Neural Regulation of Paternal Behavior in Mammals: Sensory, Neuroendocrine, and Experiential Influences on the Paternal Brain

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Contents

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Abstract Across the animal kingdom, parents in many species devote extraordinary effort toward caring for offspring, often risking their lives and exhausting limited resources. Understanding how the brain orchestrates parental care, biasing effort over the many competing demands, is an important topic in social neuroscience. In mammals, maternal care is necessary for offspring survival and is largely mediated by changes in hormones and neuropeptides that fluctuate massively during pregnancy, parturition, and lactation (e.g., progesterone, estradiol, oxytocin, and prolactin). In the relatively small number of mammalian species in which parental care by fathers enhances offspring survival and development, males also undergo endocrine changes concurrent with birth of their offspring, but on a smaller scale than females. Thus, fathers additionally rely on sensory signals from their mates, environment, and/or offspring to orchestrate paternal behavior. Males can engage in a variety of infant-directed behaviors that range from infanticide to avoidance to care; in many species, males can display all three behaviors in their lifetime. The neural plasticity that underlies such stark changes in behavior is not well understood. In this chapter we summarize current data on the neural circuitry that has been proposed to underlie paternal care in mammals, as well as sensory, neuroendocrine, and experiential influences on paternal behavior and on the underlying circuitry. We highlight some of the gaps in our current knowledge of this system and propose future directions that will enable the development of a more comprehensive understanding of the proximate control of parenting by fathers.

Keywords Alloparental behavior · Medial preoptic area · Neuroendocrinology · Parental behavior · Parental care · Social behavior

1 Introduction

In all 5,000–6,000 extant mammalian species, maternal care is essential for the survival and development of offspring. At a minimum, mothers must undergo the physiological processes of gestation, parturition, and lactation, some of the major hallmarks of mammalian evolution. Typically, however, species-specific behaviors performed by mothers, such as warming, transporting, and protecting young, are also critical for infant survival. Because mothers are uniquely capable of gestating and lactating and can provide all behavioral components of maternal care, female mammals presumably evolved to independently support their own offspring following insemination, a pattern observed in most mammalian species. In contrast, males often provide as much care of offspring as mothers, if not more, in birds, as well as in the relatively small number of fish and amphibian species that engage in parental care (Clutton-Brock 1991; Cockburn 2006; Crump 1996; Goodwin et al. 1998; Gross and Sargent 1985), taxa in which offspring development (and in some cases fertilization) often occur outside of the mother's body and in which both parents are capable of feeding and protecting the young. Nonetheless, fathers provide care for their offspring in approximately 10% of mammalian genera, especially among

canids, rodents, and primates (Kleiman and Malcolm 1981; Woodroffe and Vincent 1994).

Both the specific behaviors performed and the amount of resources invested in offspring by mammalian fathers can vary substantially. For example, fathers in biparental canid species, such as the gray wolf (*Canis lupus*), coyote (*C. latrans*), and African wild dog (*Lycaon pictus*), play with, babysit and defend their pups, and provision them with food (Bruin et al. 2016; Kleiman and Malcolm 1981; Mech et al. 1999). In many biparental rodents, such as California mice (*Peromyscus californicus*), prairie voles (*Microtus ochrogaster*), and Campbell's Russian dwarf hamsters (*Phodopus campbelli*), fathers retrieve, huddle, and lick their pups, as well as build nests (Gubernick and Alberts 1987; Wang et al. 1994; Wynne-Edwards 1995). Fathers in some biparental rodent species also commonly perform the kyphotic posture typical of nursing mothers, although males do not lactate, and may even help to deliver pups during parturition and ingest placenta and amniotic fluid (Jones and Wynne-Edwards 2000; Perea-Rodriguez and Saltzman 2014). In the biparental nonhuman primates in which paternal care has been studied extensively, particularly titi monkeys (*Callicebus* spp.), marmosets (*Callithrix* spp.), and tamarins (*Saguinus* spp.), fathers often play a major role in transporting infants, thought to be an energetically expensive behavior. Fathers in these species also groom their infants, as well as play and share food with them (Fernandez-Duque et al. 2009; Spence-Aizenberg et al. 2016). In all of these taxa, the amounts and proportions of parental behaviors performed by fathers, as compared to mothers and alloparents, can differ markedly among species as well as across the offspring's development. Paternal care can be essential for survival of offspring and can have lasting impacts on offspring behavioral, neural, cognitive, affective, and social development (Bales and Saltzman 2016; Braun and Champagne 2014; Kentner et al. 2009).

In accordance with the ubiquity of maternal care among mammals, the neural substrates and endocrine determinants of both physiological and behavioral aspects of maternal care have been studied extensively, especially in rodents. Much less is known about paternal care. The neural circuitry underlying paternal behavior, in particular, remains relatively unexplored. While both the neural substrates and endocrine influences on parental care overlap between mothers and fathers, the extent of this overlap is not yet clear. Similarly, although some of the sensory and experiential influences on male parental behavior resemble those in mothers, these influences are also likely to differ substantially between the sexes; however, the extent of these similarities and differences has received little attention.

In this chapter we review neural, sensory, hormonal, and experiential influences on the expression of paternal behavior in mammals. We focus largely on rodents because they are the best-studied; however, we incorporate findings from primates where data exist. Moreover, we present results from both biparental species (e.g., California mouse, prairie vole, Campbell's Russian dwarf hamster, mandarin vole [*Microtus mandarinus*], Mongolian gerbil [*Meriones unguiculatus*]; common marmoset [*Callithrix jacchus*], cotton-top tamarin [*Saguinus oedipus*], human), in which fathers spontaneously provide care for their offspring, and uniparental mammals, such as laboratory mice (*Mus*) and rats (*Rattus*), in which paternal care may be

expressed under captive conditions but does not seem to occur spontaneously in natural environments.

Given that paternal care has evolved multiple times among mammals, even within individual orders (West and Capelllini 2016), we should not assume that it is governed by identical mechanisms in all taxa. Moreover, paternal care can encompass several motivational states (e.g., inhibition of aversion or aggression toward infants, attraction to infants) as well as multiple behaviors, which typically change across the period of infant development. In addition, different mechanisms may underlie the expression of paternal (or allopaternal) behavior in reproductively inexperienced males, new fathers, and experienced fathers. Thus, neural, hormonal, sensory, and experiential influences may differ both among the components of paternal care and over time. Furthermore, many, if not most, studies of paternal care have evaluated males' responses to unrelated young, which might not be expressed and/or mediated identically to responses toward a male's own infants. Therefore, we refer to males' behavior toward their own offspring as "paternal" and behavior toward non-descendant young as "allopaternal." Finally, the vast majority of studies on proximate determinants of paternal care have been conducted under highly artificial laboratory conditions; therefore, we cannot yet determine the precise role of these factors in natural settings.

With these caveats in mind, we summarize current understanding of the neural circuitry underlying parental behavior in mammals, followed by discussions of sensory, endocrine, and experiential influences on this circuitry and on the expression of paternal care. Our review of the neural circuity is based heavily on data from mothers, as limited data are available from fathers. In the remaining sections, however, we focus almost exclusively on males.

2 Neural Circuitry of Paternal Care

Building a complete model of the neurobiological basis of mammalian behavior is a daunting task; a legion of genetic, epigenetic, ontogenetic, and proximate causal factors influence a vast glial-neuronal network with intricate and myriad connectivities and signaling mechanisms. While all circuit diagrams are reductive, they do depict evidence-based theories of connectivity and function of nuclei implicated in behavior and therefore provide useful models to ultimately build a complete picture of a particular behavioral outcome. Furthermore, even incomplete information can shed light on distinct and shared mechanisms underlying behaviors and provide clues for understanding and treating disruptions of these behaviors.

One of the earliest parental-care circuit diagrams was published in 1988 by Michael Numan (1988). Since its inception, the parental-care circuit diagram has evolved substantially, with some versions depicting circuitry starting with sensory inputs and ending in motor outputs (Bridges 2015; Gammie 2005; Lambert and Kinsley 2012; Numan 2014; Olazábal et al. 2013; Zilkha et al. 2017). Contemporary parental-care circuitry diagrams are quite complex, as they integrate decades of

studies; a recent iteration depicts 23 brain nuclei involved in regulation of infant-directed behavior in rodents (Dulac et al. 2014). Here we produce another circuit diagram iteration of what we consider the core parental-care circuitry underlying the expression of infant-directed care in mammals.

2.1 Overview

Many circuit diagrams, including the one shown in Fig. 1, depict infant-related sensory information being funneled into the medial preoptic area of the hypothalamus (MPOA) and bed nucleus of the stria terminalis (BNST) via several pathways: sensory cues from several modalities are routed through the amygdala via the stria terminalis and amygdalofugal pathway; through the prefrontal cortex, brainstem, and septum via the medial forebrain bundle; and through the thalamus via projections from at least the intralaminar complex, which conveys suckling information to the MPOA (Berk and Finkelstein 1981; Cservenák et al. 2013, 2017; Chiba and Murata 1985; Hoover and Vertes 2007; Leonard and Scott 1971; Myers et al. 2014; De Olmos and Ingram 1972; Vertes 2004). The MPOA is hypothesized to integrate these inputs, a process influenced by the hormonal milieu, and to facilitate parental care in two ways: (1) by inhibiting nuclei in the aggression/fear circuitry, such as the

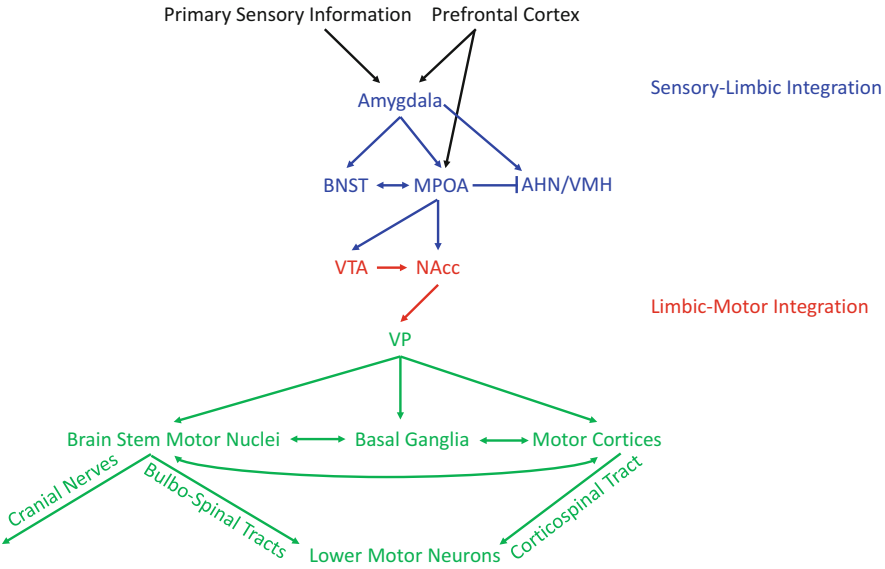

Fig. 1 Simple circuit diagram of parental care in mammals. Blue represents areas associated with sensory-limbic integration, red represents areas associated with limbic-motor integration, and green represents motor areas (see text for details). Abbreviations of brain areas: *BNST* bed nucleus of stria terminalis, *MPOA* medial preoptic area, *AHN* anterior hypothalamic nucleus, *VMH* ventromedial hypothalamus, *VTA* ventral tegmental area, *NAcc* nucleus accumbens, *VP* ventral pallidum

anterior hypothalamic nucleus, ventromedial nucleus of the hypothalamus, and periaqueductal gray, and (2) by exciting the reward circuitry via projections to the ventral tegmental area (VTA) and nucleus accumbens (NAcc). Thus, the MPOA has been conceptualized as a gate for infant-related stimuli to reach the mesolimbic reward pathway and mediate the hedonic tone of infant stimuli (Numan and Stolzenberg 2008).

The NAcc projects to the ventral pallidum. Together these nuclei have been referred to as the "final common pathway" (Mogenson 1987; Smith et al. 2009) for limbic information to influence motor systems, due in part to the ventral pallidum's projection to brainstem motor nuclei such as the pedunculopontine nucleus. The pedunculopontine nucleus sends descending projections to the spinal cord, as well as ascending projections to nuclei heavily implicated in voluntary behavior: the dorsal striatum, globus pallidus, and subthalamic nucleus, as well as supplementary, premotor, and primary motor cortices that contribute to signaling in Betz cells, the upper motor neurons of the descending corticospinal tract (Martinez-Gonzalez et al. 2011; Mena-Segovia et al. 2004; Winn 2006).

2.2 Medial Preoptic Area

Many studies implicate the MPOA in parental care in both males and females. In female rodents, the MPOA plays a key role in the expression of maternal behavior, as demonstrated by studies using a variety of techniques (e.g., lesions, stimulation, quantification of immediate-early gene expression, and glucose uptake) (Numan 2014). This brain region expresses receptors for prolactin, oxytocin, estrogen, and progesterone, hormones that fluctuate during the peripartum period in females; correspondingly, these hormones have been found to modulate maternal behavior, at least partly through actions on the MPOA (Ahdieh et al. 1987; Bosch and Neumann 2012; Bridges 1996; Bridges and Freemark 1995; Bridges and Mann 1994; Bridges et al. 1990; Brown et al. 2017; Fahrbach et al. 1986; Pedersen et al. 1994; Ribeiro et al. 2012).

Several studies have also implicated the MPOA in the expression of parental and alloparental behavior by males (Bales and Saltzman 2016), suggesting that paternal care in biparental species may be facilitated by increased activity in "maternal-care circuitry" present in mammals. For example, exposure to pups increases expression of the immediate-early gene protein product fos in the MPOA of fathers and/or allopaternally behaving virgin males in mice, rats, California mice, and prairie voles (De Jong et al. 2009; Horrell et al. 2017; Kirkpatrick et al. 1994a; Lambert et al. 2013). However, one study found no increase in fos expression in the MPOA of male California mice exposed to an unrelated pup compared to those exposed to a novel object (De Jong et al. 2010). In *Mus*, fathers that behave more paternally toward unrelated pups have greater fos expression in the MPOA following pup exposure than males that exhibit less allopaternal behavior (Tsuneoka et al. 2015). Stimulation of the MPOA increases paternal care, while lesions decrease paternal and allo-paternal care, including mate-dependent paternal care, in *Mus* (Akther et al. 2014;

Tsuneoka et al. 2015). Similarly, MPOA lesions in male rats prevent and disrupt pup-induced (i.e., sensitized) allopaternal behavior (Rosenblatt et al. 1996; Sturgis and Bridges 1997). MPOA lesions also disrupt paternal and allopaternal behavior in naturally biparental species such as the California mouse (Lee and Brown 2002, 2007).

Identification of the MPOA cells responsible for the effects observed in these lesion studies has proved more difficult. Colocalization of an immediate-early gene signal (fos, egr-1, or jun protein or mRNA) after parental-care behavior with a cell-type-specific marker can reveal which cell types, categorized by gene expression, are involved in paternal care. Such studies have implicated many cell types in maternal behavior (see Wu et al. 2014), with little evidence of the cell types involved in paternal care (Tsuneoka et al. 2017). Estradiol implants in the MPOA of male rats decrease sensitization times, demonstrating the MPOA to be an action site for estrogenic facilitation of allopaternal care in rats (Rosenblatt and Ceus 1998). Activity in MPOA neurons that express the neuropeptide galanin (Gal+ neurons), which are largely GABAergic, plays a causal role in paternal care in *Mus*: optogenetic activation of Gal+ neurons induced allopaternal behavior, while lesioning them reduced allopaternal care (Wu et al. 2014). These elegant experiments indicate that this Gal+ population is involved in paternal care, but it does not rule out possible roles for other neuronal populations in the MPOA, nor does it explain why only a subset of Gal+ neurons are active during paternal behavior. Recent work in female rats suggests that some Gal+ neurons are responsive to prolactin and receive thalamic projections responsive to nursing stimulation (Cservenák et al. 2017). Because males do not nurse, a role of these inputs in paternal care is questionable, though perhaps ventral tactile stimulation during thermoregulation/huddling may activate this pathway in males. The efferent connectivity of Gal+ MPOA neurons has yet to be determined.

Colocalizing indicators of neural activity can be paired not only with indicators of gene expression to increase our understanding of specific cell types involved in parental care but also with tracers to increase understanding of the functional connectivities of relevant neurons. The cells that express fos after maternal-care behavior in the MPOA of rats show a variety of efferent connectivities, including at least the ventromedial nucleus of the hypothalamus, lateral septum, VTA, and periaqueductal gray (Numan and Numan 1997; Numan and Sheehan 1997). Tsuneoka et al. (2013) suggest that a GABAergic pathway from the central MPOA to the rhomboid nucleus of the BNST regulates infant-directed behavior in male *Mus*. How this pathway relates to the Gal+ findings detailed above is not known. In particular, how distinct populations of MPOA neurons account for the enhancement of activity in reward circuitry and the decrease in activity in aggression circuitry (Numan 2014) in response to a pup stimulus is not understood.

2.3 Medial Amygdala

As with the MPOA, cues from multiple sensory modalities converge on the amygdala, which drives hypothalamic activity directly via the stria terminalis and amygdalofugal pathways. Medial amygdala (MeA) lesions facilitate maternal behavior in rats (Fleming et al. 1980; Numan et al. 1993; Oxley and Fleming 2000). In contrast, lesions of the MeA (or corticomedial amygdala) reduce allopaternal care in virgin male prairie voles (Kirkpatrick et al. 1994a). Lesions of the basolateral amygdala have been reported to decrease allopaternal care in California mice but not in prairie voles (Kirkpatrick et al. 1994a; Lee and Brown 2007).

Limited data are available on the MeA projections to the MPOA. In adult female rats that do not exhibit allomaternal care upon first exposure to pups, indiscriminate stimulation of the MeA produces inhibition or no response (and never excitation) in the MPOA (Gardner and Phillips 1977). The MeA also projects to many other nuclei, including hypothalamic regions associated with defensive and aggressive behaviors such as the anterior hypothalamic nucleus and ventromedial nucleus of the hypothalamus, which likely modulate infant-directed behaviors (Canteras et al. 1995).

The cell types in the MeA or other subnuclei of the amygdala that relay pup-related information to the MPOA or other brain regions have yet to be identified. After identification, investigation into the cues that influence the activity of these cells (e.g., olfactory and auditory cues from pups and mates, hormones, neuropeptides) can be conducted. The identification of these cells, the characterization of their properties, and manipulation of their activity would validate (or weaken) and extend hypotheses about the parental-care circuitry.

2.4 Mesolimbic Reward Pathway

The mesolimbic reward pathway plays a role in parental care, demonstrated mainly by research in female rats. Electrical lesions and $GABA_A$ and $GABA_B$ receptor agonists in the VTA reduce maternal care (Numan and Smith 1984; Numan et al. 2009). The VTA sends dopaminergic projections to the NAcc; however, the role of NAcc in parental care is debated. Some studies report that NAcc lesions profoundly decrease maternal care, while other studies report mixed, minor, or no effects (Lee et al. 1999, 2000; Li and Fleming 2003a, b; Numan et al. 2005; Smith and Holland 1975). The role of dopamine in NAcc is unclear as well. Dopamine levels in this region increase when rat dams interact with their young (Champagne et al. 2004; Hansen et al. 1993). Cis-flupenthixol, a nonspecific dopamine receptor antagonist, decreases retrieval and licking of pups as well as nest building, but so does cocaine, which increases dopamine levels (Keer and Stern 1999; Vernotica et al. 1999). Dopamine-depleting 6-hydroxydopamine lesions of the NAcc increase retrieval latency unless dams are deprived of pups

for 3–6 h before retrieval tests (Hansen 1994; Hansen et al. 1991). D1- and D2-type receptors are present in the NAcc: administration of a D1 receptor-specific agonist in the NAcc increases retrieval of pups, while a D1 receptor antagonist into the NAcc shell decreases retrieval (Numan et al. 2005; Stolzenberg et al. 2007). Administration of D2 receptor-specific antagonists in the NAcc shell has been shown to have no effect on or decrease maternal behavior in rats, while administration of a D2 receptor agonist in the NAcc has no effect on maternal behavior (Numan et al. 2005; Silva et al. 2003). These data led Numan and Stolzenberg (2008) to hypothesize that inhibitory D1 receptor signaling in the NAcc disinhibits the ventral pallidum, allowing for the expression of parental behavior, especially the appetitive components.

The preoptic area and ventral BNST (vBNST) are often thought to alter activity in the mesolimbic reward pathway in response to infant-related stimuli via projections to both the VTA and NAcc (Kaufling et al. 2009; Numan and Numan 1997). Both the vBNST and MPOA have glutamatergic and GABAergic projections to the VTA (Geisler et al. 2007; Jennings et al. 2013; Tobiansky et al. 2013, 2016); however, a role of these projections in parental care has yet to be demonstrated. Lesions of the central MPOA (cMPOA) disrupt parental behavior in female *Mus* more strongly than lesions of other regions of the MPOA, and the majority of neurons in the cMPOA that express fos after maternal behavior are GABAergic, while very few are glutamatergic (Tsuneoka et al. 2013). Interestingly, in female rats, the majority of cMPOA neurons that project to the VTA express estrogen receptors (ER), while almost none express progesterone receptors (Fahrbach et al. 1986; Morrell et al. 1984; Tobiansky et al. 2016), which strongly implicates estrogen in gating of pup-related information to the mesolimbic reward pathway through actions on the MPOA. Oxytocin+ and neurotensin+ neurons in the MPOA have also been demonstrated to project to the VTA in female mice and rats, respectively (Geisler and Zahm 2006; Shahrokh et al. 2010; Tsuneoka et al. 2013). Selective manipulation of the activity of any subpopulation of MPOA neurons (e.g., GABAergic, glutamatergic, neurotensin+, oxytocin+) that project to mesolimbic reward circuitry in the context of parental care has not yet been conducted in any species.

As mentioned above, the NAcc projects to the ventral pallidum in what has been called the final common pathway for limbic information to reach the motor system (Mogenson 1987; Smith et al. 2009). Along with the VTA, these areas are responsible for limbic-motor integration and ultimately the control of output (Fig. 1). Excitotoxic lesions or muscimol inactivations of the ventral pallidum decrease maternal behavior in rats (Numan et al. 1988, 2005). NAcc lesions mildly decrease pup retrieval in male California mice but do not affect retrieval in female California mice, partially supporting this view (Lee and Brown 2007). Ventral pallidum lesions decrease paternal care in *Mus* (Akther et al. 2014). Finally, the ventral pallidum projects to brainstem motor nuclei, such as the pedunculopontine nucleus, that project to the basal ganglia and motor cortices, thereby contributing to descending motor pathways (Winn 2006). Limbic areas including the amygdala, MPOA, and BNST are thought to integrate sensory information and facilitate the

activity of this part of the circuit to produce the appropriate infant-directed behaviors while suppressing aggressive behaviors (see Fig. 1).

3 Sensory Influences on Paternal Care

The expression of paternal and allopaternal care is influenced by numerous stimuli from both the internal and external environments, detected through multiple sensory modalities (Fig. 2; Brown 1993). Most studies have focused on cues from adult females and offspring. In biparental mammals, fathers typically begin to engage in paternal care after copulation and a period of cohabitation with their pregnant mate. Not surprisingly, therefore, cues from both the mate and pups, including olfactory, auditory, and tactile stimuli, can facilitate the onset and maintenance of paternal care and influence activity in the underlying neural circuitry. Additionally, copulation, specifically ejaculation, activates time-delayed neural mechanisms in male mice and rats, independent of further exposure to the

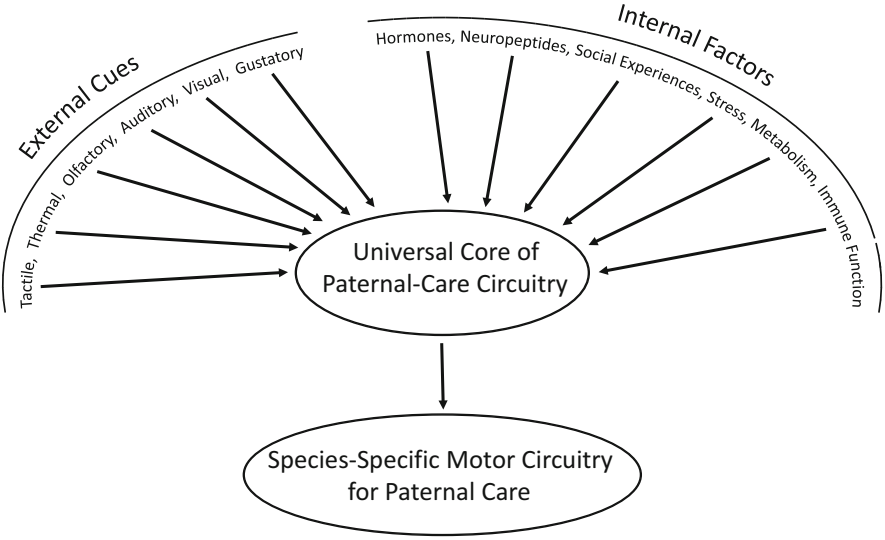

Fig. 2 Overview of external (environmental) and internal factors potentially influencing expression of mammalian paternal behavior via actions on the paternal-care neural circuitry. The specific factors affecting paternal behavior are likely to differ among and potentially within species and may change over time within individual animals based on such variables as age and parental experience. Moreover, these influences are likely to interact in complex ways. For example, social experience (e.g., mating, parental care received) might affect male parental behavior by eliciting changes in hormones (e.g., testosterone, estrogen), which in turn can alter signaling by neuropeptides (e.g., arginine vasopressin, oxytocin). Finally, influences on parental care can occur over different time scales. For example, exposure to specific hormones or neuropeptides during early development, or type of parental behavior received, can affect parental behavior expressed later in life, whereas sensory or metabolic cues might have more acute effects

mate, such that infanticidal behavior is inhibited and paternal behavior is promoted around the time that the males' pups are born (Brown 1993; Mennella and Moltz 1988b; vom Saal 1985). The relative importance of cues from copulation, from females, and from pups in both inhibiting aggression toward pups and facilitating paternal behavior differs markedly among species. Moreover, although olfactory cues play a key role in rodents, the roles of other sensory modalities are largely unknown.

3.1 Olfaction

Olfaction is a major sensory modality of rodents. Thus, it is not surprising that olfactory cues from females facilitate paternal care in multiple rodent species. In ICR mice (an outbred strain of *Mus*), olfactory cues from the mate both increase the number of fathers that retrieve pups and elicit fos expression in fathers' MPOA (Liang et al. 2014; Zhong et al. 2014). (Note that we specify strain of mice only when different results have been obtained in other strains.) In the biparental California mouse, fathers engage in high levels of paternal behavior after the birth of their own pups, but paternal responsiveness wanes within the first few days postpartum unless fathers are housed continuously with their mates or exposed to a chemosignal from their mates' urine; exposure to urinary chemosignals from an unfamiliar lactating female, rather than from the familiar mate, does not facilitate paternal care (Gubernick 1990; Gubernick and Alberts 1989). In male prairie voles, in contrast, paternal responsiveness rises following 3 days of housing and mating with a female, but olfactory cues do not appear to play a role in subsequent maintenance of this responsiveness: following removal from their mate, males continue to show high levels of paternal responsiveness whether or not they are continuously exposed to excreta from the female (Jean-Baptiste et al. 2008). Similarly, in Mongolian gerbils, first-time fathers show pronounced inhibition of infanticide around the time of the birth of their first litter, which is dependent upon interactions with the mate. Again, however, olfactory cues do not appear to be important: males removed from their mates during late pregnancy again become infanticidal toward unfamiliar pups, and this effect is not influenced by continuous exposure to excreta or soiled bedding from the mate (Elwood and Ostermeyer 1984).

The olfactory chemical messenger(s) that are emitted from females and influence paternal care have yet to be fully identified, but analyses of the composition of urine have been conducted in multiple species, including house mice and California mice (e.g., Idborg et al. 2005; Jemiolo et al. 1989, 1994; Plumb et al. 2003). Urine and secretions of the preputial gland have been implicated in maternal behavior (Brouette-lahlou et al. 1991b; Londei et al. 1989). In particular, dodecyl propionate, a component of preputial gland secretions, has been implicated in anogenital licking, a component of parental care in rodents. Further analysis of the exact olfactory chemosignals, their effect on olfactory neurons, the connectivity of those neurons,

and the modulation by hormones and neuropeptides implicated in parental-care behavior has not been conducted (Brouette-lahlou et al. 1991a).

In reductive parental-care circuitry diagrams, olfactory information is often portrayed as being relayed from the main and accessory olfactory bulbs through the MeA and then conveyed through the stria terminalis to hypothalamic nuclei, which alter activity in the mesolimbic reward circuitry. It is important to remember, though, that the main and accessory olfactory bulbs project to many nuclei, in addition to the MeA, that might influence parental care and, conversely, that hypothalamic nuclei such as the MPOA receive olfactory information from other nuclei besides the MeA (for reviews see Courtiol and Wilson 2014; Pro-Sistiaga et al. 2007; Spehr et al. 2006). Both the main and accessory/vomeronasal (VNO) olfactory systems have been implicated in paternal care in rodents (see below), and at least some main and accessory olfactory bulb signals are integrated in individual MeA neurons (Guthman and Vera 2016; Keshavarzi et al. 2014).

The main olfactory bulb has been implicated in infant-directed behaviors in males of several rodent species. Olfactory bulb lesions increase pup-directed aggression in virgin male prairie voles, which typically display allopaternal care (Kirkpatrick et al. 1994a, b). In adult virgin male rats, the opposite effect is seen: olfactory bulbectomy or zinc sulfate treatment of the nasal epithelium decreases sensitization times (Fleischer et al. 1981; Mayer et al. 1979). In C57BL6 mouse fathers, offspring recognition is at least partly mediated by the integration of newly generated interneurons in the main olfactory bulb and hippocampus (Mak and Weiss 2010).

Lesions or inactivation of the VNO in virgin male mice reduce infanticide and increase allopaternal behavior toward pups (Orikasa et al. 2017; Tachikawa et al. 2013; Wu et al. 2014). Similarly, VNO removal decreases infanticide in male rats (Mennella and Moltz 1988a). Until recently, the cell type(s) in the VNO that process pup-related cues implicated in paternal care were not known. Odorant receptor Olfr692 is highly expressed in the VNO of adult male mice, and correlational studies suggest that VNO sensory neurons expressing Olfr692 may play a crucial role in infant-directed behavior: exposure to pups, to pups encased in wire mesh balls preventing direct contact, or to ligands washed off pups increases expression of the immediate-early gene Egr1 in Olfr692-positive VNO neurons in virgin males, while exposure to odors from predators or adult conspecifics does not (Nakahara et al. 2016). Fathers exposed to unrelated pups show less activity in Olfr692-positive cells than virgin males, although the two groups have the same number of Olfr692-positive cells (Nakahara et al. 2016). Virgin females and mothers also have Olfr692-positive neurons in the VNO, but very few of these neurons express EGR-1 after pup exposure. These correlational studies are intriguing, but studies investigating the causal relationship between activity of Olfr692-expressing neurons and parental behavior remain to be conducted. Moreover, the pup-emitted ligand(s) for Olfr692 has not yet been identified. Other cell types in the VNO have not been investigated with respect to paternal behavior.

Although the bed nucleus of the accessory olfactory tract (BAOT) does not appear in many circuit diagrams to date, BAOT lesions decrease sensitization latencies in male rats (Cruz and Del Cerro 1998; Izquierdo et al. 1992). The

particular cell types in the BAOT that respond to pup cues, the properties and connectivities of those cells, and whether they undergo plasticity during the transition into fatherhood have yet to be determined.

3.2 Audition

Infants of virtually all mammalian species cry (i.e., produce age-specific vocalizations when distressed or separated from caregivers) (Newman 2007). Rodent pups produce a variety of vocalizations, some of which are ultrasonic (USVs). USVs may be produced in response to a change in temperature, olfactory stimuli, abnormal tactile stimulation, and/or loss of social contact (e.g., Conely and Bell 1978; Ehret 2005; Geyer 1979; Marchlewska-Koj et al. 1999). In *Mus*, production of USVs in the range of 40–80 kHz raises the pup's body temperature and elicits parental care (Blumberg and Sokoloff 2001; Ehret 2005). Fathers and virgin male *Mus* that have prior experience with pups, but not inexperienced virgin males, show a preference for modeled USVs compared to ultrasonic sounds dissimilar to pup USVs (Ehret 2005; Ehret and Buckenmaier 1994; Ehret and Koch 1989).

Vocalizations from female mates also elicit paternal care in *Mus*. Adult female ICR mice emit a series of 38-kHz USVs when deprived of their pups. When played back to their mates, these vocalizations can increase both retrieval of related pups and fos expression in the MPOA (Liang et al. 2014; Liu et al. 2013; Zhong et al. 2014).

In two biparental primate species, humans and common marmosets, fathers show enhanced behavioral or affective responses to infant distress vocalizations compared to non-fathers, suggesting that infant cries are more likely to elicit nurturing behavior from fathers (Fleming et al. 2002; Ziegler and Sosa 2016). Moreover, responses to infant distress cries are in some cases correlated with or influenced by hormone (estrogen, testosterone, prolactin) or neuropeptide (oxytocin) levels in adult males (Fleming et al. 2002; Li et al. 2017; Ziegler and Sosa 2016).

3.3 Somatosensation

Physical contact can promote paternal care in both rodent and human fathers. In prairie voles, males that have direct physical contact with their mate spend more time in contact with experimentally presented pups, compared to males that receive only distal cues from their mate (Simoncelli et al. 2010). Similarly, in Mongolian gerbils, inhibition of infanticide prior to the birth of a male's first litter appears to be largely dependent upon physical (and possibly visual) contact with the mate (Elwood and Ostermeyer 1984). Skin-to-skin contact between men and their infants has beneficial effects on both infants and fathers, including elevating fathers' feelings of attachment toward their infant (Chen et al. 2017; Cong et al. 2015; Shorey et al. 2016).

The neuroendocrine pathways by which tactile cues (except those from suckling infants) facilitate parental care in either sex are not well known. In primates and rodents, physical contact with an infant can stimulate release of both prolactin and oxytocin in mothers and potentially in fathers (Cong et al. 2015; Dixson and George 1982; Lonstein 2007), which in turn might promote nurturant behavior. At the level of neural circuitry, Seelke et al. (2016) found numerous differences in both extrinsic and intrinsic connections of S1 somatosensory cortex in adult prairie voles that had received different patterns of care, including different amounts of contact, from their own parents, which the authors categorized as "low-contact" and "high-contact" offspring. The two categories of prairie vole offspring express behavioral responses to infants consistent with the parental care that they themselves received (Perkeybile et al. 2015); thus, patterns of S1 connectivity are associated with both parental care received and parental care performed. It is unknown, however, whether these associations reflect causal or simply correlational relationships among parental care, tactile cues, and somatosensory cortex.

In female *Mus*, neurons in the posterior intralaminar complex of the thalamus that express tuberoinfundibular peptide of 39 residues (Tip39) are activated by suckling, project to neurons in the MPOA including galanin+ neurons, and play a role in maternal care (see Cservenák et al. 2017; Dobolyi et al. 2014). The posterior intralaminar complex may also convey auditory information to the MPOA (Campeau and Watson 2000; Dobolyi et al. 2014). The role of these pathways in male parental behavior, if any, has not been investigated.

3.4 Sensory Influences: Conclusions

Clearly, we are far from understanding the neural circuitry of sensory inputs influencing the expression of paternal care. In addition to the olfactory, auditory, and tactile cues discussed above, other types of sensory information from pups and/or mates (i.e., visual, thermal, gustatory), and possibly from other social or nonsocial sources (e.g., male rivals, predators), might converge on central paternal-care circuitry to facilitate or inhibit paternal behavior. Where and how different sensory systems act on core paternal circuitry, and potential interactions among diverse sensory inputs, are not fully understood. In ICR mice, for example, both auditory and olfactory stimuli from dams increase MPOA fos expression and elicit paternal care in their male mates (Zhong et al. 2014). Neither deafening nor anosmia alone decreases the percentage of ICR mouse sires that retrieve pups; however, concurrent deafness and anosmia abolish retrieval, suggesting redundancy between auditory and olfactory cues (Liu et al. 2013). Similarly, in female *Mus*, olfactory and auditory cues from pups presented simultaneously cause more fos expression in the MPOA than either stimulus presented alone (Okabe et al. 2013). In both males and females, it is unknown if olfactory and auditory cues from mates or pups converge on the same MPOA neurons. Compartment analysis of temporal activity by fluorescent in situ hybridization (catFISH), quantifying immediate-early gene expression

after sequential presentation of pup-related olfactory and auditory cues, would advance our knowledge of how multimodal sensory cues converge on core parental-care circuitry.

Finally, potential effects of fatherhood and its attendant neuroendocrine changes on plasticity within sensory systems have received little attention. In *Mus* fathers, however, interactions with neonates during the early postpartum period, likely involving physical contact, stimulate neurogenesis in the hippocampus and olfactory bulb, mediated by prolactin (Mak and Weiss 2010). These newly generated neurons respond preferentially to odors from the father's adult offspring and are thought to be involved in kin recognition. Further studies of effects of fatherhood and of so-called "paternal hormones" on sensory plasticity might yield fascinating insights into the proximate control of paternal behavior.

4 Hormonal and Neuropeptide Influences on Paternal Care

Similar to the multiplicity of sensory modalities involved in parental behavior, reviewed above, paternal care involves a confluence of changes in endocrine and neuropeptide signaling acting on multiple sites throughout the brain to orchestrate infant-directed behavior. Many studies in rodents and primates have identified hormonal fluctuations in males during the transition into fatherhood. In most cases, however, these changes have not been shown to have causal effects on the expression of paternal care (reviewed in Saltzman and Ziegler 2014) (Table 1).

Below we briefly review findings on potential neuroendocrine influences on paternal behavior and its underlying neural circuitry. We focus on several categories of steroid hormones (androgens, estrogens, progestagens, glucocorticoids), the peptide hormone prolactin, and the neuropeptides arginine vasopressin (AVP) and oxytocin, all of which have been implicated in paternal behavior in mammals. For each of these signaling systems, we first describe observed changes across reproductive states in fathers and correlations between hormone or neuropeptide levels and paternal behavior. Several recent papers provide detailed reviews of hormonal changes in mammalian fathers (Bales and Saltzman 2016; Gettler 2014; Saltzman and Ziegler 2014; Storey and Ziegler 2016); therefore, we discuss this topic rather briefly. We then review experimental evidence, where available, that these changes influence paternal care. Finally, we discuss known or postulated effects of these hormonal and neuropeptide changes on the neural circuitry underlying paternal care.

Table 1 Changes in circulating or excreted hormone levels of male mammals during the transition into fatherhood

Species	Androgens	Estrogens	Progesterone	Prolactin	Vasopressin	Oxytocin	Glucocorticoids
Norway rat (*Rattus norvegicus*)	nd	nd	nd	nd	nd	nd	nd
House mouse (*Mus musculus*)	nd	nd	nd	nd	nd	nd	nd
California mouse (*Peromyscus californicus*)	No change (Gubernick and Nelson 1989), decrease (Trainor et al. 2003)	nd	Decrease (Trainor et al. 2003)	Increase (Gubernick and Nelson 1989)	nd	Decrease (compared to expectant fathers, Gubernick et al. 1995), no change (compared to virgins, Gubernick et al. 1995)	No change (Chauke et al. 2011; Harris et al. 2013)
Prairie vole (*Microtus ochrogaster*)	nd	nd	nd	nd	nd	nd	No change (Campbell et al. 2009)
Campbell's dwarf hamster (*Phodopus campbelli*)	No change (Schum and Wynne-Edwards 2005), decrease (Reburn and Wynne-Edwards 1999)	No change (Schum and Wynne-Edwards 2005)	Increase (Schum and Wynne-Edwards 2005)	Increase (Reburn and Wynne-Edwards 1999)	nd	nd	Decrease (Reburn and Wynne-Edwards 1999)
Djungarian hamster (*Phodopus sungorus*)	Decrease (Reburn and Wynne-Edwards 1999; Schum and Wynne-Edwards 2005)	Decrease (Schum and Wynne-Edwards 2005)	No change (Schum and Wynne-Edwards 2005)	No change (Reburn and Wynne-Edwards 1999)	nd	nd	No change (Reburn and Wynne-Edwards 1999)
Mongolian gerbil (*Meriones unguiculatus*)	Decrease (Brown et al. 1995)	nd	nd	Increase (Brown et al. 1995)	nd	nd	nd

Volcano mouse (*Neotomodon alstoni*)	No change (Luis et al. 2009)	nd	nd	nd	nd	nd	nd
Striped mouse (*Rhabdomys pumilio*)	Decrease (Schradin and Yuen 2011)	nd	nd	Increase (Schradin 2008)	nd	nd	nd
Mandarin vole (*Microtus mandarinus*)	nd	nd	nd	nd	nd	nd	nd
Common marmoset (*Callithrix jacchus*)	Decrease (Ziegler et al. 2009b)	nd	nd	No change (but increases with infant contact: Mota and Sousa 2000; Mota et al. 2006), increase (Schradin et al. 2003)	nd	nd	nd
Wied's black-tufted-ear marmoset (*Callithrix kuhlii*)	Decrease (Nunes et al. 2000)	Decrease (Nunes et al. 2000)	nd	nd	nd	nd	nd
White-faced marmoset (*Callithrix geoffroyi*)	No change (Cavanaugh and French 2013)	No change (Cavanaugh and French 2013)	nd	nd	nd	nd	No change (Cavanaugh and French 2013)
Cotton-top tamarin (*Saguinus oedipus*)	No change (Ziegler et al. 2000)	nd	nd	No change (Ziegler et al. 2000)	nd	nd	No change (Ziegler et al. 2000)
Titi monkey (*Callicebus cupreus*)	nd	nd	nd	Increase (Schradin et al. 2003)	nd	nd	nd

(continued)

Table 1 (continued)

Species	Androgens	Estrogens	Progesterone	Prolactin	Vasopressin	Oxytocin	Glucocorticoids
Human (*Homo sapiens*)	No change (Magid 2011), decrease (Alvergne et al. 2009; Berg and Wynne-Edwards 2001; Gettler et al. 2011, 2013; Kuzawa et al. 2009; Gray et al. 2002, 2006; Gray and Campbell 2009; Storey et al. 2000; Van Anders and Gray 2007)	nd	Increase (Berg and Wynne-Edwards 2001), decrease (Storey et al. 2000)	nd	No change (Gray et al. 2007)	No change (Gray et al. 2007)	No change (Gray et al. 2007), decrease (Berg and Wynne-Edwards 2001)

Data from both longitudinal and cross-sectional designs are included. "Increase" and "decrease" refer to hormone levels of fathers at any time point after parturition compared to any time point before parturition or in non-fathers (e.g., virgins or mated males that have not produced offspring). *nd* no data

4.1 Androgens

4.1.1 Effects of Fatherhood on Androgen Signaling

Males in many species undergo decreases in circulating or urinary testosterone levels around the time of their mates' parturition. Among rodents, studies of biparental Campbell's dwarf hamsters, Mongolian gerbils, and California mice, as well as uniparental Djungarian hamsters (*Phodopus sungorus*), have found lower plasma testosterone levels in fathers after parturition than during their mates' gestation, before pairing, and/or virgin controls (Brown et al. 1995; Reburn and Wynne-Edwards 1999; Trainor et al. 2003). Other studies, however, have found no differences in plasma testosterone levels of fathers, mated males before parturition, and/or virgin controls in these same biparental species (Gubernick and Nelson 1989; Reburn and Wynne-Edwards 1999; Schum and Wynne-Edwards 2005) as well as in the biparental volcano mouse (*Neotomodon alstoni*) (Luis et al. 2009). Some of these disparities may be due to the lack of daily sampling, circadian effects on androgen levels, and/or the pooling of data from multiple days or weeks for analysis.

Among nonhuman primates, endocrine correlates of and influences on paternal care have been studied primarily in the New World callitrichid monkeys (marmosets and tamarins). Common marmosets and black-tufted-ear marmosets (*C. kuhlii*) have been reported to exhibit decreases in plasma or urinary testosterone levels from before to after their mates' parturition (Ziegler et al. 2009b; Nunes et al. 2000). Consistent with these findings, urinary testosterone levels and infant-carrying are negatively correlated in black-tufted-ear marmoset fathers (Nunes et al. 2001), and exposure to infant scents decreases plasma testosterone in experienced, but not inexperienced, common marmoset fathers (Prudom et al. 2008; Ziegler et al. 2009a). Other studies, however, report no change in testosterone levels in common marmosets, white-faced marmosets (*C. geoffroyi*), and cotton-top tamarins (Cavanaugh and French 2013; Dixson and George 1982; Ziegler and Snowdon 2000), and two studies found elevated urinary testosterone and dihydrotestosterone levels in the final month(s) of their mate's gestation in cotton-top tamarins (Ziegler and Snowdon 2000; Ziegler et al. 2004). Importantly, marmosets and tamarins typically undergo postpartum ovulation (Digby et al. 2007); consequently, the gestation and lactation periods may overlap substantially, complicating the interpretation of changes in males' endocrine function across reproductive stages.

Studies of humans, both cross-sectional and longitudinal, have found reduced salivary or plasma testosterone concentrations in fathers compared to non-fathers in a wide range of countries and cultures (reviewed by Gettler 2014; Storey and Ziegler 2016). Both within and between cultures, testosterone levels often correlate negatively with the amount of time men spend with their children, especially the amount of time in positive interactions. Although causality cannot be inferred from these correlational findings, several experimental studies have found that exposure to infant cues associated with negative affect (e.g., distress cries, sad facial expressions)

acutely elevate fathers' testosterone levels, especially when the fathers are not able to comfort the infant (see Storey and Ziegler 2016). Thus, engaging in caretaking behavior, rather than fatherhood per se, may suppress testosterone concentrations in human fathers.

4.1.2 Effects of Androgen Signaling on Paternal Care and the Underlying Neural Circuitry

Androgens can influence the expression of paternal behavior through both long-term organizational effects originating during early stages of development and acute activational effects later in life; however, these effects differ both within and among species. For example, early-life exposure to androgens reduces adult levels of alloparental responsiveness in male rats (McCullough et al. 1974; Rosenberg and Herrenkohl 1976) but increases alloparental responsiveness in adult male prairie voles (Kramer et al. 2009; Lonstein et al. 2002; reviewed in Bales and Saltzman 2016).

Activational effects of androgens on paternal responsiveness, like organizational effects, vary within and among species. In rats, administration of testosterone increases infanticide in males that were castrated in adulthood (Lubin et al. 1972; Rosenberg 1974; Rosenblatt et al. 1996). In California mouse fathers, on the other hand, castration reduces and testosterone replacement restores paternal and/or allopaternal behavior, an effect mediated, in large part, by aromatization of testosterone to estrogen (Trainor and Marler 2002). Similarly, in Mongolian gerbils housed in same-sex groups, testosterone increases allopaternal responsiveness in virgin males castrated in adulthood; however, treatment with either estrogen or dihydrotestosterone (which cannot be aromatized) has the same effect, suggesting that stimulatory effects of androgens in this species do not require aromatization (Martinez et al. 2015). Interestingly, opposite – i.e., inhibitory – effects of testosterone have been found in virgin male gerbils housed with a lactating female (Clark and Galef 1999). Studies of prairie voles have likewise yielded mixed results: castration either reduces (Wang and De Vries 1993) or does not alter (Lonstein and De Vries 1999) responses to unrelated pups in virgin males. Finally, castration did not alter paternal behavior in a study of Campbell's dwarf hamster fathers (Hume and Wynne-Edwards 2005).

Little is known about the neurobiological effects of androgen signaling that mediate paternal care, though substantial research has investigated effects of androgen signaling in limbic circuitry, including regions considered to be part of the parental-care circuitry. Androgen receptors are widely distributed in rat brain, including the limbic areas of canonical parental-care circuitry and throughout the olfactory and auditory sensory systems (Kritzer 2004; Simerly et al. 1990). Cellular effects of testosterone, at least in uniparental rodents, include increasing spine densities (Cunningham et al. 2007; de Castilhos et al. 2008; Garelick and Swann 2014; Zancan et al. 2017); modulating signaling by dopamine, nitric oxide, and substance P (Dees and Kozlowski 1984; Du and Hull 1999; Du et al. 1998; Hadeishi

and Wood 1996; Malsbury and McKay 1994; Swann and Newman 1992); and altering Na+/K+-ATPase activity (Guerra et al. 1987). Whether any of these effects contribute to androgenic modulation of paternal care is not known.

Testosterone also exerts organizational effects in the MPOA, often studied in the context of sexual behavior. These effects include modulation of cell death, cell morphology, opiate receptor expression, volumes of subnuclei, and astrocytic development (Arai et al. 1994; Dodson and Gorski 1993; Dohler et al. 1984; Hammer 1985; Jacobson et al. 1981; Mong and McCarthy 1999; Reddy et al. 2015; Roselli et al. 2007, 2015). Androgen levels during development also influence vasopressin levels (see below) in the BNST (Han and De Vries 2003). At least some of these organizational effects of androgens are mediated by intracellular aromatization to estrogen and subsequent binding to estrogen receptors (McCarthy 2010). Again, it is unknown which of these testosterone- or estrogen-dependent processes, if any, affect expression of paternal care later in life.

4.2 Estrogen

4.2.1 Effects of Fatherhood on Estrogen Signaling

Fatherhood can influence both circulating estrogen levels and central expression of estrogen receptors in rodents. Plasma estradiol concentrations in California mouse fathers are significantly higher than those of virgin males in the early postpartum period but not the mid- or late postpartum period (Hyer et al. 2017). In the biparental Campbell's dwarf hamster, on the other hand, fathers exhibit no changes in plasma estradiol levels during the transition into fatherhood (Schum and Wynne-Edwards 2005). Surprisingly, uniparental Djungarian hamster fathers undergo systematic fluctuations in plasma estradiol levels across reproductive stages: estradiol rises from before pairing to late gestation, decreases around parturition, and then significantly increases again at day 12 of the mate's lactation period (Schum and Wynne-Edwards 2005). The biological significance of these changes is not clear, since fathers in this species do not provide parental care.

ERα-immunoreactivity in several brain regions studied (MPOA, MeA, BNST) does not change during the transition into fatherhood in either biparental or uniparental hamsters (Timonin et al. 2008). Similarly, ERα mRNA expression in the MPOA, MeA, and BNST does not differ between California mouse fathers and virgin males (Perea-Rodriguez et al. 2015), although fathers in this species have higher activity of aromatase, the enzyme that converts androgens to estrogens, in the MPOA than non-fathers (Trainor et al. 2003). Mandarin vole fathers, in contrast to both hamsters and California mice, have lower ERα-immunoreactivity in the MPOA and BNST and higher ERα-immunoreactivity in the ventromedial nucleus of the hypothalamus, central nucleus of the amygdala, and MeA than virgin males (Song et al. 2010).

Findings to date do not suggest a consistent relationship between estrogen levels and paternal status in nonhuman primates: male common marmosets exhibit no changes in plasma estrogen concentrations from before to after their mate's parturition, while black-tufted-ear marmosets exhibit a decline or strong trend for a decline in urinary estradiol after parturition (Nunes et al. 2000, 2001; Ziegler et al. 2009a, b). White-faced marmoset fathers exhibit no change in urinary estrogen levels 2–8 weeks postpartum; however, no data were collected prepartum (Cavanaugh and French 2013). In paternally experienced, but not inexperienced, cotton-top tamarin fathers, urinary estrogen and estrone levels increase during the mate's late pregnancy (Ziegler et al. 2004), with no data collected after parturition.

Few studies have investigated the relationship between estrogen and fatherhood in men. Fathers were reported to have higher salivary estradiol levels than age-matched non-fathers in a small, cross-sectional study (Berg and Wynne-Edwards 2001); however other studies have found a decrease in men's estradiol levels during the partner's pregnancy or after parturition (Edelstein et al. 2015; Storey et al. 2000). Finally, no changes in estradiol were seen 40 or 70 min after fathers interacted with their toddlers (Gettler et al. 2013).

4.2.2 Effects of Estrogen Signaling on Paternal Care and the Underlying Neural Circuitry

Estrogen signaling has been found to both enhance and inhibit paternal care in rodents. Implantation of 17β-estradiol-releasing capsules in the MPOA of virgin male rats decreases sensitization latencies (Rosenblatt and Ceus 1998), implicating the MPOA as a site of action for estrogenic activation of paternal care. In ICR mouse fathers, aromatase immunoreactivity is stimulated by cues from the female mate and, more potently, suppressed by cues from pups, in brain regions implicated in paternal care, including the MPOA, MeA, NAcc, and ventral pallidum (Akther et al. 2015). Further, suppression of estrogen synthesis by the aromatase inhibitor letrozole inhibits retrieval of related pups by these mouse fathers (Akther et al. 2015). Deletion of either the aromatase gene or the ERα gene increases rates of infanticide and/or decreases expression of paternal behavior in male mice, but whether these effects reflect disruption of estrogen signaling in early life or in adulthood is not clear (Matsumoto et al. 2003; Ogawa et al. 1998). Estrogen also facilitates paternal behavior in California mouse fathers, as stated above (Trainor and Marler 2002). The site of the stimulatory effect of estrogen in this species is not known; however, fathers have higher aromatase activity in the MPOA than males housed with females that have not yet produced a litter (Trainor et al. 2003).

In contrast to uniparental rats and mice, as well as biparental California mice, estrogen inhibits paternal behavior in adult male prairie voles in a site-specific manner: increasing ERα expression in the MeA via viral vector decreases allopaternal behavior (Cushing et al. 2008), while increasing ERα expression in the BNST via viral vector has no effect (Lei et al. 2010). Finally, neither castration nor treatment with an aromatase inhibitor alters paternal behavior in Campbell's

dwarf hamster fathers, suggesting that estrogen does not play an important role in the maintenance of paternal care in this biparental species (Hume and Wynne-Edwards 2005, 2006).

The specific cellular mechanisms by which estrogen influences paternal behavior in rats, California mice, prairie voles, and perhaps other species are not known. In general, estrogen can exert both slow effects on target cells by binding to intracellular receptors and inducing changes in gene transcription and rapid effects by binding to membrane receptors and altering cellular activity through nongenomic mechanisms (for reviews see Alexander et al. 2016; Arevalo et al. 2015; Kow and Pfaff 2016; Mani et al. 2012; McEwen et al. 2012; Pfaff et al. 2011). Acting through these mechanisms, estrogen can influence numerous characteristics of preoptic area neurons, including electrical activity, neurogenesis, synaptic plasticity, neurotransmitter release, and cellular morphology (for reviews see Garcia-Galiano et al. 2012; Herbison 1997; Kelly et al. 2013; Ronnekleiv et al. 2012, Zhang et al. 2013). Estrogen modulates many signaling pathways in the preoptic area of rats, including GABAergic (Herbison 1997; Herbison et al. 1989, 1990), glutamatergic (Mahesh and Brann 2005), adrenergic (MacKinnon et al. 1985), noradrenergic (Kelly and Wagner 1999; Szawka et al. 2013), and oxytocinergic pathways (Caldwell et al. 1994; Champagne et al. 2001), among others (see Etgen and Pfaff 2010). In female rats, estrogen decreases excitability of MPOA neurons that project to the MeA (Yoshida et al. 1994). Thus, estrogen has many effects on neuronal signaling in the MPOA in at least some rodent species and therefore might alter activity of MPOA neurons that influence the occurrence of paternal care.

Although no research has been performed on males, intriguing studies have been conducted on the effects of estrogen and motherhood on responses to auditory cues in female rodents (Caras 2013; Liu and Schreiner 2007; Miranda and Liu 2009; Miranda et al. 2014). Estrogen receptors are located throughout the central auditory system in mice (Charitidi and Canlon 2010). In female mice and rats, ERα levels in the cochlea vary over the estrous cycle, as do behavioral responses to infant vocalizations (Charitidi et al. 2012; Ehret and Schmid 2009; Simonoska et al. 2009). Furthermore, estradiol has been implicated in the development of a preference for USVs in female mice (Koch and Ehret 1989). Aromatase and ERs are also expressed in the main and accessory olfactory bulbs of male rats and mice (e.g., Cherian et al. 2014; Dillon et al. 2013; Guo et al. 2001; Hoyk et al. 2014); however, their role in paternal care, if any, is unknown. Effects of hormones on sensory processing in fathers remain a promising area for further research.

4.3 Progesterone

4.3.1 Effects of Fatherhood on Progesterone Signaling

Little is known about associations between paternal care and progesterone signaling. Plasma progesterone concentrations are lower in California mouse fathers 2–3 weeks after the birth of their pups than in virgin males (Trainor et al. 2003). In the same species, however, expression of progesterone receptor mRNA in the BNST is lower in fathers than in virgin males (Perea-Rodriguez et al. 2015). In the biparental Campbell's dwarf hamster, males' circulating progesterone levels are elevated on the day of their mates' parturition, whereas uniparental Djungarian male hamsters do not show any change in plasma progesterone levels throughout their mate's gestation and lactation (Schum and Wynne-Edwards 2005). Progesterone concentrations of human fathers do not change across their partners' pregnancy and have not been studied under baseline conditions during the postpartum period (Edelstein et al. 2015); however, salivary progesterone levels decrease in fathers 40 and 70 min after they play with their infants (Gettler et al. 2013).

4.3.2 Effects of Progesterone Signaling on Paternal Care and the Underlying Neural Circuitry

In female rodents, high levels of progesterone typically inhibit maternal behavior during late pregnancy (Bridges 2015). Similarly, progesterone signaling increases infanticide and reduces paternal and allopaternal behavior in adult male house mice (Schneider et al. 2003, 2009). To our knowledge, however, effects of progesterone on paternal care have not been examined in biparental mammals.

The mechanism by which progesterone reduces paternal care in mice is unknown. Progesterone signaling modulates olfaction in the main and accessory olfactory bulbs, though a connection to parental care has yet to be made (Dey et al. 2015; Kanageswaran et al. 2016). Progesterone can also be metabolized into allopregnanolone, an allosteric modulator of $GABA_A$ receptors, in multiple nuclei, including the MPOA (for review see Henderson 2007). Interestingly, a recent genetic analysis of 32 primate species revealed that the biparental New World monkeys have progesterone response elements in the oxytocin receptor promoter region, implicating progestagenic regulation of oxytocin receptor expression in paternal care in this taxon (Vargas-Pinilla et al. 2015, 2017). Finally, estrogen and progesterone alter volumes of subregions of the MPOA in adult male rats (Bloch and Gorski 1988).

4.4 Glucocorticoids

4.4.1 Effects of Fatherhood on Glucocorticoid Signaling

The glucocorticoid hormones (primarily cortisol and corticosterone) have a multitude of effects on physiology, cognition, affect, and behavior under both baseline and stressful conditions (Sapolsky et al. 2000) and therefore seem likely to influence paternal care. Baseline concentrations of glucocorticoids are notoriously difficult to measure, due to the pronounced sensitivity of glucocorticoid secretion to environmental and organismal influences such as time of day, physical activity, food intake, and stress. Such effects may contribute to differences both within and between studies. Correspondingly, perhaps, findings on associations between glucocorticoid signaling and fatherhood or parental care have been highly variable. Among biparental rodents, for example, male Campbell's dwarf hamsters show a transient elevation of circulating cortisol concentrations during their mate's mid-pregnancy (Reburn and Wynne-Edwards 1999), whereas basal corticosterone levels of male California mice and prairie voles do not differ between fathers and non-fathers (Campbell et al. 2009; Chauke et al. 2011; Harris et al. 2013). Further, repeated exposure of virgin male California mice enhances their paternal responsiveness to unrelated pups but does not alter either baseline plasma corticosterone levels or corticosterone responses to pups (Horrell et al. 2017).

Among nonhuman primates, urinary glucocorticoid levels of male cotton-top tamarins increase around the mate's mid or late pregnancy (Almond et al. 2008; Ziegler and Snowdon 2000; Ziegler et al. 2004) and are lower in experienced fathers living with multiple offspring than in new fathers or unmated males (Ziegler et al. 1996). In black-tufted-ear marmosets, males that carry infants at high rates have lower cortisol than males that carry infants at low rates. White-faced marmoset fathers exhibit no change in urinary cortisol levels 2–8 weeks postpartum, with no data before parturition (Cavanaugh and French 2013).

In humans, salivary cortisol levels of expectant fathers have been reported both to increase during the partner's late pregnancy (Berg and Wynne-Edwards 2001, 2002; Storey et al. 2000) and to remain unchanged throughout pregnancy (Edelstein et al. 2015). Moreover, some studies report no difference in salivary cortisol levels between fathers and non-fathers (Fleming et al. 2002; Gray et al. 2007), while others report lower morning cortisol concentrations in fathers compared to non-fathers (Berg and Wynne-Edwards 2001). Cortisol levels decrease after fathers spend 30 min with their toddlers (Storey et al. 2011).

4.4.2 Effects of Glucocorticoid Signaling on Paternal Care and the Underlying Neural Circuitry

Surprisingly little is known about effects of glucocorticoids on mammalian paternal behavior. In virgin male prairie voles, acute exposure to a swim stressor

elevates circulating corticosterone concentrations and enhances paternal responsiveness to an unrelated pup; it is not known, however, whether the endocrine and behavioral consequences of the swim stressor are causally related (Bales et al. 2006). On the other hand, acute treatment of California mouse fathers with supraphysiological doses of corticosterone has little effect on pup-directed behavior (Harris et al. 2011). Moreover, exposure of California mouse fathers to a chronic variable stress paradigm can chronically elevate baseline corticosterone levels but causes only modest reductions in paternal care (Harris et al. 2013).

As there is very limited evidence to date that glucocorticoids affect paternal behavior, the relevant mechanisms mediating such effects remain poorly understood. However, research has begun to characterize effects of glucocorticoid signaling on social circuitry and behavior via genomic and nongenomic mechanisms (for reviews see de Kloet et al. 2008; Groeneweg et al. 2012; Haller et al. 2008).

4.5 Prolactin

4.5.1 Effects of Fatherhood on Prolactin Signaling

The anterior pituitary hormone prolactin has received significant interest as a "paternal hormone" (e.g., Hashemian et al. 2016; Schradin and Anzenberger 1999), as prolactin concentrations are elevated in mammalian fathers in numerous biparental species (e.g., rodents: Mongolian gerbils, California mice, and Campbell's dwarf hamsters [Brown et al. 1995; Gubernick and Nelson 1989; Reburn and Wynne-Edwards 1999]; primates: titi monkeys [*Callicebus cupreus*], Goeldi's monkeys [*Callimico goeldii*], common marmosets, and cotton-top tamarins [Ziegler et al. 1996; Dixson and George 1982; Schradin et al. 2003]). Prolactin levels can also be higher in experienced fathers than in first-time fathers (Ziegler et al. 1996, 2000, 2004), and acute changes in prolactin concentrations can occur in association with paternal care, especially tactile cues from infants. For example, common marmoset fathers have significantly higher plasma prolactin concentrations immediately after carrying their infants than at other times (Dixson and George 1982).

In humans, as in other biparental mammals, fathers have been reported to have higher baseline prolactin concentrations than non-fathers (Gettler et al. 2012), and baseline prolactin levels of fathers predict their emotional and behavioral responses to infants. For example, men with higher baseline prolactin concentrations have more positive feelings and more concern in response to infant cries and engage in more coordinated exploratory play with their infants (Fleming et al. 2002; Gordon et al. 2010; Storey et al. 2000). Human fathers also show acute changes in prolactin levels in response to interactions with or cues from infants; however, the direction of these changes is inconsistent: prolactin can either increase or decrease in response to stimuli such as hearing infant cries or holding an infant, effects that can be

modulated by the fathers' parity or previous experience with infants (Delahunty et al. 2007; Fleming et al. 2002, 2011).

4.5.2 Effects of Prolactin Signaling on Paternal Care and the Underlying Neural Circuitry

Prolactin promotes the onset of sensitized paternal behavior in virgin male rats (Sakaguchi et al. 1996). Studies in biparental mammals, however, have failed to support a stimulatory effect of prolactin on paternal care. In Campbell's dwarf hamster, treatment of first-time fathers with either bromocriptine, which antagonizes both the D1 and D2 dopamine receptors, or cabergoline, a selective D2 agonist, 1–3 days before the birth of their pups successfully reduces peripheral prolactin concentrations but does not impair paternal behavior (Brooks et al. 2005). Similarly, treatment of common marmoset fathers with cabergoline does not impair the expression of paternal behavior (Almond et al. 2006). Treatment of parentally inexperienced common marmosets with bromocriptine did reduce infant-carrying; however, only two males, including one juvenile and one adult, were tested (Roberts et al. 2001). Thus, in spite of the weight of published evidence documenting a positive association between prolactin and paternal behavior, experiments that pharmacologically reduce prolactin signaling in naturally paternal animal models do not support a causal link.

4.6 Vasopressin

4.6.1 Effects of Fatherhood on Arginine Vasopressin Signaling

The neuropeptide AVP acts both peripherally, where it plays a key role in regulation of fluid volume and the stress response, and centrally, where it influences aggressive and affiliative behaviors, affect, and cognition (Caldwell et al. 2008; Zimmermann-Peruzatto et al. 2015). Numerous correlational and experimental studies in several biparental rodents have implicated AVP, especially vasopressinergic projections from the MeA and BNST to the lateral septum and lateral habenular nucleus, in regulating paternal care (reviewed by Bales and Saltzman 2016; Frazier et al. 2006; Perkeybile and Bales 2017; Saltzman et al. 2017). Both within and among species, paternal behavior correlates with expression of AVP and/or AVP V1a receptors. For example, prairie vole fathers have reduced densities of AVP-immunoreactive fibers in the lateral septum and lateral habenular nucleus compared to virgin males and males housed with a pregnant mate, apparently due to increased synthesis and release of AVP from the BNST and MeA following both copulation and parturition (Bamshad et al. 1993, 1994). AVP expression in the paraventricular nucleus of the hypothalamus also correlates with paternal behavior in prairie voles (Perkeybile et al. 2013, 2015), mandarin voles (Wang et al. 2014), and California mice (De Jong

et al. 2012; Frazier et al. 2006), generally showing a negative relationship that may be associated with stress, anxiety, and/or activation of the hypothalamic-pituitary-adrenal axis (reviewed by Saltzman et al. 2017).

Few studies have examined the relationship between AVP and fatherhood in either nonhuman or human primates. In common marmosets, fathers have greater expression of AVP V1a receptors in the prefrontal cortex than non-fathers (Kozorovitskiy et al. 2006), whereas in humans, urinary AVP concentrations do not differ between fathers and non-fathers but are negatively correlated with the age of a father's youngest child (Gray et al. 2007). Urinary and circulating AVP levels likely reflect peripheral, rather than central, secretion, and AVP does not readily cross the blood-brain barrier; hence, the neural and behavioral relevance of these levels is not clear.

4.6.2 Effects of AVP Signaling on Paternal Care and the Underlying Neural Circuitry

Experimental manipulations of vasopressinergic signaling support a role of this neuropeptide system in paternal or allopaternal behavior. In both biparental prairie voles (Wang et al. 1994) and facultatively paternal meadow voles (*M. pennsylvanicus*) (Parker et al. 2001), infusion of AVP into the cerebral ventricles or lateral septum increases allopaternal behavior in adult virgin males, whereas similar treatment with AVP antagonists has the opposite effect. Manipulations of AVP (and oxytocin; see below) in nonhuman primates and humans have typically involved intranasal administration of the neuropeptide; however, the physiological relevance of this technique, as well as its efficacy in delivering neuropeptides to the brain, is controversial (Fortuna et al. 2014; Leng and Ludwig 2016). Intranasal AVP treatment of expectant human fathers increased interest in infant-related stimuli (baby-related avatars) in an immersive virtual environment (Cohen-Bendahan et al. 2015); however, intranasal AVP had no effect on fathers' responses to infant-related stimuli in another study of men (Li et al. 2017) and in a study of common marmosets (Taylor and French 2015). Effects of AVP on paternal behavior have not, to our knowledge, been examined directly in other species.

Very little is known about how vasopressinergic signaling modulates transduction or processing of infant-related stimuli and/or activity in the parental-care circuitry. AVP and its receptors are found in many nuclei (Barberis and Tribollet 1996; Kato et al. 1995); however, specific effects of AVP on specific neural substrates of paternal care have not been identified in any species.

4.7 *Oxytocin*

4.7.1 Effects of Fatherhood on Oxytocin Signaling

Like its sister neuropeptide, AVP, oxytocin acts both in the periphery, where it is essential for parturition and milk letdown, and in the brain, where it plays key roles in affiliative and maternal behavior, affect, and social cognition (Caldwell and Albers 2016). Studies of the prosocial effects of oxytocin have traditionally focused on females, whereas those on AVP have focused on males; however, recent evidence has implicated oxytocin in the expression of parental behavior in both sexes.

Oxytocin signaling differs between fathers and virgin males in several biparental and facultatively biparental rodent species, but not in a consistent manner. For example, mandarin vole fathers have higher numbers of oxytocin-immunoreactive fibers in the PVN and SON than virgin males (Song et al. 2010), and several studies of this species have found correlations between paternal behavior and oxytocin-immunoreactivity in the supraoptic nucleus and/or paraventricular nucleus of the hypothalamus (Li et al. 2015; Song et al. 2010; Wang et al. 2014). Paternally behaving meadow vole fathers have higher oxytocin receptor binding in several brain areas, including the BNST and lateral septum, than non-allopaternally behaving virgin males (Parker et al. 2001), whereas California mouse fathers have lower expression of oxytocin receptor mRNA in the BNST compared to virgins (Perea-Rodriguez et al. 2015). Studies of oxytocin-immunoreactivity and oxytocin receptor binding in prairie voles have yielded inconsistent results (Kenkel et al. 2014; Wang et al. 2000). Importantly, where differences between fathers and virgins have been detected, males differed not only in paternal experience but also in sexual experience and/or cohabitation with a female, which appears to contribute to differences in oxytocin signaling. Thus, effects of fatherhood per se on oxytocin signaling are not clear.

In a study examining in vitro hypothalamic release of several neurocrines in common marmosets, cultured hypothalamic explants from fathers released significantly more oxytocin (and significantly less dopamine) than those from virgin males; in contrast, AVP release did not differ between the groups (Woller et al. 2011). Salivary and/or oxytocin concentrations in human fathers rise during the first 6 months of fatherhood (Gordon et al. 2010), can be increased acutely by interactions with infants (Feldman et al. 2010), and correlate with several affiliative components of father-infant interactions (Gordon et al. 2010).

4.7.2 Effects of Oxytocin Signaling on Paternal Care and the Underlying Neural Circuitry

Surprisingly few experimental studies have evaluated effects of oxytocin on paternal or allopaternal behavior in animal models. In a recent, unpublished study of prairie voles, however, the oxytocin receptor antagonist L-368,899 acutely inhibited

allopaternal behavior in a dose-dependent manner (see Kenkel et al. 2017), while intranasal oxytocin (but not AVP) treatment increases interest in infant-related stimuli in adult male marmosets. In men, intranasal administration of oxytocin to fathers acutely enhances several components of father-infant interactions, such as positive vocalizations toward and touching of the infant. Several authors have suggested that interactions between oxytocin and paternal behavior may be modulated or mediated by steroid hormones (testosterone, Gordon et al. 2017; progesterone, Vargas-Pinilla et al. 2017).

Very little is known about how oxytocin signaling modulates transduction or processing of infant-related stimuli and/or activity in the paternal-care circuitry in males. The densest collections of oxytocin-containing cell bodies are in the supraoptic nucleus and paraventricular nucleus of the hypothalamus, although cell bodies can also be found in other hypothalamic nuclei and BNST of some species (Sofroniew 1983; Wang et al. 1996). Oxytocin fibers and/or receptors can be found throughout almost the entire brain, including regions critical for parental care such as the main and accessory olfactory bulbs, amygdala, and mesolimbic limbic reward circuitry (Lee et al. 2009; Ross and Young 2009). Oxytocin can be released both synaptically and non-synaptically, which is thought to result in diffuse activation of receptors (Landgraf and Neumann 2004).

One theory of how oxytocin influences parental care is that it reduces the sensitivity of $GABA_A$ receptors to steroids such as allopregnanolone, thus decreasing inhibitory tone in the parental-care circuitry (Koksma et al. 2003). Oxytocin may also act largely in the amygdala to reduce anxiety and neophobia around infants (Bale et al. 2001). Systemic oxytocin administration generally decreases basal- and stress-induced activity of the hypothalamic-pituitary-adrenal axis, which may facilitate parental care (reviewed by Landgraf and Neumann 2004). Oxytocin, perhaps originating from the paraventricular nucleus of the hypothalamus, can also act in the main olfactory bulbs to facilitate maternal care in rats; however, no experiments have been performed in males (Yu et al. 1996a, b).

5 Experiential Influences on Paternal Care and Neural Plasticity

Parental care exhibited by adult males can be influenced by a multitude of experiences occurring during prenatal, early postnatal, and juvenile development and into adulthood. A comprehensive discussion of these factors is beyond the scope of this chapter (but see Saltzman et al. 2017). Briefly, experiential influences on paternal behavior in rodents include intrauterine position (i.e., the number of adjacent brothers during prenatal development), quality and/or amount of parental care received, exposure to younger siblings, stress, cues from the mate and pups, and prior paternal experience. In some cases, these influences are associated with changes in hormonal (e.g., testosterone) or neuropeptide (e.g., AVP, oxytocin)

signaling in fathers. Much less is known about experiential effects in primates, but prior experience with infants affects responses of adult males to infant-related stimuli in common marmosets and humans (Storey and Ziegler 2016; Ziegler and Sosa 2016; Ziegler et al. 2009a).

Fatherhood can modulate plasticity in brain regions subserving cognitive, affective, and sensory functions in rodents and primates. Glasper et al. (2011) used the cell-division marker bromodeoxyuridine (BrdU) to evaluate patterns of neurogenesis in male California mice and found evidence that fatherhood inhibits neurogenesis in the hippocampus but not in the subventricular zone. A subsequent study by the same group (Hyer et al. 2016) found that proliferation of new cells in the dentate gyrus did not differ between non-fathers and fathers; however, fathers had reduced 1-week survival but increased 2-week survival of new neurons in the dentate gyrus, as well as a greater proportion of cells with a neuronal phenotype, effects that appear to be estrogen-dependent (Hyer et al. 2017). Franssen et al. (2011), in contrast, found no differences between California mouse fathers and virgin males in indices of hippocampal plasticity, including markers of cell proliferation, number of new neurons, restructuring in mature neurons, or astrocytes.

Fatherhood can also modulate neural plasticity in prairie voles. Lieberwirth et al. (2013) found evidence that fatherhood reduces the survival of new cells in the amygdala, dentate gyrus, and ventromedial hypothalamus, but not in the basolateral amygdala or main olfactory bulbs. In the house mouse, interactions of an adult male with its own pups increase neurogenesis in the father's subventricular zone and dentate gyrus, an effect mediated by prolactin signaling (Mak and Weiss 2010). Some of the new cells mature into olfactory interneurons in the olfactory bulb, where, as described above, they respond preferentially to odors from offspring and appear to function in recognition of mature offspring. Exposure to pups can elicit hippocampal cell proliferation in virgin prairie voles (Ruscio et al. 2008).

In the common marmoset, fatherhood increases spine density on pyramidal neurons in the prefrontal cortex (Kozorovitskiy et al. 2006). Human fathers show increased neural activation in response to pictures of children in several brain regions associated with processing of emotional facial expressions (caudal middle frontal gyrus), mentalizing (temporoparietal junction), and reward processing (medial orbitofrontal cortex), compared to non-fathers (Mascaro et al. 2014).

In sum, these findings from rodents and primates demonstrate that fatherhood can modulate proliferation and survival of neurons, as well as neuronal morphology, in several limbic structures, with pronounced differences among species in both the sites and mechanisms of plasticity. Given the effects of hormones, such as estrogens, on synaptic plasticity in brain areas such as the hippocampus (e.g., Ogiue-Ikeda et al. 2008), it is likely that hormones associated with paternal behavior may also have effects on synapses of the MPOA during the transition to fatherhood.

6 Conclusions and Future Directions

Much work remains to be done to validate, refine, and expand current theories of parental-care circuitry and to elucidate the mechanisms by which activity in this circuitry is modulated by sensory, hormonal, neuropeptide, and experiential factors. Parental-care circuit diagrams have been built mostly by decades of non-cell-type-specific examinations of certain nuclei, including knife cuts, electrolytic lesions, excitotoxic lesions, kindling, electrical stimulation, delivery of various chemicals via intracranial cannula, and quantification of immediate-early gene expression. While these techniques demonstrate that the activity of particular brain regions can affect parental behavior, we know little about which cell types within those regions are involved, what the properties and connectivities of those cell types are, and what plasticity occurs in those particular cells, if any, during the transition into fatherhood.

Future research should identify and characterize specific types of neurons in nuclei that have been implicated in paternal care. For example, optogenetic and chemogenetic techniques can target specific cell types based on gene expression and/or connectivity. To the best of our knowledge, only one study has been conducted using optogenetics to target a specific cell type in terms of either connectivity or gene expression (rather than all the cells in a particular brain region) and examine effects on paternal behavior (Wu et al. 2014). Colocalizing an immunohistochemical or in situ hybridization immediate-early gene signal with another immunohistochemical or in situ hybridization signal in individual animals that have or have not been exposed to infants will also increase our understanding of the cell-type-specific signaling within brain regions implicated in paternal care. New transgenics and gene silencing/inducible knockout techniques can also be used. Localization of immediate-early gene expression after pup exposure in combination with anterograde or retrograde tracers would also be useful in elucidating neural pathways associated with paternal care. With a contemporary toolkit, much will be revealed about the neuroendocrine basis of paternal care that was hidden previously, and paternal-care circuit diagrams will be much refined.

While several brain regions have been implicated strongly in paternal care, very little is known about how specific cell types in these regions change in terms of their gene-expression profiles, morphological properties, and electrophysiological characteristics during the transition into fatherhood. At an even more fundamental level, the MPOA, like many other brain regions, is also poorly characterized in terms of its basic synaptic, intrinsic, and morphological properties. An understanding of these circuit-level characteristics and how they change during the transition to fatherhood is vital for any understanding of larger issues of neural systems or sensory, hormonal, neuropeptide, or experiential influences. Recent preliminary data from California mice demonstrate that such properties can be recorded from MPOA slices and that these circuit properties undergo detectable changes in in fathers (Horrell et al. 2016).

Beyond mammals, a “common core” of paternal-care circuitry may exist across vertebrate taxa. For example, manipulating activity in the preoptic area can affect

paternal care in rodents, fish, and birds (Demski and Knigge 1971; Slawski and Buntin 1995; Tsuneoka et al. 2015). If such a "common core" exists, an explanation of how different infant-related sensory information gets funneled into this circuitry and how different parental behaviors emerge from it is needed. These are type-token distinctions: the "types" are infant-related sensory cues and parental-care behavior, and the "tokens" are distinct sensory information and distinct parental-care behaviors of various species. To give a particular example supported by experimental evidence, how does stimulating the preoptic area lead to suppression of infanticide and stimulation of pup grooming in male mice while leading to nest building in male cichlid bluegill (*Lepomis macrochirus*) (Demski and Knigge 1971; Fisher 1956; Wu et al. 2014)? As another example, how does lesioning the preoptic area in male mice decrease pup retrieval while lesioning it in male ring doves (*Streptopelia risoria*) decreases feeding invitations and bouts of feeding (Slawski and Buntin 1995; Tsuneoka et al. 2015; Wu et al. 2014)? The differences in circuitry across taxa that result in the activation of the same hypothalamic nuclei to produce quite different behavioral tokens of the same behavioral type is unknown and is one of the major frontiers in current neuroscience.

Multifunctionality of neurons should be considered as well. Should certain neurons that are active in parental care be considered particular "parental-care" neurons rather than general "prosocial behavior" neurons? For example, while MPOA lesions disrupt paternal care in a number of species, they also disrupt sexual behavior in every species studied thus far (Numan 2014). In fact, recent evidence using compartment analysis of temporal activity by catFISH suggests 20–30% overlap between neurons in the MPOA of mice that express fos during parental care and during sexual behavior (Wu et al. 2014). What are the exact neurons in the MPOA responsible for parental behavior vs. sexual behavior? What causes an MPOA neuron to express fos during parental-care and not during sexual behavior? What causes another MPOA neuron to express fos during both parental care and sexual behavior? Because of the likely multifunctionality of many neurons, analogous to genetic pleiotropy, structures and pathways identified as part of the "parental-care circuitry" may in fact be components of a more general "social circuitry" or other type of circuitry (Goodson and Kabelik 2009; Goodson and Kingsbury 2013). Moreover, within the general "parental-care circuitry" there are more specific circuits for different types of infant-directed behavior. For example, Rosenblatt and Mayer (1995) have posited theories of approach and withdrawal circuitries, and Numan (2014) has proposed theories of appetitive (e.g., retrieval) and consummatory (e.g., thermoregulating and grooming) circuitries in rodents. Thus, we should try not only to differentiate parental-care circuitry from other social circuitries but also to distinguish subtypes of parental-care circuitry. We should also specifically investigate multifunctionality, overlap, and communication between different circuits, as such inquiry may allow us to better understand phenomena like pseudokinship and alloparental care (conflations of kin and non-kin stimuli) and disorders of sociality such as infantile paraphilia and chronophilia (conflations of parental care-inducing and copulation-inducing stimuli).

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