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Fathering in rodents: Neurobiological substrates and consequences for offspring

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ABSTRACT

This article is part of a Special Issue "Parental Care".

Paternal care, though rare among mammals, is routinely displayed by several species of rodents. Here we review the neuroanatomical and hormonal bases of paternal behavior, as well as the behavioral and neuroendocrine consequences of paternal behavior for offspring. Fathering behavior is subserved by many of the same neural substrates which are also involved in maternal behavior (for example, the medial preoptic area of the hypothalamus). While gonadal hormones such as testosterone, estrogen, and progesterone, as well as hypothalamic neuropeptides such as oxytocin and vasopressin, and the pituitary hormone prolactin, are implicated in the activation of paternal behavior, there are significant gaps in our knowledge of their actions, as well as pronounced differences between species. Removal of the father in biparental species has long-lasting effects on behavior, as well as on these same neuroendocrine systems, in offspring. Finally, individual differences in paternal behavior can have similarly long-lasting, if more subtle, effects on offspring behavior. Future studies should examine similar outcome measures in multiple species, including both biparental species and closely related uniparental species. Careful phylogenetic analyses of the neuroendocrine systems presumably important to male parenting, as well as their patterns of gene expression, will also be important in establishing the next generation of hypotheses regarding the regulation of male parenting behavior.

Introduction

Male parenting behavior is rare among mammals and displayed mostly by socially monogamous species (Kleiman, 1977; Lukas and Clutton-Brock, 2013). The fact that fathering behavior is displayed by humans (Cabrera and Tamis-LeMonda, 2012), and that human paternal behavior is highly variable, has led to a keen interest in the hormonal and neural substrates of this behavior (Bales et al., 2011b; Saltzman and Ziegler, 2014), as well as its effects on offspring (Braun and Champagne, 2014). Rodent species have been particularly informative in this area, due to the ease of experimentation with them, but also to the relatively high number of biparental species in this order, including prairie voles (*Microtus ochrogaster*), mandarin voles (*Microtus mandarinus*), Mongolian gerbils (*Meriones unguiculatus*), California mice (*Peromyscus californicus*), Djungarian hamsters (*Phodopus campbelli*), and Octodon degus (*Octodon degus*). In this paper, we review the current understanding of the neuroanatomical and hormonal bases of paternal care in rodents. We also summarize what is known about the effects of fathering behavior on offspring, which has mostly been studied by removing fathers from the family group and, more rarely, by examining effects of individual variation in paternal behavior on offspring in intact groups.

Neuroanatomical basis of paternal behavior

The neural circuitry underlying maternal behavior has been studied extensively in the rat and provides a useful starting point for investigating the neuroanatomical basis of male parental care. Maternal behavior in Norway rats (*Rattus norvegicus*) is thought to be regulated largely by two opposing neural systems, both of which are activated in response to output from the main and accessory olfactory systems to the medial nucleus of the amygdala (MeA) (reviewed by Numan (2014); Numan and Insel (2003)). In the absence of specific hormonal and neurochemical inputs (estrogen, progesterone, oxytocin), MeA activity leads to activation of the anterior hypothalamus and ventromedial nucleus of the hypothalamus. These regions in turn project to the periaqueductal gray, which promotes aversion to pup stimuli as well as defensiveness and avoidance, thereby inhibiting the expression of maternal behavior. In contrast, in the hormonal milieu associated with late pregnancy

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and parturition, stimulation of the MeA leads to activation of the bed nucleus of the stria terminalis (BST) and the medial preoptic area of the hypothalamus (MPOA), stimulating attraction to stimuli (primarily odors) from pups and promoting maternal behavior.

As in females, the brain region most consistently implicated in male parental behavior is the MPOA. Adult male Norway rats do not engage in spontaneous parental behavior but can be induced to behave paternally through continuous exposure to pups, as is also the case for virgin female rats (i.e., sensitization (Rosenblatt, 1967)). Several studies indicate that the MPOA is essential for this process in adult males. For example, Rosenblatt et al. (1996) found that radiofrequency lesions of the MPOA prevented sensitization in adult males, at least for the 13 days of pup exposure over which males were tested. Sturgis and Bridges (1997) used the neurotoxin NMA to lesion the MPOA in castrated adult males treated with estrogen and progesterone. In contrast to radiofrequency lesions, NMA selectively targets cell bodies, sparing fibers of passage. MPOA lesions in this study inhibited the expression of paternal behavior (i.e., retrieving and crouching over pups) in previously sensitized rats. Collectively, these findings indicate that the MPOA is important for the expression of several specific behavioral components of paternal care during both the initiation and maintenance of pup-induced paternal behavior in the adult male rat. In addition, the MPOA appears to be a critical site for estrogenic facilitation of rat paternal behavior (Rosenblatt and Ceus, 1998). Most recently, a series of studies in the uniparental laboratory house mouse found that galaninin-expressing neurons in the MPOA are essential for expression of paternal behavior (Z. Wu et al., 2014).

Because male rats do not show spontaneous infant care, this species is not a particularly appropriate model for studies of paternal behavior. In fact, Rosenblatt et al. (1996) refer to sensitization in male rats as maternal behavior, because in this species only females display parental behavior under natural conditions. In this context, it is notable that both biparental California mice and uniparental white-footed mice (*Peromyscus maniculatus*) show increases in Fos-ir in the MPOA in response to pups (Lambert et al., 2013). More recent studies, therefore, have focused on neural and endocrine influences on paternal behavior in biparental species, in which both parents provide infant care under natural conditions (Bales et al., 2011b); (Table 1). In rodents, most of these studies have focused on the biparental prairie vole and California mouse. In these species, as in female rodents and male rats, the MPOA is crucial for the expression of paternal behavior. Lee and Brown (2002, 2007) characterized pup-directed behavior in male California mice that underwent electrolytic lesions of the MPOA three days after the birth of their first litter. Over the subsequent 10 days of testing, lesioned males showed a slower onset of paternal behavior, as well as less time engaging in paternal behavior (retrieving, sniffing, licking, or crouching over pups), less time in proximity to pups, and longer latencies to retrieve pups, compared to sham-lesioned males. Consistent with these findings, several studies of Fos-immunoreactivity (Fos-ir), an index of neuronal activation, have found increased Fos expression in the MPOA following exposure of males to pups. California mouse fathers, but not virgins or males housed with primigravid females (females in their first pregnancy), had elevated Fos-ir in the MPOA following exposure to a foster pup, compared to fathers similarly exposed to a control object (De Jong et al., 2009); but see De Jong et al. (2010). In prairie voles, virgin males had increased MPOA Fos-ir following exposure to an unrelated pup compared to exposure to a novel object (Kirkpatrick et al., 1994b). (Please note that affiliative behavior toward an unrelated pup, also known as alloparenting, is a common behavior in prairie voles, especially in males.)

Several studies of biparental rodents provide evidence that the amygdala, in addition to the MPOA, is involved in paternal behavior. In California mice, lesions of the basolateral nucleus of the amygdala (BLA) had effects on parental behavior that were very similar to those of MPOA lesions (Lee and Brown, 2007). Specifically, new, first-time fathers with BLA lesions spent less time engaging in paternal behavior, licking pups, and in proximity to pups, as well as longer latencies to retrieve pups, compared to sham-lesioned males. In contrast, Kirkpatrick et al. (1994a) found that in young adult male prairie voles housed with ovariectomized females, electrolytic lesions of the BLA had no effect on responses to pups, whereas electrolytic lesions of the corticomedial amygdala or the MeA reduced males' contact time with pups. Immunohistochemical studies have further implicated the amygdala and the BST, considered part of the "extended amygdala" (Davis et al., 2010), in paternal behavior. Virgin male prairie voles exposed to a pup had higher Fos-ir in the MeA and medial BST, compared to males exposed to a control object (Kirkpatrick et al., 1994b), while in California mice exposed to a foster pup, fathers had significantly higher Fos-ir in both the medioventral and medial posteromedial amygdala, compared to virgin males (De Jong et al., 2009).

Not surprisingly, the olfactory bulbs also appear to play a critical role in rodent paternal behavior. This region has received little attention; however, bilaterally bulbectomized, virgin adult male prairie voles were significantly more likely to attack pups than were sham-lesioned males (Kirkpatrick et al., 1994c), suggesting that olfactory cues normally inhibit pup-directed aggression. In the same species, exposure to a pup elevated Fos-ir in the accessory olfactory bulbs, compared with exposure to a control object (Kirkpatrick et al., 1994b).

Immunohistochemical studies have identified several additional brain regions that might be associated with paternal care in biparental rodents. In California mouse fathers, exposure to a pup increased Fos-ir in the caudal dorsal raphe nucleus and the lateral habenula (De Jong et al., 2009, 2010), whereas in virgin male prairie voles, pup exposure elevated Fos-ir in the lateral septum, paraventricular nucleus of the thalamus, and nucleus reuniens of the thalamus (Kirkpatrick et al., 1994b). Virgin male California mice also exhibited elevated Fos-ir in the lateral septum when compared to either pup-exposed virgins or fathers (Lambert et al., 2011). The roles of these regions in paternal care, if any, are unknown.

In summary, findings from immunohistochemical and lesion studies suggest that paternal care in biparental rodents is associated with some of the same brain regions implicated in maternal care, including the olfactory bulbs, MeA, BST, and MPOA. The precise roles of these and other brain regions in both the initiation and maintenance of paternal behavior are not yet known, however, and the generalizability of these findings are not clear, as they come from only two cricetid rodents.

Intriguingly, recent studies have found that fatherhood influences neural plasticity in several rodent species. Lieberwirth and colleagues (Lieberwirth et al., 2013) used the cell-division marker bromodeoxyuridine (BrdU) to investigate neurogenesis in male prairie voles, and found that fatherhood reduced the survival of new cells in the amygdala, dentate gyrus, and hypothalamus, but not the main olfactory bulbs. In the California mouse, Glasper and colleagues (Glasper et al., 2011) found that fatherhood inhibited hippocampal neurogenesis in the California mouse. Lambert et al. (2011) found that biparental California mice had higher levels of nestin-ir in CA2 and CA3, while uniparental white-footed mice had higher glial fibrillary acid protein in dentate gyrus and hippocampal fissure (Lambert et al., 2011). They interpreted this as indicating higher neuroplasticity in the biparental species and higher glial plasticity in the uniparental species. Finally, a fascinating series of studies in the uniparental house mouse (*Mus*) indicated that interactions of adult male mice with their own pups stimulated neurogenesis in the father's subventricular zone and dentate gyrus under the influence of prolactin signaling (Mak et al., 2013; Mak and Weiss, 2010). Some of the new cells matured into olfactory interneurons in the olfactory bulb, where they responded preferentially to offspring odors and appeared to subserve later recognition of mature offspring. These results highlight potential differences in the role of pup cues in neurogenesis in males of different species, and may highlight differences between males of biparental and uniparental species;

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however, additional studies will be necessary to tease apart these differences.

Hormonal influences on paternal behavior

Neuroendocrine regulation of parental behavior has been studied extensively in female rodents, mostly rats. In new mothers, maternal responsiveness toward pups is activated under the hormonal conditions of late pregnancy, parturition, and lactation. Declining progesterone levels, as well as high levels of estrogen, oxytocin, and prolactin, are especially important in this process (Numan and Insel, 2003). These same hormones and neuropeptides are implicated in the modulation of paternal behavior in male rodents (Table 2).

As described above, adult male rats do not display paternal behavior spontaneously; however, they can be induced to behave paternally by continuous exposure to pups (Rosenblatt, 1967). The onset of this pup-induced paternal behavior can be influenced by exposure of males to specific hormones both in the early postnatal period and in adulthood. Most importantly, gonadal steroids act early in life to organize paternal behavior: castration during the early postnatal period increases males' paternal responsiveness in adulthood, whereas early androgen treatment reverses this effect (McCullough et al., 1974; Rosenberg and Herrenkohl, 1976). In adult males, display of pup-induced parental behavior is not dependent on activational effects of hormones (Rosenblatt, 1967); nonetheless, both sensitization and infanticide can be influenced by gonadal steroids in adulthood. In males castrated as adults, treatment with high doses of estrogen, following priming with estrogen and progesterone, decreases the latency to the onset of paternal behavior during sensitization, whereas testosterone treatment increases the likelihood of infanticide (Lubin et al., 1972; Rosenberg, 1974; Rosenblatt et al., 1996). The onset of pup-induced paternal behavior can also be facilitated by treatment with prolactin (Sakaguchi et al., 1996).

As mentioned above, findings from rats and other uniparental rodents may not be particularly informative with respect to influences on spontaneously occurring paternal care in biparental species. Accordingly, recent studies of hormonal and neuropeptide consequences of fatherhood and influences on paternal care have focused on species in which fathers routinely provide care to their offspring under natural conditions (reviewed by Bales et al. (2011b); Saltzman and Ziegler (2014)).

Developmental effects of hormones

Studies of developmental influences on paternal behavior in rodents have focused on the prairie vole and yield a complex picture of early organizational effects of hormones. First, treatment of pregnant dams with either testosterone propionate (TP), corticosterone, the androgen receptor antagonist flutamide (FTD), or the aromatase inhibitor 1,4,6-androstatriene-3,17-dione (ATD) did not alter behavioral responses of male offspring to unrelated pups during either the juvenile period or adulthood (Lonstein and De Vries, 2000; Lonstein et al., 2002; Roberts et al., 1996). Similarly, treatment of pups with TP, FTD or ATD during the first week after birth had minimal effects on males' responses to pups in adulthood (Lonstein and De Vries, 2000). On the other hand, paternal behavior during the juvenile period or adulthood was reduced markedly by either castration immediately after birth (Lonstein et al., 2002) or treatment with ATD or FTD during the second postnatal week (Kramer et al., 2009). Together, these findings suggest that early-life exposure to both androgens and estrogens is critical for the later expression of paternal behavior in male prairie voles, and that the sensitive period for these actions of gonadal steroids is during the second week after birth, rather than earlier.

Paternal behavior in prairie voles can also be modulated by early exposure to neuropeptides. Male pups that received a single injection of an oxytocin (OT) receptor antagonist ([d(CH2)5, Tyr(Me)2, Orn8]-Vasotocin) on the first postnatal day exhibited reduced parental behavior and increased aggression toward unrelated pups during the juvenile period, but no effects were seen in adulthood (Bales et al., 2004b). In the same study, however, a single injection of neonates with exogenous OT had no discernible effects on males' later paternal or aggressive responses to pups (Bales et al., 2004b). This dosage of OT given neonatally did alter other outcome measures, including pair-bond formation (Bales and Carter, 2003), and the neonatal rodent blood-brain barrier is not fully formed on day 1 (Vorbrodt, 1993), suggesting that neonatal treatment with OT can potentially alter behavior via central actions. However, it is also possible that these effects (and the intranasal ones described below), could be due to peripheral binding of OT, and/or binding of OT to V1a receptors (Gimpl and Fahrenholz, 2001). In fact, daily intranasal treatment of juvenile males with OT did not alter their alloparental responsiveness to pups in early adulthood, compared to controls (Bales et al., 2013), whereas it did alter pair-bonding behavior. The failure of exogenous OT to enhance alloparental responsiveness in these two studies is likely due to the high baseline levels of alloparental behavior in young male prairie voles, which might obscure any potential stimulatory effects of OT treatment.

Activational effects of hormones

In many biparental rodents, fathers undergo systematic changes in central and/or peripheral concentrations of several hormones and neuropeptides in association with reproductive condition. In some cases, changes in central expression of hormone or neuropeptide receptors have also been described. While some of these changes in hormone and neuropeptide signaling appear to facilitate the expression of paternal behavior, most are of unknown significance (Bales et al., 2011b; Saltzman and Ziegler, 2014). Below we review profiles of several hormones (prolactin, gonadal steroids, glucocorticoids) and neuropeptides (vasopressin [AVP], OT) associated with fatherhood, as well as the evidence that these profiles may play a causal role in the activation of paternal care (see also Table 2).

Prolactin

Effects of fatherhood

In several biparental rodents, including Mongolian gerbils (Brown et al., 1995), California mice (Gubernick and Nelson, 1989), and Djungarian hamsters (Reburn and Wynne-Edwards, 1999), circulating prolactin levels are significantly higher in fathers living with their mate and pups than in virgin males, newly mated males, and/or expectant fathers (see also Schradin (2008)) on striped mice, *Rhabdomys pumilio*). Male Djungarian hamsters also have increased prolactin receptor mRNA transcript levels in the choroid plexus of the hypothalamus during their mate's early postpartum period, indicating that prolactin signaling in the brain is elevated during periods when males are interacting with pups (Ma et al., 2005).

Effects on paternal behavior

In contrast to the numerous studies demonstrating positive correlations between circulating prolactin levels and paternal behavior, no evidence is available, to our knowledge, to support a causal role of prolactin in the onset or maintenance of paternal care in biparental rodents (Wynne-Edwards and Timonin, 2007). In the only study that experimentally tested the effect of prolactin on paternal behavior in biparental rodents, Brooks et al. (2005) treated first-time Djungarian hamster fathers with the dopamine agonists bromocriptine and cabergoline in order to suppress secretion of prolactin. Although this treatment markedly reduced plasma prolactin concentrations, no differences in paternal behavior (pup-retrieval) in fathers, or growth and survival of pups, were found between agonist-treated and control males.

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Gonadal steroids

Effects of fatherhood

Testosterone generally shows a negative relationship with paternal care. In some biparental rodents, testosterone levels of expectant fathers rise across the mate's pregnancy (e.g., Djungarian hamster: (Reburn and Wynne-Edwards, 1999)) and decline following the birth of their pups (e.g., Mongolian gerbil: (Brown et al., 1995)); Djungarian hamster: (Reburn and Wynne-Edwards, 1999); California mouse: (Trainor et al., 2003; Gubernick and Nelson, 1989).

Few studies have characterized changes in estrogen signaling in rodent fathers, and in the small number of species that have been studied, no consistent picture has emerged. In male Djungarian hamsters, serum estradiol levels do not appear to change with paternal status (Schum and Wynne-Edwards, 2005), and estrogen receptor alpha (ERα)-ir in several brain regions (MPOA, BST, and MeA) does not differ between fathers and non-fathers (Timonin et al., 2008). Similarly, a recent study comparing California mouse fathers and virgin males found no differences in mRNA expression for ERα in the MPOA, BST, or MeA (Perea-Rodriguez et al., 2015). In contrast, biparental mandarin vole fathers have lower levels of ERα-ir in the MPOA and BST, and higher levels in the ventromedial hypothalamus, compared to non-fathers (Song et al., 2010). Virgin male mandarin voles that display high levels of paternal care had more ERα-ir in the MPOA, BST, the arcuate nucleus, and the MeA (Li et al., 2015).

Findings on progesterone are sparse and inconsistent. Male Djungarian hamsters show a significant increase in circulating progesterone levels at the end of the mate's pregnancy (Schum and Wynne-Edwards, 2005), whereas in California mice, circulating progesterone levels (Trainor et al., 2003) and expression of mRNA for progesterone receptors in the BST (Perea-Rodriguez et al., 2015) are significantly lower in fathers than in virgin males (Trainor et al., 2003).

Effects on paternal behavior

Although circulating or excreted testosterone levels correlate negatively with measures of paternal behavior in several rodents (reviewed by Numan and Insel (2003); Wynne-Edwards and Timonin (2007)), experimental studies indicate that effects of testosterone on paternal care differ markedly across species. In the Djungarian hamster (Hume and Wynne-Edwards, 2005) and in one study of prairie voles (Lonstein and De Vries, 1999), for example, castration of adult males had minimal effects on paternal behavior, whereas castrated male Mongolian gerbils engaged in significantly more paternal behavior than either castrated, testosterone-treated males or sham-castrated males (Clark and Galef, 1999). The opposite pattern has been found in another study of prairie voles (Wang and De Vries, 1993) and in California mice (Trainor and Marler, 2001), in which castration reduced and testosterone treatment restored paternal behavior. In the California mouse, this effect is mediated by aromatization of testosterone to estrogen within the brain: paternal behavior of castrated, reproductively experienced males was restored by treatment with testosterone or estrogen, but not by treatment with the non-aromatizable androgen dihydrotestosterone (Trainor and Marler, 2002). Moreover, fathers had higher aromatase activity within the MPOA than non-fathers (Trainor et al., 2003). Therefore, even though California mouse fathers have lower circulating concentrations of testosterone than non-fathers, they might have higher local concentrations of estrogen within the MPOA and possibly other brain regions.

The MeA appears to be an important site for estrogenic modulation of male parental behavior. Cushing et al. (2008) used a viral vector to increase ERα expression in the MeA of adult male prairie voles. Subsequently, these males showed reduced rates of paternal behavior toward an unrelated pup, as compared to controls. Using the same methods, Lei and colleagues (Lei et al., 2010) found no effect of increased ERα expression in the BST on behavioral responses to a pup in adult male prairie voles. These findings suggest that estrogen has site-specific effects within the neural circuitry underlying paternal behavior.

In the uniparental house mouse (*Mus* spp.), progesterone signaling has been shown to promote infanticide and inhibit paternal behavior in adult males (Lightman et al., 2001; Schneider et al., 2003). Progesterone receptor knockout mice, as well as mice treated with the progesterone receptor antagonist RU486, showed markedly reduced aggression toward pups and enhanced paternal behavior, whereas progesterone treatment of wild-type males significantly increased aggression toward pups. To our knowledge, however, effects of progesterone on paternal care have not been tested in biparental mammals.

Glucocorticoids

Effects of fatherhood

Studies of basal glucocorticoid (corticosterone and cortisol) concentrations in biparental rodents typically find no differences between fathers and non-breeding males (e.g., California mouse: (Chauke et al., 2011; Harris and Saltzman, 2013), prairie vole: (Campbell et al., 2009)). In the Djungarian hamster, however, males had significantly higher serum cortisol levels prior to pair formation than during their mate's pregnancy, and higher levels during the mate's late pregnancy than during mid-pregnancy and the early lactation period (Reburn and Wynne-Edwards, 1999).

Effects on paternal behavior

Very few studies have examined effects of glucocorticoids on paternal care. In California mouse fathers, acute treatment with high doses of corticosterone had neither short-term effects on paternal behavior nor long-term effects on pup survival or development (Harris et al., 2011). To determine effects of chronic stress, including chronic elevations of circulating corticosterone levels, on paternal care, Harris et al. (2013) subjected California mouse fathers to a chronic variable stress paradigm for 7 days. Stressed fathers showed both significant elevations in plasma corticosterone levels and subtle reductions in their interactions with their mate and pups compared to control fathers, but no differences were detected in pup survival or development. In male prairie voles, a swim stressor, which reliably doubles corticosterone concentrations in this species (Taymans et al., 1997), led to increased huddling over a strange pup. These effects were not seen in females (Bales et al., 2006), although long-term effects of the stressor on fathers or offspring were not studied. These findings suggest that neither acute nor chronic glucocorticoid elevations have pronounced effects on parental care in males, but clearly, additional data are needed from other species.

Vasopressin

Effects of fatherhood

AVP in fathers has been studied most thoroughly in the prairie vole, with a strong emphasis on AVP signaling within the brain. In this species, new fathers have reduced densities of AVP-immunoreactive fibers in the lateral septum and lateral habenular nucleus compared to both sexually naïve males and males housed with late-pregnant mates. This finding might reflect increased synthesis and release of AVP from the BST and MeA, the likely source of the vasopressinergic fibers, following both copulation and parturition (Bamshad et al., 1993, 1994). Prairie vole fathers (as well as mothers) also exhibit elevated AVP mRNA levels in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) in the postpartum period compared to sexually naïve controls (Wang et al., 2000). In the California mouse, in contrast, AVP mRNA levels in the PVN do not differ between fathers and either virgin males or males housed with tubally ligated females (De Jong et al., 2013), but levels of mRNA for AVP V1a receptors in the BST are significantly lower in fathers than in virgin males (Perea-Rodriguez et al., 2015). In virgin male prairie voles, exposure to a pup increased activation

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(as determined by Fos-ir expression) of AVP-immunoreactive cells in the PVN, but not plasma AVP (Kenkel et al., 2012). Effects of fatherhood on AVP signaling therefore appear to differ across species and might be clarified by additional studies.

Effects on paternal behavior

Both within and among species, paternal behavior correlates with patterns of AVP-ir and AVP binding, especially in the lateral septum and other parts of the extended amygdala (Bester-Meredith et al., 1999; Insel and Shapiro, 1992; Parker et al., 2001). Moreover, central infusion of AVP or AVP receptor antagonists promotes or inhibits paternal behavior, respectively, in the biparental prairie vole (Wang et al., 1994) and in the facultatively biparental meadow vole (*M. pennsylvanicus*: (Parker and Lee, 2001)). Nonetheless, castration of male prairie voles virtually eliminates AVP-ir in the lateral septum and lateral habenula but does not affect paternal behavior, suggesting that AVP signaling in these areas is not essential for the expression of paternal care (Lonstein and De Vries, 1999).

Oxytocin

Effects of fatherhood

Several studies have investigated changes in intracerebral OT signaling or peripheral OT concentrations in rodent fathers. In the facultatively biparental meadow vole, sexually and paternally experienced, paternally behaving males were found to have significantly higher OT receptor binding in several brain regions (accessory olfactory nucleus, lateral septum, BST, and lateral amygdala) than sexually and paternally inexperienced, non-paternally behaving males; however, it could not be determined whether these neural differences were caused by differences in sexual activity, cohabitation with a female, and/or paternal experience (Parker et al., 2001). Similarly, fathers have increased numbers of OT-immunoreactive fibers in the PVN and SON in mandarin voles, compared to virgin males; however, similar effects were seen in non-fathers that were either exposed briefly to pups or housed with a female prior to parturition (Song et al., 2010). Virgin mandarin vole males that engaged in more paternal behavior had elevated OT-immunoreactive fibers in the PVN and SON as well (Li et al., 2015).

In male prairie voles, fathers, compared to virgins, were recently found to have more OT-immunoreactive neurons in the PVN, as well as higher densities of OT-immunoreactive fibers in the nucleus ambiguus and nucleus of the solitary tract, but fewer OT-immunoreactive neurons in the BST (Kenkel et al., 2014). Another study on prairie voles, however, found no differences between fathers and virgin males in OT gene expression in either the PVN or the SON (Wang et al., 2000), or in OT receptor binding in the lateral septum, BST, or the ventromedial nucleus of the hypothalamus (Wang et al., 2000). Finally, California mouse fathers have reduced expression of mRNA for the OT receptor in the BST, but not in the MPOA or medial amygdala, compared to virgin males (Perea-Rodriguez et al., 2015). Thus, effects of fatherhood on the brain's OT system seem to be inconsistent across species, and where effects have been detected, they may correspond to cohabitation with a female rather than fatherhood per se.

In addition to central OT signaling, circulating OT concentrations may be altered by fatherhood and interactions with pups. Male California mice exhibit elevated circulating OT concentrations during the first half of their mate's pregnancy, but OT levels decline prior to parturition and remain low throughout the postpartum period (Gubernick et al., 1995). Moreover, in virgin male prairie voles (which had not been exposed to a female), pups elicited a rise in plasma OT levels as well as an increase in OT-ir staining in the PVN (Kenkel et al., 2012), suggesting that pups present a potent stimulus to the OT system. It is unclear, however, whether circulating OT concentrations reliably reflect levels in the brain (Churchland and Winkielman, 2012).

Effects on paternal behavior

In virgin male prairie voles, paternal behavior was inhibited by combined treatment with an AVP receptor antagonist and an OT receptor antagonist, but not either antagonist alone (Bales et al., 2004a). No other published studies, to our knowledge, have manipulated OT signaling in adult male rodents to identify possible effects on paternal behavior.

Effects of male parenting on offspring

Effects of paternal deprivation

Paternal deprivation, or paradigms where the father in a biparental species is removed during offspring development, has often been used to explore the role of the father in offspring development and behavior. These studies have revealed extensive, often sex-specific effects on offspring, including effects on survival, especially under adverse conditions (Cantoni and Brown, 1997; Gubernick et al., 1993; Wright and Brown, 2002), developmental markers (Elwood and Broom, 1978; Piovanotti and Vieira, 2004; Wang and Novak, 1992), and behavior (Ahern et al., 2010; Ahern and Young, 2009; Bredy et al., 2004).

Behavioral effects of father absence are particularly intriguing and span cognitive, emotional, and reproductive behavior (Table 3). In California mice removal of the father interacted with experimenter handling to predict offspring performance in cognitive tasks such as the Barnes maze, a test of spatial learning (Bredy et al., 2004). Non-handled, father-absent offspring received the least licking/grooming and performed worst in the Barnes maze, although this effect was primarily in male offspring, and father absence had little effect on top of the handling effect. In prairie voles, female offspring that had been raised without fathers displayed less alloparenting (Ahern and Young, 2009), did not form normal pair-bonds (Ahern et al., 2010; Ahern and Young, 2009), and exhibited less licking and grooming of their own offspring when later raising them without a male pair-mate (Ahern et al., 2010), compared to female offspring that had been raised by both parents. Male offspring raised without a father also displayed deficits in pair-bonding (Ahern and Young, 2009).

A growing body of evidence shows systematic changes in behavior caused by paternal deprivation in mandarin voles. Paternally deprived pups of both sexes displayed higher levels of anxiety in an open field and less time in social behavior in a social interaction test, compared to pups raised by both parents (Jia et al., 2009). Social recognition in a habituation–dishabituation paradigm was also impaired in both sexes of paternally deprived offspring (Cao et al., 2014). Paternally deprived male voles displayed less play behavior (boxing and wrestling) on PND 35, and higher contact with littermates (Wang et al., 2012). Finally, paternal deprivation significantly inhibited partner preference formation in females and increased aggression toward their pair-mate and toward an unfamiliar male (Yu et al., 2012). In males, paternal deprivation reduced contact with both the partner and the stranger, as well as increasing attacks toward the strange female (Yu et al., 2012). The overall picture of paternally deprived mandarin voles is broadly consistent with that of paternally deprived prairie voles, with offspring being more anxious and less social on multiple measures (although in a socially monogamous species, aggression toward an outside animal can be interpreted as mate-guarding, an essential aspect of the pair-bond).

Recent studies in voles (mandarin and prairie) and Octodon degus have also examined the neuroendocrine consequences of paternal deprivation for offspring (Table 3). Female prairie vole pups in the study cited above (Ahern and Young, 2009), when raised in paternally deprived groups, showed increased numbers of clusters of OT mRNA in the PVN compared to females raised in biparental groups. In addition, both sexes had higher density of receptor binding of corticotropin-releasing factor type 2 receptors (CRFR2) in the dorsal raphe; these two measures (OT mRNA and CRFR2 in the dorsal raphe) correlated in females, but not in males.

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Table 1
Summary of findings on neural influences on and correlates of paternal care in biparental rodents. IHC — immunohistochemistry; ERα — estrogen receptor alpha.

Species	Brain region	Method	Experimental group	Results	Reference
California mouse	Medial preoptic area	Electrolytic lesions	First-time fathers	Increased latencies to retrieve, lick, and hover over pups; decreased time spent sniffing, licking, and near pups	Lee and Brown (2002)
			Fathers	Decreased time licking and hovering over pups; increased latencies to retrieve pups	
California mouse	Medial preoptic area	Fos IHC	Adult males	Increased Fos-ir in new fathers exposed to a pup; no effect in virgin males or first-time expectant fathers	De Jong et al. (2009)
California mouse	Basolateral amygdala	Electrolytic lesions	Fathers	Increased latency to approach pups; decreased time licking pups and near pups	Lee and Brown (2007)
California mouse	Medioventral amygdala	Fos IHC	Adult males	Increased Fos-ir following exposure to a pup in fathers compared to virgin males	De Jong et al. (2009)
California mouse	Medial posteromedial amygdala	Fos IHC	Adult males	Increased Fos-ir following exposure to a pup in fathers compared to virgin males	De Jong et al. (2009)
California mouse	Nucleus accumbens	Electrolytic lesions	Fathers	Decreased latency to retrieve pups	Lee and Brown (2007)
California mouse	Caudal dorse raphe nucleus	Fos IHC	Fathers	Increased Fos-ir following exposure to a pup	De Jong et al. (2009), De Jong et al. (2010)
California mouse	Lateral habenula	Fos IHC	Fathers	Increased Fos-ir following exposure to a pup	De Jong et al. (2009), De Jong et al. (2010)
California mouse	Medial preoptic area	Fos IHC	Fathers	Increased Fos-ir following exposure to a pup	Lambert et al. (2013)
	Posterior cingulate cortex			Decreased Fos-ir following exposure to a pup	Lambert et al. (2011, 2013)
Prairie vole	Basolateral amygdala	Excitotoxic lesions	Adult virgin males	No effect on responses to pups	Kirkpatrick et al. (1994a)
	Medial amygdala	Electrolytic lesions		Decreased contact time with pup	
	Corticomedial amygdala	Electrolytic lesions		Decreased contact time with pup, increased time away from pup	
Prairie vole	Medial preoptic area, Medial amygdala, Lateral septum, Paraventricular nucleus of the thalamus, Nucleus reuniens, Accessory olfactory bulbs, Medial bed nucleus of the stria terminalis	Fos IHC	Young adult virgin males	Increased Fos-ir following exposure to a pup	Kirkpatrick et al. (1994b)
Prairie vole	Medial amygdala	Increased expression of ERα via viral vector	Adult males	Decreased alloparental behavior	Cushing et al. (2008)
Prairie vole	Bed nucleus of stria terminalis	Increased expression of ERα via viral vector	Adult males	No effect	Lei et al. (2010)
Prairie vole	Olfactory bulbs	Surgical removal (bilateral)	Adult virgin males	Increased likelihood of attacking pups	Kirkpatrick et al. (1994c)

Similarly, in mandarin voles, paternal deprivation resulted in sex-specific changes in neuroendocrine systems. In females, paternal deprivation resulted in decreases in glucocorticoid receptors (GR) and brain-derived neurotrophic factor (BDNF) in the dentate gyrus (R. Wu et al., 2014), increased serum levels of adrenocorticotrophin (ACTH) (R. Wu et al., 2014), reduced levels of dopamine type 1 (D1) and type 2 (D2) receptors in the nucleus accumbens (NAcc) (Yu et al., 2012), reduced serum OT, and reduced ERα mRNA in the MeA, with no change in OTR mRNA in the MeA but a reduction in OTR mRNA in the NAcc (Cao et al., 2014). Corticosterone in paternally deprived females was higher than in pair-reared females in one study (R. Wu et al., 2014) and lower in another (Yu et al., 2012).

In contrast, male mandarin voles did not display changes in GR or BDNF in dentate gyrus, or changes in ACTH (R. Wu et al., 2014), and had enhanced expression of D1 and D2 in the NAcc (Yu et al., 2012), increased AVP-ir in the PVN, reduced AVP-ir in the anterior hypothalamus and reduced OT-ir in the PVN (Wang et al., 2012). Further, paternally deprived males showed no change in serum OT or in ERα in the MeA, and reductions of OTR in both the MeA and NAcc (Cao et al., 2014). Corticosterone in paternally deprived males did not change in one study (R. Wu et al., 2014) and increased in two others (Wang et al., 2012; Yu et al., 2012).

Both sexes of paternally deprived mandarin voles displayed decreased levels of GR and BDNF in CA1 and CA 2/3 of the hippocampus (R. Wu et al., 2014). Timelines of corticosterone and ACTH levels throughout early development (Wang et al., 2014) suggest that paternal deprivation alters development of these systems, including disruption of the stress-hyporesponsive period. As a whole, father absence in this socially monogamous species results in an anxious, less social phenotype in both sexes, with sex differences in the underlying neurobiology generally suggesting lower responsiveness of the OT system, altered AVP systems particularly in males, sex-specific changes in the reward system, and conflicting effects on corticosterone.

Octodon degus are an interesting comparison species in that they are from a different rodent lineage than the voles and California mice, are not socially monogamous, but do often display care by males (Ebensperger et al., 2010). While research on paternal deprivation in this species has mostly focused on the cerebral cortex, some studies have included limbic areas as well. In male degus, number of CRF-positive neurons decreased globally over development; however, paternal deprivation led to even greater reductions in numbers of CRF-positive pyramidal cells in CA1 at PND21 and 90, reduced cells in the dentate gyrus at day 21 but not 90, increased cells in the BLA at day 21 (Seidel et al., 2011), decreased cells in the medial BST at day 21,

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Table 2
Summary of findings on hormonal and neuropeptide influences on paternal care in biparental rodents. All manipulations were performed on adult animals unless otherwise indicated. T — testosterone, E — estrogen, DHT — dihydrotestosterone, ERα — estrogen receptor alpha, PR — progesterone receptor, BST — bed nucleus of the stria terminalis, ICV — intracerebroventricular, AVP — vasopressin, OT — oxytocin.

Species	Hormone/neuropeptide	Organizational or activational	Method	Experimental group	Results	Reference
Djungarian hamster	Prolactin	Activational	Treatment with dopamine agonists bromocriptine or cabergoline to decrease prolactin secretion	First-time fathers	No effect on paternal behavior	Brooks et al. (2005)
Djungarian hamster	Gonadal steroids	Activational	Castration	Fathers	No effect on paternal behavior	Hume and Wynne-Edwards (2005)
Djungarian hamster	Estrogen	Activational	Treatment with letrozole (aromatase inhibitor)	First-time fathers	No effect on paternal behavior	Hume and Wynne-Edwards (2006)
Mongolian gerbil	Testosterone	Activational	Castration + T replacement	Males paired with pregnant females	Castration increased and T replacement decreased paternal behavior	Clark and Galef (1999)
California mouse	Gonadal steroids	Activational	Castration + E, T, or DHT replacement	Fathers	Paternal behavior was decreased by castration and reinstated by treatment with E or T, but not with DHT (non-aromatizable) or T + fadrozole (aromatase inhibitor)	Trainor and Marler (2001, 2002)
Prairie vole	Estrogen	Activational	Castration + Estradiol replacement	Adult virgin males	No effect on paternal behavior	Lonstein and De Vries (1999)
Prairie vole	Estrogen	Activational	Increase expression of ERα in medial amygdala via viral vector	Adult males	Decreased paternal behavior	Cushing et al. (2008)
Prairie vole	Estrogen	Activational	Increase expression of ERα in BST via viral vector	Adult virgin males	No effect on paternal behavior	Lei et al. (2010)
Prairie vole	Testosterone	Activational	Castration + T replacement	Adult virgin males	Castration decreased paternal behavior and increased pup-directed aggression; T replacement reversed these effects	Wang and De Vries, 1993
California mouse	Corticosterone	Activational	Acute corticosterone treatment	First-time fathers	No effect on paternal behavior	Harris et al., 2011
California mouse	Corticosterone	Activational	Variable chronic stress, leading to chronic increase in corticosterone	First-time fathers	Transient decreases in paternal behavior	Harris et al. (2013)
Prairie vole	Corticosterone	Activational	Acute swim stressor, leading to likely increases in corticosterone	Adult virgin males	Increased paternal behavior	Bales et al. (2006)
Prairie vole	Vasopressin	Activational	Infusion of AVP or AVP receptor V1a antagonist into lateral septum	Adult virgin males	AVP increased and V1a receptor antagonist decreased paternal behavior	Wang et al., 1994
Meadow vole (facultative paternal care)	Vasopressin	Activational	ICV infusion of AVP or AVP V1a receptor antagonist	Adult virgin males	AVP decreased pup-directed aggression and increased paternal behavior; V1a antagonist decreased paternal behavior	Parker and Lee (2001)
Prairie vole	Vasopressin, oxytocin	Activational	ICV infusion of AVP, OT or both; or of AVP, antagonist, OT antagonist, or both	Adult virgin males	Combined treatment with AP antagonist and OT antagonist increased latency to approach pup, increased proportion of males attacking pup, decreased kyphosis, and decreased proportion of males behaving paternally	Bales et al. (2004a)
Prairie vole	Oxytocin	Organizational	OT or OT antagonist injection on PND1	Weanlings and adult virgin males	OT antagonist decreased paternal behavior and increased pup-directed aggression in weanlings	Bales et al., 2004b
Prairie vole	Oxytocin	Organizational (developmental)	Intranasal OT treatment during juvenile period	Adult virgin males	No effect on paternal behavior	Bales et al. (2013)

and no change in the PVN (Gos et al., 2014). Tyrosine hydroxylase fibers, indicating catecholaminergic innervations, were elevated at PND21 in many areas in paternally deprived male degus, including the NAcc, CeA, and CA1. These elevations remained in adulthood in the hippocampus, but the effect was reversed in the NAcc (Braun et al., 2013). Paternal deprivation in degus also results in widespread developmental changes in interneuron expression patterns (Braun et al., 2011), reduced dendritic spine numbers in the somatosensory neurons (Pinkernelle et al., 2009), as well as in the neurons of the anterior cingulate cortex (Outscharoff et al., 2006).

In summary, the absence of the father in biparental species has profound effects on the offspring. The behavioral effects seem to be

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Table 3
Summary of findings on effects of paternal deprivation on brain and hormone levels in biparental species, organized by species. PVN = paraventricular nucleus of the hypothalamus, OT = oxytocin, GR = glucocorticoid receptors, BDNF = brain-derived neurotrophic factor, ACTH = adrenocorticotrophin, D1R = dopamine type 1 receptors, D2R = dopamine type 2 receptors, ERα = estrogen receptor alpha, OTR = oxytocin receptor, CRFR2 = corticotrophin-release factor type 2 receptors.

Species	Brain region/hormonal change	Experimental group	Results (compared to animals raised by both parents)	Reference
Prairie vole	PVN	Paternally deprived females	Increased numbers of clusters of OT mRNA	Ahern et al. (2010)
	Dorsal raphe	Paternally deprived, both sexes	Higher density of CRFR2 receptors	
Mandarin vole	Dentate gyrus CA1, CA 2/3	Paternally deprived females	Decreases in GR and BDNF	R. Wu et al. (2014) and Z. Wu et al. (2014)
Mandarin vole	Nucleus accumbens	Paternally deprived females	Reduced D1R and D2R	Yu et al. (2012)
			Reduced OTR mRNA	Cao et al. (2014)
Mandarin vole	Medial amygdala	Paternally deprived females	Reduced ERα	Cao et al. (2014)
	Serum		No change in OTR mRNA	
			Reduced serum OT	
Mandarin vole	Dentate gyrus CA1, CA 2/3	Paternally deprived males	No change in GR and BDNF in Dentate	R. Wu et al. (2014) and Z. Wu et al. (2014)
			Reductions in GR and BDNF in CA1, CA 2/3	
Mandarin vole	Nucleus accumbens	Paternally deprived males	Higher D1R and D2R	Yu et al. (2012)
			Reduced OTR mRNA	Cao et al. (2014)
Mandarin vole	Medial amygdala	Paternally deprived males	No change in ERα	Cao et al. (2014)
			Lower OTR mRNA	
Mandarin vole	Hypothalamus	Paternally deprived males	Reduced AVP-ir in anterior hypothalamus	Wang et al., 2012
			Reduced OT-ir in PVN	
Mandarin vole	Serum	Paternally deprived males	No change in serum OT	Cao et al. (2014)
Octodon degus	Dentate gyrus CA1	Paternally deprived males	Fewer CRF-positive pyramidal cells at PND21	Seidel et al. (2011)
			Fewer CRF-positive pyramidal cells at PND21 and 90	
Octodon degus	Medial BST	Paternally deprived males	Fewer CRF-positive cells at PND21	Gos et al. (2014)
	PVN	Paternally deprived males	No change in CRF-positive cells	
	Basolateral amygdala	Paternally deprived males	More CRF-positive cells at PND21	
Octodon degus	CA1, nucleus accumbens, central amygdala	Paternally deprived males	Elevated tyrosine hydroxylase	Braun et al. (2013)

relatively consistent in that, when they occur, they result in less social and more anxious animals. These effects can be sex- and species-specific. Consistent in the underlying neurobiology are changes in stress-responsive systems including catecholaminergic systems. However, different outcomes of paternal deprivation have been studied in different species; it is thus not always easy to make direct comparisons between species.

Effects of individual differences in paternal behavior on offspring

Less common than studies of paternal deprivation are those in which the role of the father is explored in intact groups. These effects are often more subtle than those described above for paternal deprivation, but suggest that male care affects pup development in a species- and sex-specific manner.

In California mice, retrievals by fathers predict aggression in male pups (Frazier et al., 2007), which appears to be subserved by AVP-immunoreactivity in the ventral BST (Frazier et al., 2007). Retrievals also lead to increased testosterone levels in prepubertal pups 45 min post-retrieval (Becker et al., 2010). Castrated males lick and groom young at lower rates than intact males. Male pups raised by castrated males also lick and groom at lower rates; however they also retrieve pups more frequently, which their fathers did not (Gleason and Marler, 2013). Male California mouse pups cross-fostered to white-footed mouse (*Peromyscus leucopus*) parents were retrieved less frequently as pups, and then retrieved their own pups less frequently as adults (Bester-Meredith and Marler, 2003).

In prairie voles, fathers displayed apparent compensation for mothers that spent low amounts of time in contact with offspring (Perkeybile et al., 2013), with offspring in which mothers displayed high contact receiving less fathering, and offspring that received low contact from mothers receiving more fathering. Low-contact offspring developed at a higher rate, but were less social with a strange juvenile, displayed more autogrooming, and showed more retrievals but less contact with a strange pup compared to high-contact offspring. They also showed greater potentiation of an acoustic startle response. However, it is unclear whether these changes can be attributed specifically to changes in paternal care. When parental care was analyzed by principal component analysis and a "paternal care factor" identified, correlations between this factor and offspring behavioral outcomes did not survive statistical correction.

In another series of studies, prairie vole pups underwent a handling manipulation that had long-lasting effects on social and anxiety-like behavior (Bales et al., 2007, 2011a). Specifically, adults that experienced reduce handling as pups had F1 offspring that displayed deficits in social behavior (alloparenting and pair-bonding). The F2 generation continued to display these deficits if either their mother or father had come from a reduced-handling litter (Stone and Bales, 2010), thus suggesting that in this case, maternal and paternal experience were interchangeable in their effects on the offspring.

Alloparenting experience in cooperatively breeding species can potentially have long-lasting effects on the alloparent's behavior (Greenberg et al., 2012), neuroendocrine systems such as BDNF (Greenberg et al., 2012), and reproductive success (Tardif et al., 1984); as well as lasting effects on the offspring of experienced alloparents. Stone and colleagues (Stone et al., 2010) paired male and female prairie voles with varying levels of alloparenting experience, and looked at offspring outcomes. Offspring of parents that had two litters of alloparental experience (either through two litters of experience for one parent, or one litter of experience for each parent) developed faster and displayed more male alloparenting themselves. This effect did not depend on which parent had the alloparenting experience.

Another aspect of paternal experience that might affect offspring development is previous experience as a father (as opposed to alloparenting

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experience). Offspring of experienced Mongolian gerbil fathers locomote more outside the nest than offspring of inexperienced fathers (Piovanotti and Vieira, 2004).

Discussion

We have reviewed what is known regarding the neurobiological substrates of male parenting behavior in rodents. This has provided a clear view of the multitude of species differences in the biological regulation and the consequences of male parenting behavior. Male parenting is typically displayed in socially monogamous or cooperatively breeding species, and as such it is clear that it has evolved many different times. Recent phylogenetic analyses of social monogamy, biparental care, and infanticide have debated the order in which these traits evolved (Dixson, 2013; Lukas and Clutton-Brock, 2013; Lukas and Huchard, 2014; Opie et al., 2013a,b, 2014); however, mostly they agree that biparental care is a consequence rather than a cause of social monogamy. If biparental care evolved independently so many times, why would we expect mechanisms to be similar across species? It is possible that convergent evolution has repeatedly co-opted the same neural and hormonal systems. One recent study, while on a completely different topic, is enlightening in this respect (Parker et al., 2013). Parker and colleagues identified convergence in genes for echolocation in 200 loci in bats and the rather distantly related bottlenose dolphin. A similar study on biparental care in rodents, or mammals in general, would be highly informative as to the underlying evolution and mechanisms of male care.

The work that we review here thus suggests that while fathering is clearly regulated by neuroendocrine systems, our current state of knowledge is insufficient. We need more studies that use similar outcome measures and similar methodologies, carried out across multiple species. For instance, the effects of paternal deprivation have been studied in depth in both mandarin voles and degus, but the focus has been on very different brain areas and outcomes. One great advantage of many biparental rodent species is that they come from taxa that display differing levels of male parenting at either the species level (i.e. *P. californicus* vs. *P. maniculatus*), or even within populations of the same species (i.e. strongly biparental and monogamous Illinois prairie voles vs. mostly uniparental Kansas prairie voles (Roberts et al., 1998)). Continued use of closely related species that are either obligately biparental, facultatively biparental, or uniparental will be highly informative.

Other areas in the literature that need to be fleshed out include the distinctions between fathering in obligate and facultative species, and between the neurobiology of parental care in parents and alloparents. Literature on fathering in "facultatively paternal" species such as rats and mice has greatly informed our knowledge of neural substrates (Rosenblatt, 1967; Rosenblatt and Ceus, 1998), especially with regard to induced hormonal changes and to communication between the mother and father in these species (Liang et al., 2014; Liu et al., 2013). Similarly, work with non-fathers in "obligately paternal" species such as prairie voles can inform our understanding of what may *not* be necessary for the display of care. However, we do need to carefully distinguish these different categories in the literature, particularly in respect to their natural occurrence under field conditions rather than artificial conditions of captivity.

Future studies might also focus on what is "unique" to paternal care vs. other types of care. For instance, studies of paternal deprivation have provided ample evidence for long-term consequences on offspring development. However, we were unable to find any studies in which a father was removed but the total number of caregivers remained the same (for example, by leaving an adult sibling in the cage with the mother to help her provide care). As such, the quantity of caregiving, in contrast to (potentially) the quality, varied in all of the studies cited here, and we are unable to make statements about whether consequences for offspring are the results specifically of father absence or simply less care. This provides an important avenue for future studies.

Finally, relationships between parents, for example the effects of the mother's behavior on the father and vice versa, have rarely been studied in biparental rodents and provide an important area in which to consider the family as a system. Exceptions include a recent, extensive study of parental behavior in California mice (Rosenfeld et al., 2013), as well as the prairie vole study in which principal component analysis was used to examine the latent variables underlying the expression of parental behavior (Perkeybile et al., 2013). However, neither of these studies examined the effects of one parent on the other in a manner that measured bidirectional statistical dependence over time (Butler and Randall, 2013). Dyadic statistical techniques used to study relationships in humans could be useful in characterizing the interdependent nature of the parents' behaviors. This understanding could be crucial to illuminating variation in the behavior of each parent and consequences for offspring development.

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