Academic Press.

Numan M, & Insel TR (2003). The neurobiology of parental behavior (Vol. 1). New York, NY: Springer-Verlag.

Numan M, & Sheehan TP (1997). Neuroanatomical circuitry for mammalian maternal behavior. Annals of the New York Academy of Sciences, 807(1), 101–125. [PubMed: 9071346]

Pain EL, Koenig A, & Borries C (2013). Paternity confusion or reassurance? Why pregnant hanuman langurs (Semnopithecus schistaceus) are proceptive. American Journal of Physical Anthropology, 150, 214–214.

Palanza P, & Parmigiani S (1991). Inhibition of infanticide in male Swiss mice: Behavioral polymorphism in response to multiple mediating factors. Physiology & Behavior, 49(4), 797–802. [PubMed: 1881986]

Parker KJ, & Lee TM (2001). Central vasopressin administration regulates the onset of facultative paternal behavior in Microtus pennsylvanicus (meadow voles). Hormones and Behavior, 39(4), 285–294. [PubMed: 11374914]

Paul L (1986). Infanticide and maternal aggression: Synchrony of male and female reproductive strategies in mice. Aggressive Behavior, 12(1), 1–11.

Perrigo G, Bryant WC, Belvin L, & vom Saal FS (1989). The use of live pups in a humane, injury-free test for infanticidal behaviour in male mice. Animal Behaviour, 38(5), 897–898.

Perrigo G, Bryant WC, & vom Saal FS (1990). A unique neural timing system prevents male mice from harming their own offspring. Animal Behaviour, 39(3), 535–539.

Perrigo G, Belvin L, & vom Saal FS (1991). Individual variation in the neural timing of infanticide and parental behavior in male house mice. Physiology and Behavior, 50, 287–296. [PubMed: 1745671]

Perrigo G, & vom Saal FS (1994). Behavioral cycles and the neural timing of infanticide and parental behavior in male house mice. In Parmigiani S, & vom Saal FS (Eds.), Infanticide and parental care (pp. 365–396). Chur, Switzerland: Harwood Academic Publishers.

Rilling JK, & Mascaro JS (2017). The neurobiology of fatherhood. Current Opinion in Psychology, 15, 26–32. [PubMed: 28813264]

Romero-Morales L, C ardenas M, Martínez-Torres M, Cárdenas R, Álvarez-Rodríguez C, & Luis J (2020). Estradiol and estrogen receptor α in the mPOA and MeA in dwarf hamster (Phodopus campbelli) fathers. Hormones and Behavior, 119, 104653. [PubMed: 31816282]

Romero-Morales L, Cárdenas M, Martínez-Torres M, García-Saucedo B, Carmona A, & Luis J (2018). Neuronal activation associated with paternal and aversive interactions toward pups in the Mongolian gerbils (Meriones unguiculatus). Hormones and Behavior, 105, 47–57. [PubMed: 30056092]

Rosenberg KM, & Sherman GF (1975). The role of testosterone in the organization, maintenance and activation of pup-killing in the male rat. Hormones and Behavior, 6, 173–179. [PubMed: 1240860]

Rosenblatt JS, & Ceus K (1998). Estrogen implants in the medial preoptic area stimulate maternal behavior in male rats. Hormones and Behavior, 33(1), 23–30. [PubMed: 9571010]

Rymer TL, & Pillay N (2018). An integrated understanding of paternal care in mammals: Lessons from the rodents. Journal of Zoology, 306(2), 69–76.

Saltzman W, Harris BN, De Jong TR, Perea-Rodriguez JP, Horrell ND, Zhao M, et al. (2017). Paternal care in biparental rodents: Intra-and inter-individual variation. Integrative and Comparative Biology, 57(3), 589–602. [PubMed: 28641377]

Samuels O, Jason G, Mann M, & Svare B (1981). Pup-killing behavior in mice: Suppression by early androgen exposure. Physiology & Behavior, 26(3), 473–477. [PubMed: 7243962]

Santucci D, Masterson D, & Elwood RW (1994). Effects of age, sex, and odours from conspecific adult males on ultrasonic vocalizations of infant CS1 mice. Behavioural Processes, 32(3), 285–295. [PubMed: 24896507]

Sato A, Nakagawasai O, Tan-No K, Onogi H, Niijima F, & Tadano T (2010). Influence of olfactory bulbectomy on maternal behavior and dopaminergic function in nucleus accumbens in mice. Behavioural Brain Research, 215(1), 141–145. [PubMed: 20638419]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Schneider JS, Stone MK, Wynne-Edwards KE, Horton TH, Lydon J, O'Malley B, et al. (2003). Progesterone receptors mediate male aggression toward infants. Proceedings of the National Academy of Sciences, 100, 2951–2956.

Schradin C, & Anzenberger G (1999). Prolactin, the hormone of paternity. Physiology, 14(6), 223–231.

Sheehan TP, Paul M, Amaral E, Numan MJ, & Numan M (2001). Evidence that the medial amygdala projects to the anterior/ventromedial hypothalamic nuclei to inhibit maternal behavior in rats. Neuroscience, 106(2), 341–356. [PubMed: 11566505]

Sheng M, & Greenberg ME (1990). The regulation and function of c-fos and other immediate early genes in the nervous system. Neuron, 4(4), 477–485. [PubMed: 1969743]

Simoncelli LA, Delevan CJ, Al-Naimi OAS, & Bamshad M (2010). Female tactile cues maximize paternal behavior in prairie voles. Behavioral Ecology and Sociobiology, 64(5), 865–873.

Song Z, Tai F, Yu C, Wu R, Zhang X, Broders H, et al. (2010). Sexual or paternal experiences alter alloparental behavior and the central expression of ERα and OT in male Mandarin voles (Microtus mandarinus). Behavioural Brain Research, 214(2), 290–300. [PubMed: 20678985]

Soroker V, & Terkel J (1988). Changes in incidence of infanticidal and parental responses during the reproductive cycle in male and female wild mice Mus musculus. Animal Behaviour, 36(5), 1275–1281.

Stolzenberg DS, & Champagne FA (2016). Hormonal and non-hormonal bases of maternal behavior: The role of experience and epigenetic mechanisms. Hormones and Behavior, 77, 204–210. [PubMed: 26172856]

Stolzenberg DS, & Mayer HS (2019). Experience-dependent mechanisms in the regulation of parental care. Frontiers in Neuroendocrinology, 54, 100745. [PubMed: 31009675]

Sun N, Roberts L, & Cassell MD (1991). Rat central amygdaloid nucleus projections to the bed nucleus of the stria terminalis. Brain Research Bulletin, 27(5), 651–662. [PubMed: 1721859]

Tachikawa KS, Yoshihara Y, & Kuroda KO (2013). Behavioral transition from attack to parenting in male mice: A crucial role of the vomeronasal system. Journal of Neuroscience, 33(12), 5120–5126. [PubMed: 23516278]

Terleph TA, Jean-Baptiste N, & Bamshad M (2004). Mechanisms and time course for induction of paternal behavior in prairie voles (Microtus ochrogaster). Journal of Mammalogy, 85(6), 1124–1129.

Trainor BC, & Marler CA (2001). Testosterone, paternal behavior, and aggression in the monogamous California mouse (Peromyscus californicus). Hormones and Behavior, 40(1), 32–42. [PubMed: 11467882]

Trouillet A-C, Keller M, Weiss J, Leinders-Zufall T, Birnbaumer L, Zufall F, et al. (2019). Central role of G protein Gαi2 and Gαi2+ vomeronasal neurons in balancing territorial and infant-directed aggression of male mice. Proceedings of the National Academy of Sciences, 116(11), 5135–5143.

Tsuneoka Y, Maruyama T, Yoshida S, Nishimori K, Kato T, Numan M, et al. (2013). Functional, anatomical, and neurochemical differentiation of medial preoptic area subregions in relation to maternal behavior in the mouse. Journal of Comparative Neurology, 521(7), 1633–1663. [PubMed: 23124836]

Tsuneoka Y, Tokita K, Yoshihara C, Amano T, Esposito G, Huang AJ, et al. (2015). Distinct preoptic-BST nuclei dissociate paternal and infanticidal behavior in mice. EMBO Journal, 34(21), 2652–2670. [PubMed: 26423604]

Vihervaara H, Sundell J, & Ylönen H (2010). Is mating alone enough to inhibit infanticide in male bank voles? Ethology, 116(9), 888–894.

vom Saal FS, & Howard LS (1982). The regulation of infanticide and parental behavior: Implications for reproductive success in male mice. Science, 215(4537), 1270–1272. [PubMed: 7058349]

vom Saal FS (1985). Time-contingent change in infanticide and parental behavior induced by ejaculation in male mice. Physiology & Behavior, 34(1), 7–15. [PubMed: 4041052]

vom Saal FS (1989). Sexual differentiation in litter-bearing mammals: Influence of sex of adjacent fetuses in utero. Journal of Animal Science, 67(7), 1824–1840. [PubMed: 2670873]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Walters JR (1987). Kin recognition in non-human primates. In Fletcher DJC, & Mitchner CD (Eds.), Kin recognition in animals (pp. 359–393). Chichester, U.K.: J. Wiley.

Wang Z, Ferris CF, & De Vries GJ (1994). Role of septal vasopressin innervation in paternal behavior in prairie voles (Microtus ochrogaster). Proceedings of the National Academy of Sciences, 91(1), 400–404.

Waser PM, & De Woody JA (2006). Multiple paternity in a philopatric rodent: The interaction of competition and choice. Behavioral Ecology, 17(6), 971–978.

Webster AB, Gartshore RG, & Brooks RJ (1981). Infanticide in the meadow vole, Microtus pennsylvanicus: Significance in relation to social system and population cycling. Behavioral and Neural Biology, 31(3), 342–347. [PubMed: 7013755]

West HER, & Capellini I (2016). Male care and life history traits in mammals. Nature Communications, 7(1), 1–10.

Williamson CM, Romeo RD, & Curley JP (2017). Dynamic changes in social dominance and mPOA GnRH expression in male mice following social opportunity. Hormones and Behavior, 87, 80–88. [PubMed: 27826060]

Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, & Dulac CG (2014). Galanin neurons in the medial preoptic area govern parental behaviour. Nature, 509(7500), 325–330. [PubMed: 24828191]

Wynne-Edwards KE, & Timonin ME (2007). Paternal care in rodents: Weakening support for hormonal regulation of the transition to behavioral fatherhood in rodent animal models of biparental care. Hormones and Behavior, 52(1), 114–121. [PubMed: 17482188]

Yuan W, He Z, Hou W, Wang L, Li L, Zhang J, et al. (2019). Role of oxytocin in the medial preoptic area (MPOA) in the modulation of paternal behavior in Mandarin voles. Hormones and Behavior, 110, 46–55. [PubMed: 30836063]

Zufall F, Ukhanov K, Lucas P, & Leinders-Zufall T (2005). Neurobiology of TRPC2: From gene to behavior. Pflügers Archiv, 451(1), 61–71. [PubMed: 15971083]

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

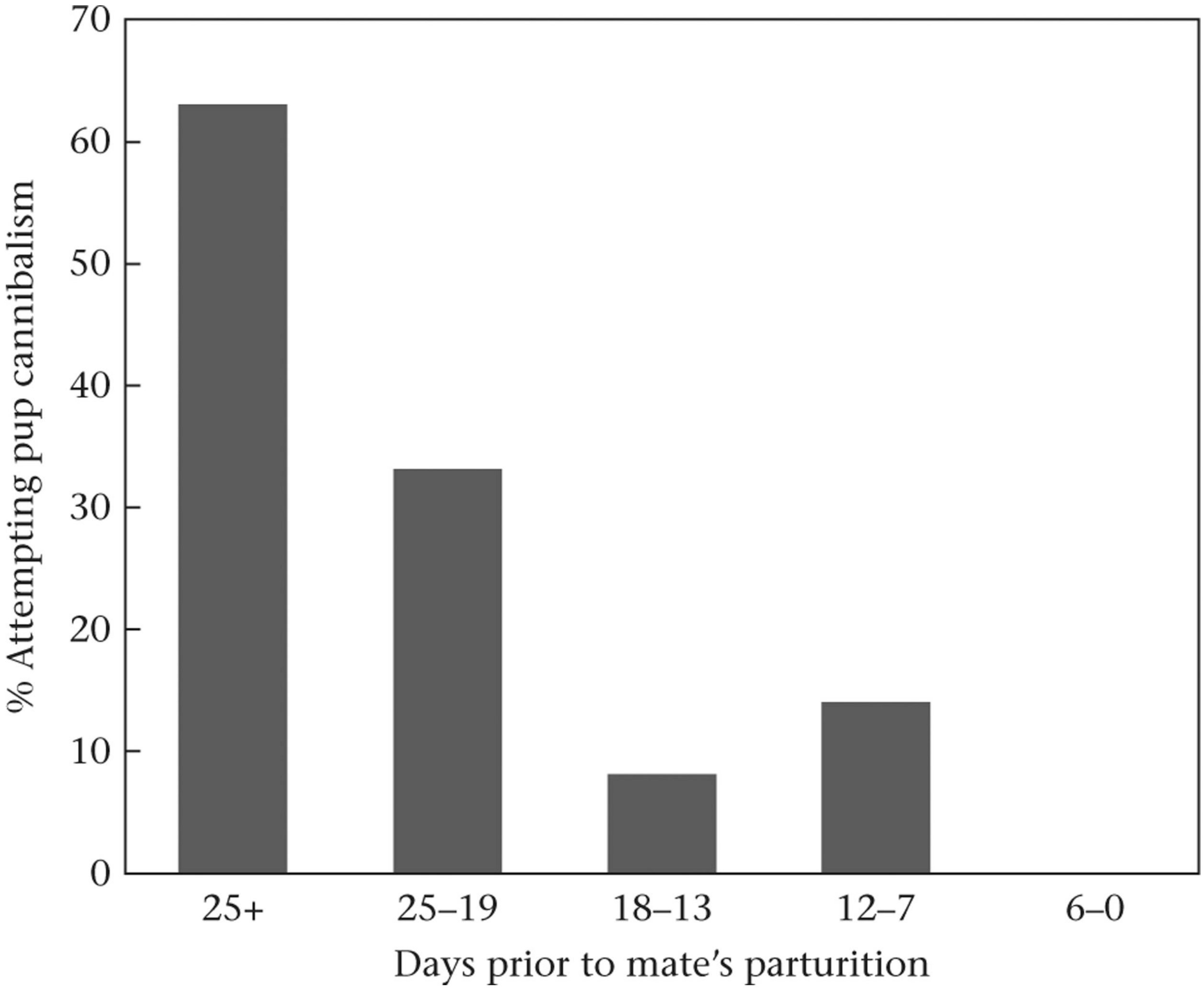

Figure 1.

Responses of naïve males towards test pups at different stages of their mate's pregnancy (25_+ refers to those with nonpregnant mates). Sample sizes from left to right are 74, 15, 12, 22, 30. Redrawn from Elwood and Ostermeyer (1984b).

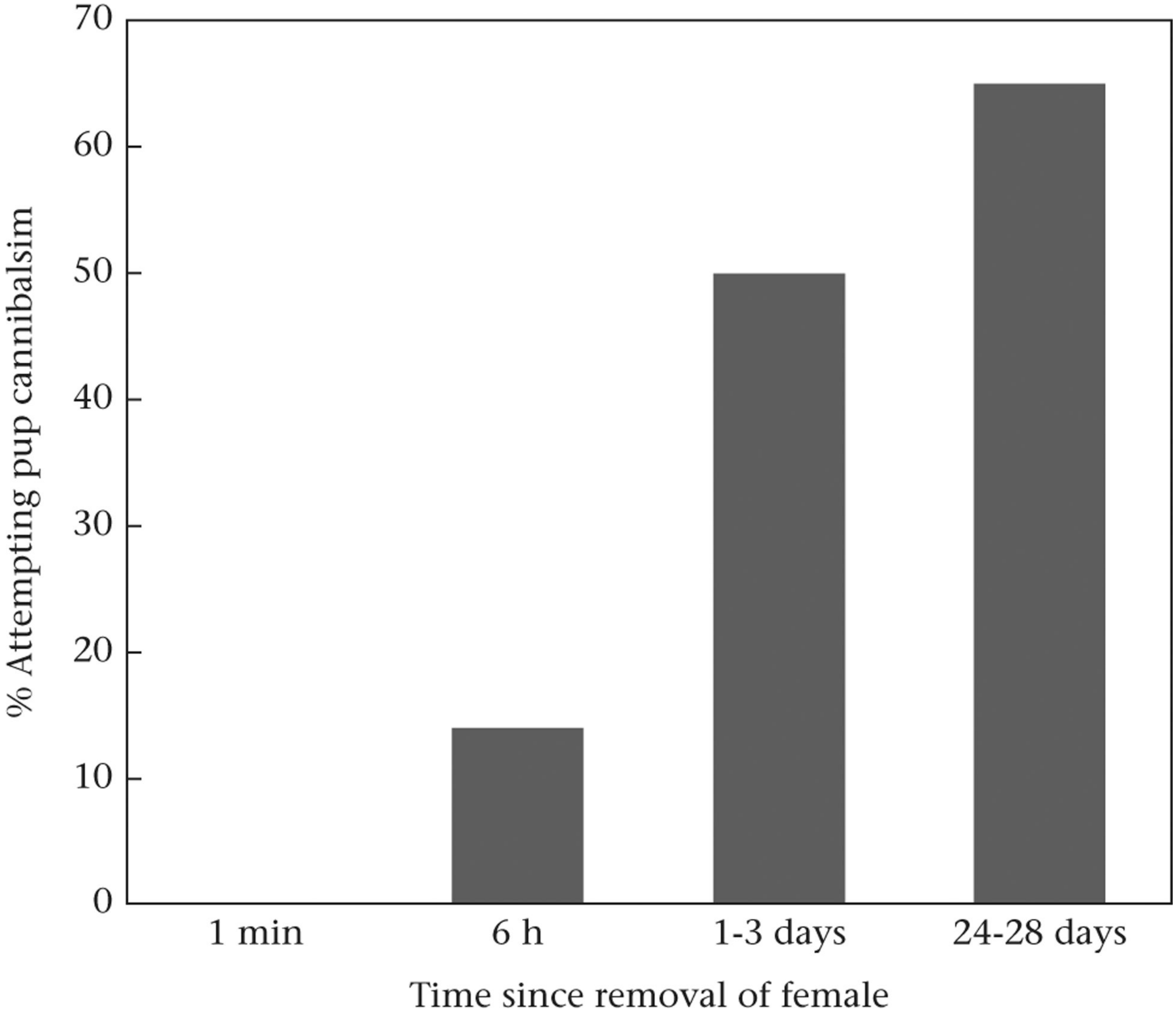

Figure 2.

The percentage of naïve males that attempted to cannibalize the test pup is shown for four groups that differ in the time since removal of the pregnant mate. Sample sizes from left to right are 19, 14, 14 and 15. Redrawn from Elwood (1980).

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

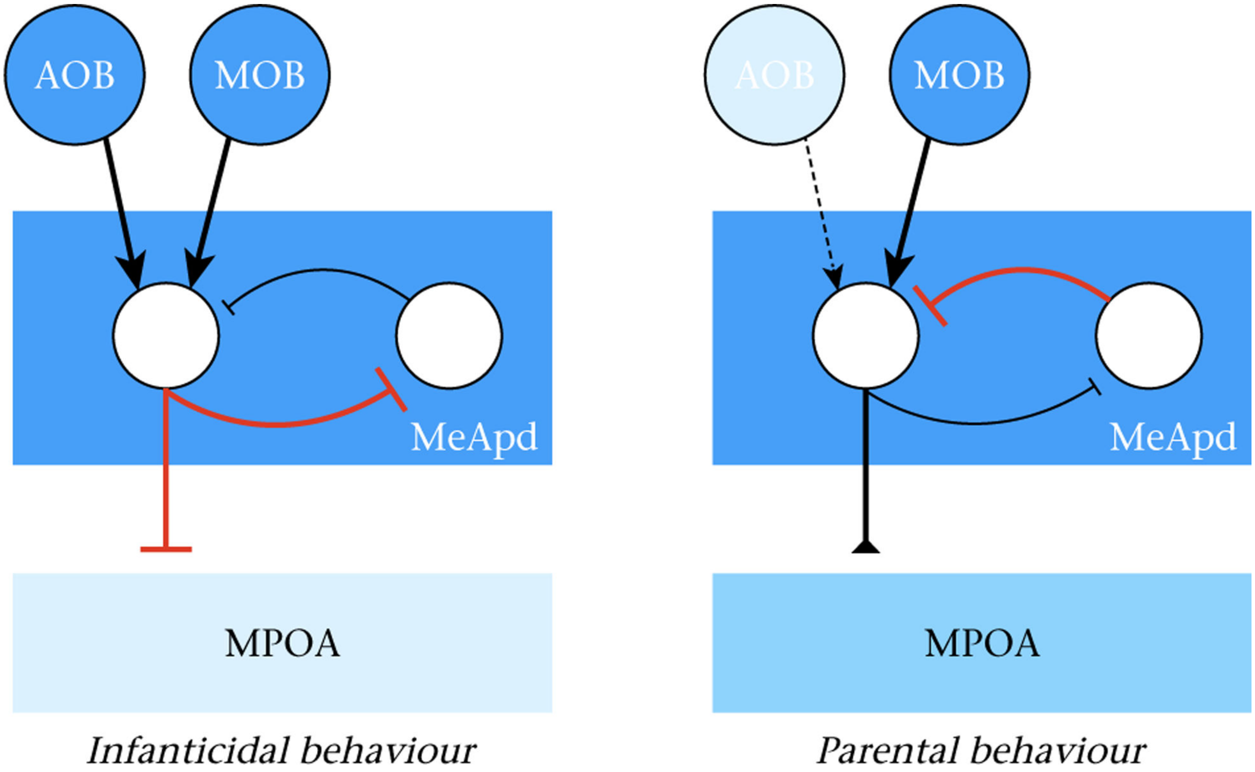

Figure 3.

Hypothetical neural model for the role of the main (MOB) and accessory (AOB) olfactory systems in the regulation of parental care or infanticide in mice. Odour information from the main olfactory system is required for caregiving behaviour in male and female mice. In contrast, odour information from the vomeronasal system drives infanticidal behaviour. Odour information from both systems converges on the medial amygdala. Strong stimulation of GABAergic neurons in the posterior dorsal medial amygdala (meApd) induces infanticide, whereas weak stimulation of these neurons induces pup grooming (Chen et al., 2019). Complex microcircuits within the amygdala have been hypothesized to allow the same signal to produce distinct behavioural responses via scalable control (Fadok et al., 2018). MeApd neurons send dense projections to the MPOA (Pardo-Bellver et al., 2012). If strong stimulation of meApd neurons causes GABA release in the medial preoptic area (MPOA), inactivation of MPOA would be expected to induce infanticide. It is unclear how weak stimulation of meApd output would impact MPOA activity, but presumably this pathway delivers critical olfactory information to the MPOA that is required for caregiving behaviour. Bold lines represent active pathways.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

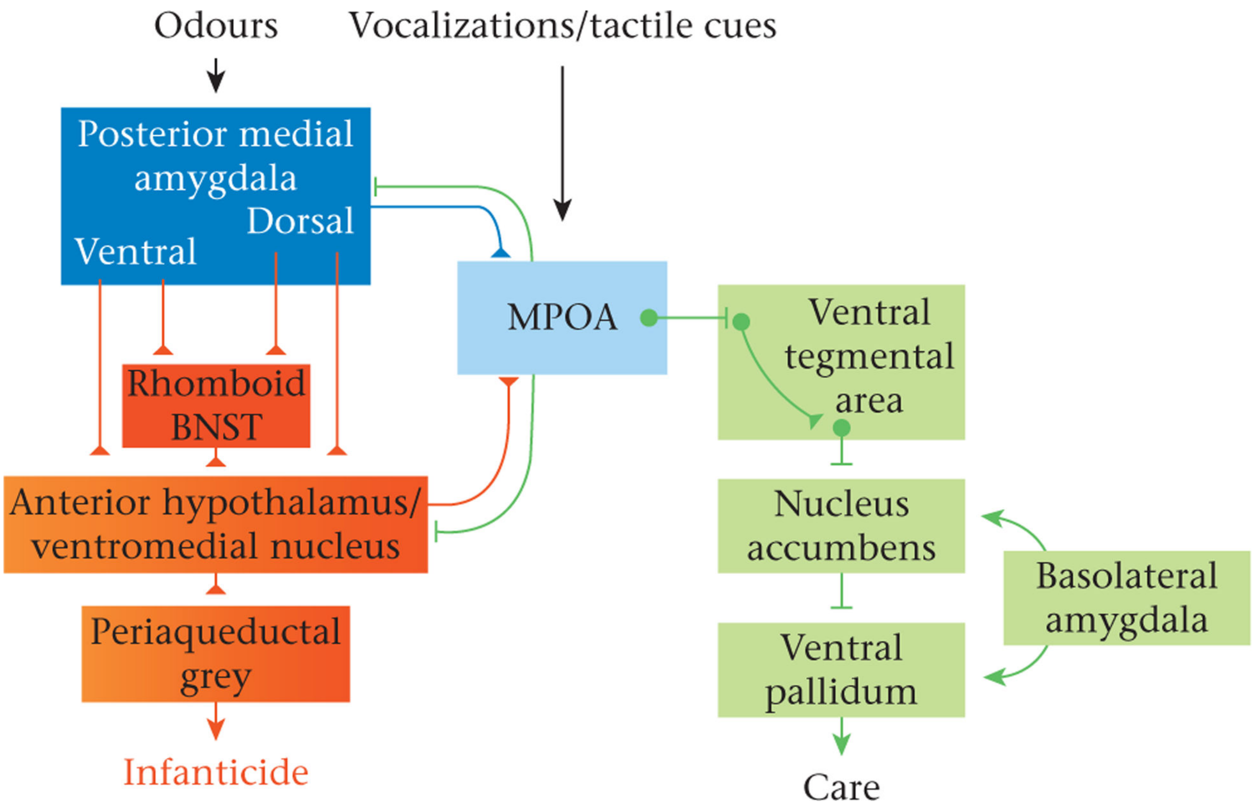

Figure 4.

A proposed neural model illustrating the regulation of infanticidal and parental behaviour in mice. The medial amygdala has dense projections to several neural sites that are highly active during infanticide including the rhomboid nucleus of the bed nucleus of the stria terminalis (BNST, medial, posterior intermediate part), anterior hypothalamus and ventromedial (ventrolateral) hypothalamus. The medial preoptic area (MPOA) coordinates caregiving behaviour through GABAergic efferent projections to several regions of this central aversion system as well as GABAergic efferent projections to the ventral tegmental area, which promote care. Reciprocal inhibitory connections between the MPOA and the central aversion system may allow for switching between parental and infanticidal behaviour.