Sexual Dimorphism of Parental Care: From Genes to Behavior

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Abstract

Parental care is found in species across the animal kingdom, from small insects to large mammals, with a conserved purpose of increasing offspring survival. Yet enormous variability exists between different species and between the sexes in the pattern and level of parental investment. Here, we review the literature on the neurobiological mechanisms underlying maternal and paternal care, especially in rodents, and discuss the relationship between sex differences in behavior and sexual dimorphism in the brain. We argue that although several brain regions and circuits regulating parental care are shared by both sexes, some of the fundamental components comprising the maternal brain are innate and sex specific. Moreover, we suggest that a more comprehensive understanding of the underlying mechanisms can be achieved by expanding the methodological toolbox, applying ethologically relevant approaches such as nontraditional wild-derived animal models and complex seminatural experimental set-ups.

Contents

INTRODUCTION

The classic definition for parental care was offered by Robert Trivers in the 1970s as "any investment by the parent in an individual offspring that increases the offspring's chance of surviving" (Trivers 1972, p. 139). Parental care is found across the animal kingdom from invertebrates up to humans (Royle et al. 2012), and evidence of male paternal care has even been found in fossils of the avian ancestral theropod dinosaur (Prum 2008). The level of parental care varies, for example, from solely laying eggs in a safe environment, in the case of turtles (Testudines) (Shine 1988), to the female of the Pacific giant octopus (*Enteroctopus dofleini*), which protects her 100,000 or so eggs for months, keeping them clean and constantly supplied with oxygen, without feeding herself, and dies soon after they hatch (Conrath & Conners 2014). Large variations in parental investment can also be seen within mammalian species. For instance, the European rabbit (*Oryctolagus cuniculus*) mother, like all lagomorph mothers, spends only a few minutes a day in the burrow with her offspring, during which lactation takes place (González-Mariscal et al. 2016). In contrast, female marsupials, such as kangaroos (*Macropus*), keep their offspring within a skin pouch, where it is permanently attached to a nipple for many months (Russell 1982). In nonhuman primates, the female orangutan (*Pongo pygmaeus*) cares for her young for up to 6–7 years (van Noordwijk & van Schaik 2005).

Uniparental care:
parental care of
offspring presented
solely by one parent

Biparental care:
provisioning of
offspring by both male
and female parents

Parental care can be carried out solely by the female or male (uniparental care) or by both sexes together (biparental care). Invertebrate parental care is very versatile; for example, tailless whip scorpion (*Phrynus marginemaculatus*) mothers care for their young alone for 11 months, and sea spider (*Ammothea hilgendorfi*) fathers carry the fertilized eggs on their legs until they hatch without assistance from the mothers (Barreto & Avise 2008). Vertebrates usually produce fewer offspring than invertebrates (Hendriks & Mulder 2008) and display a higher degree of parental care (Royle et al. 2012), whereas the sex differences and similarities in parental care vary between the classes. In fish, only 30% of species demonstrate parental care, among which paternal care is present in 50–80% of the cases and is more common than maternal or biparental care (Gross & Sargent 1985,

Reynolds et al. 2002). In the euryhaline tilapia (*Sarotherodon melanotheron*), for instance, only the male incubates the eggs and guards the young inside its mouth (Dugué et al. 2014). More than 80% of amphibians abandon their eggs after laying them; however, the remaining species present all forms of parental care (male/female uniparental or biparental), which can differ between closely related species, as seen in subspecies of poison frogs (family Dendrobatidae) (Roland & O'Connell 2015). Similar to fish and amphibians, most reptiles (>95%) present no parental care following egg laying, although most crocodilian (genus *Crocodylus*) mothers guard their nest and offspring (Ferguson 1985). No known reptile species present male uniparental care (Shine 1988). In avians, about 90–95% of species present biparental care of offspring posthatching, whereas females are sole caregivers of the chicks in approximately 5% of species and male uniparental care is found in only 1–2% of species. Both males and females can participate in building the nest, incubating the eggs, and feeding and protecting their chicks (Liker et al. 2015).

When it comes to mammals, parental care is present in all species (Royle et al. 2012), and the small variation lies mostly in the degree of parental care provided by the male. In most mammalian species, the involvement of the male ends following fertilization, as in the case of laboratory rats (*Rattus norvegicus*) (Lonstein & de Vries 2000); however, in 5–10% of species, males assist the female with parental care (Leuner & Sabihi 2016, Numan & Young 2016). These include species such as Djungarian hamsters (*Phodopus sungorus*), which actively assist their mate's delivery (Jones & Wynne-Edwards 2000), or golden lion tamarins (*Leontopithecus rosalia*), which play and socialize with their infants (Sussman 1999) as well as provide novel food to their juvenile offspring (Rapaport 2006). In titi (genus *Callicebus*) and owl (genus *Aotus*) monkeys, the father actually carries the infant for up to 90% of the time, transferring it to the mother only for nursing bouts (Dixson & Fleming 1981, Fragaszy et al. 1982). Notably, there are no known mammalian species in which parental care is completely carried out by the male (Kleiman & Malcolm 1981). Although in some mammalian species, males play a considerable role in providing protection and shelter to the offspring and food to support the mother (Kentner et al. 2010), the offspring have a fairly good chance of reaching adulthood without the father. However, they are completely dependent on maternal lactation during their early life (Jackson et al. 2014).

These enormous variabilities in parental care might lead us to inquire whether there is actually a conserved maternal brain that is shared by all mammals. Another open question concerns the connection between dimorphic behavior and dimorphic neural circuits (i.e., to what extent does the maternal brain differ from the paternal brain?). Finally, an emerging issue relates to the innate and learned nature of parental care, raising thoughts regarding the effects of past environmental experience on pup-caring behavior.
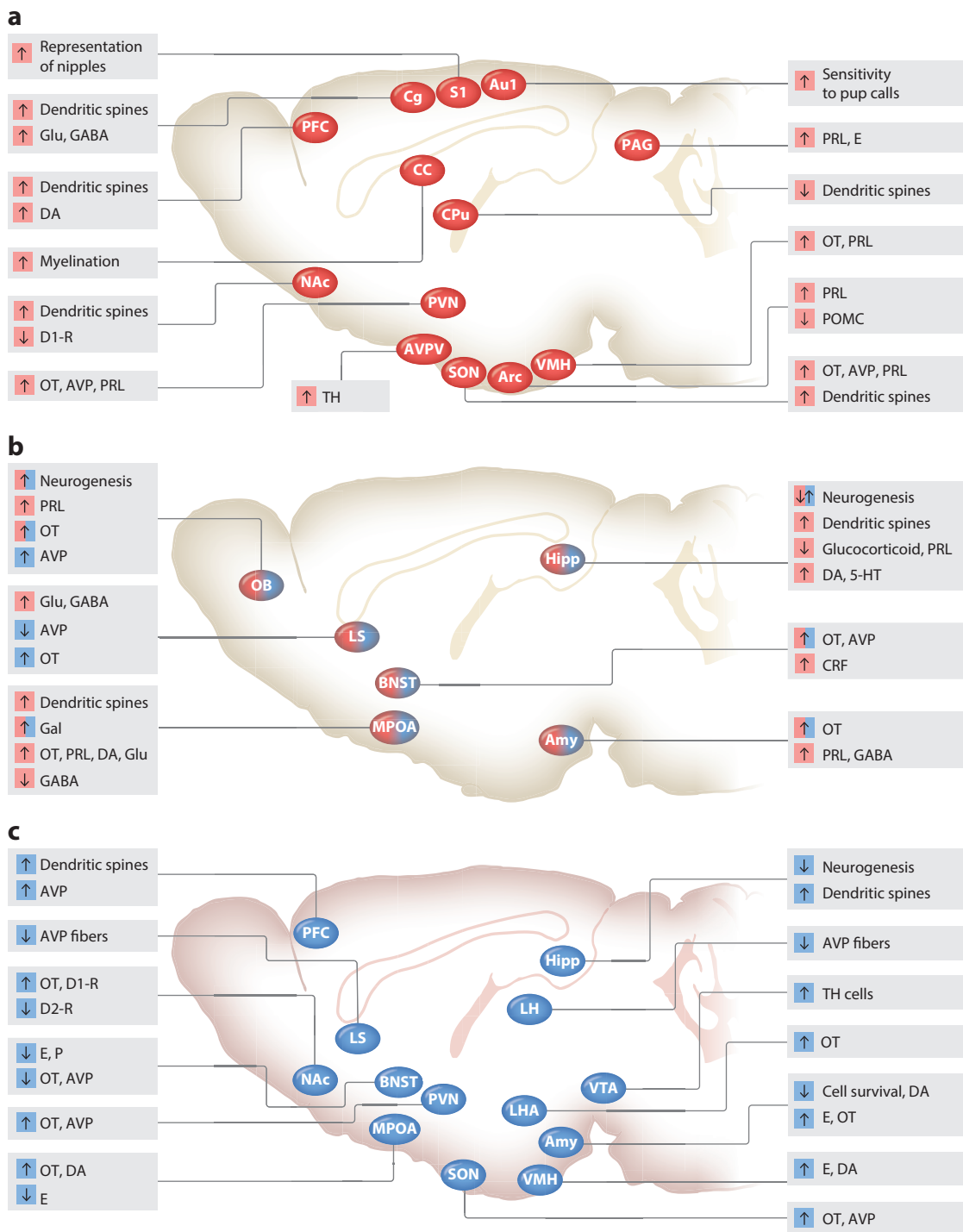
In this review, we analyze the concept of the maternal brain with emphasis on the mammalian female brain. We discuss the currently available literature on how the maternal brain is formed; what brain regions, cells, and molecules compose it; and how it differs from or is similar to the male brain. Finally, we analyze the relationship between sexually dimorphic neural circuits and sexually dimorphic behaviors in parental care.

THE MATERNAL BRAIN: WIRED FOR MOTHERHOOD?

As researchers have shown in many mammalian species, postpartum females present substantially higher degrees of maternal care compared to sexually naive (virgin) females. The difference between virgin and postpartum females can be simply quantitative, as in laboratory mice (*Mus musculus*) (Svare & Mann 1981) or naked mole-rats (Sherman et al. 1995), in which virgin females present spontaneous allomaternal care. In most cases, this difference is qualitative, as in wild mice (McCarthy 1990, Soroker & Terkel 1988), rats (Schultz & Lore 1993), hamsters (Swanson &

a

| ↑ Representation of nipples |
| ↑ Dendritic spines ↑ Glu, GABA |
| ↑ Dendritic spines ↑ DA |
| ↑ Myelination |
| ↑ Dendritic spines ↓ D1-R |
| ↑ OT, AVP, PRL |
| ↑ TH |

Cg S1 Au1
PFC
PAG
CC
CPu
NAc
PVN
AVPV SON Arc VMH

| ↑ Sensitivity to pup calls |
| ↑ PRL, E |
| ↓ Dendritic spines |
| ↑ OT, PRL |
| ↑ PRL ↓ POMC |
| ↑ OT, AVP, PRL ↑ Dendritic spines |

b

| ↑ Neurogenesis ↑ PRL ↑ OT ↑ AVP |
| ↑ Glu, GABA ↓ AVP ↑ OT |
| ↑ Dendritic spines ↑ Gal ↑ OT, PRL, DA, Glu ↓ GABA |

OB
LS
BNST
MPOA
Amy
Hipp

| ↓↑ Neurogenesis ↑ Dendritic spines ↓ Glucocorticoid, PRL ↑ DA, 5-HT |
| ↑ OT, AVP ↑ CRF |
| ↑ OT ↑ PRL, GABA |

c

| ↑ Dendritic spines ↑ AVP |
| ↓ AVP fibers |
| ↑ OT, D1-R ↓ D2-R |
| ↓ E, P ↓ OT, AVP |
| ↑ OT, AVP |
| ↑ OT, DA ↓ E |

PFC
Hipp
LS
LH
NAc BNST PVN VTA
MPOA LHA
SON Amy VMH

| ↓ Neurogenesis ↑ Dendritic spines |
| ↓ AVP fibers |
| ↑ TH cells |
| ↑ OT |
| ↓ Cell survival, DA ↑ E, OT |
| ↑ E, DA |
| ↑ OT, AVP |

Campbell 1979), and prairie voles (*Microtus ochrogaster*) (Bales et al. 2007), in which virgin females are spontaneously infanticidal toward alien pups. To prepare for maternal challenges, the female brain undergoes vast modifications that shape and adapt it throughout gestation, parturition, and lactation (reviewed in Bridges 2016, Champagne & Curley 2016, Leuner & Sabihi 2016, Pereira 2016) (**Figure 1**, **Supplemental Table 1**; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**). We use the term maternal brain to describe the female brain following these stages of pregnancy, delivery, and offspring exposure. In the following section, we present the known literature regarding the components of the maternal brain, examining to what extent they are hardwired or shaped by reproductive experience. We focus on the differences and similarities between the male and female parental brains, showing that there are in fact more distinctions than shared factors between the sexes. Yet some evidence indicates the existence of a single bipotential parental brain that is differently regulated in males and females by sex-specific elements such as hormones and sexually dimorphic neuronal populations (Dulac et al. 2014, Kohl et al. 2016).

Supplemental Material

The Expectant Brain: Effects of Pregnancy

Viviparity (live birth) is found in many vertebrate groups, including fish, amphibians, reptiles, and mammals (Lodé 2012). It is often considered a female-only trait, although there is an entire family of fish (Syngnathidae), comprising 233 species of seahorse and pipefish, in which the males incubate the fertilized eggs inside their body (Stölting & Wilson 2007). Mammalian viviparity (henceforth termed pregnancy) is different and more complex than in other classes. During gestation, a placenta forms and produces endocrine components promoting physiological and morphological changes in both the mother and embryo (Feldt-Rasmussen & Mathiesen 2011, Stölting & Wilson 2007). Researchers have assumed for several decades that at least some of the components of the maternal brain are formed during pregnancy, as classic studies have demonstrated that, compared to virgin female rats, pregnant rats undergoing a cesarean section during mid- or late pregnancy (from day 10 of pregnancy onward) display shorter latencies before presenting maternal behavior toward unfamiliar pups (Bridges 1977, Rosenblatt 1969). This effect was dependent on gonadal hormones, as rats ovariectomized during cesarean failed to show this effect (Rosenblatt 1969).

Some of the changes occurring in the female brain during pregnancy can be attributed to maintaining and supporting the fetus and pregnancy itself (Slattery & Hillerer 2016) and thus do not persist following parturition. In this review, we focus only on adaptations that commence during pregnancy and persist or are even enhanced during lactation. Of those, notable changes include increases in neurogenesis in the olfactory bulbs of dams and pregnant mice starting from

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Figure 1

Plasticity in the brain of parenting rodents. The major changes in morphology and gene expression occurring in the brain between sexually naive and postpartum parental rodents are shown. (*a*,*b*) Uniparental rodent species (i.e., rats, house mice, deer mice, meadow voles, and montane voles). Brain regions displaying modifications (*a*) in a female-exclusive pattern and (*b*) in both males and females are shown. (*c*) Brain regions with alterations in biparental males (i.e., California mice, mandarin and prairie voles). For further details, see **Supplemental Table 1**. Abbreviations: 5-HT, serotonin; Amy, amygdala; Arc, arcuate nucleus; Au1, primary auditory cortex; AVP, arginine vasopressin; AVPV, anteroventral periventricular nucleus; BNST, bed nucleus of the stria terminalis; CC, corpus callosum; Cg, cingulate cortex; CPu, caudate putamen; CRF, corticotropin-releasing factor; D1-R, dopamine receptor type 1; D2-R, dopamine receptor type 2; DA, dopamine; E, estrogen; GABA, γ-aminobutyric acid; Gal, galanin; Glu, glutamate; Hipp, hippocampus; LH, lateral habenula; LHA, lateral hypothalamic area; LS, lateral septum; MPOA, medial preoptic area; NAc, nucleus accumbens; OB, olfactory bulbs; OT, oxytocin; P, progesterone; PAG, periaqueductal gray; PFC, prefrontal cortex; POMC, proopiomelanocortin; PRL, prolactin; PVN, paraventricular nucleus; S1, primary somatosensory cortex; SON, supraoptic nucleus; TH, tyrosine hydroxylase; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

Nulliparous: a female that has never borne offspring

gestation day 7, an effect that is dependent on proper prolactin signaling (Shingo et al. 2003). In pregnant rats, studies have demonstrated increases in oxytocin (OT) signaling in various brain regions (Insel 1990, Young et al. 1997). Most changes have been shown in the hypothalamus, where researchers have also found increases in prolactin signaling in rats (Kokay et al. 2006, Torner et al. 2002) and mice (Salais-López et al. 2016), and increased synaptic densities in the medial preoptic area (MPOA) of rats (Keyser-Marcus et al. 2001). In addition, an increase in dendritic spine density was also found in the hippocampus of pregnant and postpartum rats (Kinsley et al. 2006) (**Figure 1**, **Supplemental Table 1**). Finally, a recent high-throughput analysis measured gene expression in four brain regions of virgin, pregnant, and postpartum mice and revealed hundreds of genes that are differentially expressed in different reproductive stages (Ray et al. 2016). Interestingly, in all brain regions examined, the overwhelming majority of changes were observed between the virgins and the other groups (i.e., pregnant or postpartum) (Ray et al. 2016).

Scientists assume that at least some of these modifications are driven by the dramatic fluctuations in hormonal levels during pregnancy (Bridges 2016, Stolzenberg & Champagne 2016). In rats, these include two daily increases in prolactin and a gradual increase in progesterone during the first half of gestation, followed by a gradual increase in estradiol during the final third of gestation and a rapid depletion of progesterone toward parturition (Bridges 2015). Indeed, classic attempts to mimic pregnancy-associated hormonal changes in nulliparous female rats by hormonal manipulation reduced the latency to full maternal behavior significantly (Moltz et al. 1970). The effects were also induced by a similar hormonal priming of progesterone followed by estradiol in hypophysis-intact rats or hypophysectomized rats given prolactin supplementation (Bridges et al. 1985).

In contrast to females, almost no empirical attempts have been performed to identify changes in neural circuitry or activity in males prior to the birth of their offspring (i.e., during their mate's gestation). However, in many rodents, including lab (Elwood 1985, Vom Saal 1985, Wu et al. 2014) and wild (Labov 1980, Soroker & Terkel 1988) mice, rats (Brown 1986), prairie voles (Bamshad et al. 1994), and Mongolian gerbils (*Meriones unguiculatus*) (Elwood 1977), following copulation, males reduce their level of infanticide. As the day of delivery for their future offspring approaches, these rodents display significantly less aggression and more parental care toward unfamiliar pups. In the case of lab mice, this effect occurs even without cohabitation with the mated female (Vom Saal 1985, Huck et al. 1982). Thus, we can assume that at least some of the neural alterations underlying the switching of pup-directed behavior from infanticide to parental care should also occur following mating and are independent of pup exposure. In line with this notion, studies in laboratory mice have shown that the gradual reduction of circulating testosterone in the period after mating is involved in inhibition of infanticide and induction of paternal responses toward unfamiliar pups (Perrigo et al. 1989, Svare & Mann 1981). Other studies performed in biparental prairie and mandarin voles (*Lasiopodomys mandarinus*) discovered several alterations in male fathers compared to sexually naive males, some of which were also present in expectant fathers during their mate's pregnancy. In prairie voles, densities of arginine-vasopressin (AVP) fibers in the lateral septum (LS) and lateral habenula (LH) were substantially reduced in early-pregnant mated males and to a lesser extent in fathers (Bamshad et al. 1994). Early-pregnant mandarin vole males were also similar to fathers in expression levels of OT and dopamine (DA) signaling factors in the supraoptic nucleus (SON), MPOA, nucleus accumbens (NAc), ventral tegmental area (VTA), and central amygdala (CeA) (Wang et al. 2015), whereas late-pregnant males resembled fathers in their increase in OT-expressing cells in the SON (Song et al. 2010). However, many other alterations found in fathers were absent in expectant fathers—for example, alterations in estrogen receptor densities in different brain regions of prairie voles, which were similar between sexually naive and mated late-pregnant males and significantly different from fathers (Song et al. 2010).

Nevertheless, some modifications in the paternal, as well as maternal, brains (detailed below) may have actually developed during pregnancy but have not been tested empirically before parturition.

The Postpartum Brain: Effects of Lactation and Offspring Care

Mammals are distinguished from other organisms by the ability of females to provide their young with milk secreted from the mammary glands, as newborn mammals are dependent on maternal milk as their primary nutritional source (Jonas & Woodside 2016). Lactation is induced by prolactin, which acts on mammary glands to initiate mammogenesis and milk production, and by OT, which promotes milk let-down upon suckling (Crowley 2011). Lactation is considered a female-exclusive quality trait, although mammalian male lactation (supplementary to female lactation) was discovered in two species of old world bats (*Dyacopterus spadiceus* and *Pteropus capistratus*) (Francis et al. 1994). Milk ejection in males has also been observed in humans following extreme cases of hormonal imbalance in released prisoners of war or in patients with pituitary tumors (Kunz & Hosken 2009).

During the lactation period and postpartum interaction with pups, the maternal brain undergoes additional substantial modulations (see **Figure 1** and **Supplemental Table 1** for more details). In humans, a recent functional MRI prospective study revealed that first-time mothers presented significant decreases in their gray matter volume compared to their prepregnant scan, specifically in areas related to social cognition such as frontal and cingulate cortices (Hoekzema et al. 2016). In rodents, the total weight of the brain is reduced in lactating females compared to virgin females (Hillerer et al. 2014, Shams et al. 2012), hippocampal neurogenesis is decreased (Brus et al. 2010, Darnaudéry et al. 2007, Glasper et al. 2011, Pawluski & Galea 2007), and dendritic branching is decreased in the dorsal striatum (Shams et al. 2012) and the amygdala (Rasia-Filho et al. 2004). By contrast, neurogenesis in the olfactory bulbs is increased in lactating female rodents (Kopel et al. 2012, Larsen & Grattan 2010), as is dendritic branching and synaptic plasticity in the MPOA (Gubernick et al. 1993), SON (Brussaard et al. 1999, El Majdoubi et al. 1997), hippocampus (Kinsley et al. 2006, Pawluski & Galea 2006, Tomizawa et al. 2003), and cortex (Leuner & Gould 2010, Salmaso et al. 2011). Indeed, researchers have found increased representations of pup cues in the auditory (Cohen & Mizrahi 2015, Marlin et al. 2015) and somatosensory (Xerri et al. 1994) cortices of lactating females. On the molecular level of the maternal brain, a recent high-throughput analysis identified 700 genes that are differentially expressed between virgin and postpartum female mice in several brain regions, including genes associated with reward pathways, social behavior, and hormonal signaling (Gammie et al. 2016). More localized studies showed widespread increases in expression and signaling of OT (Bosch et al. 2010, Driessen et al. 2014, Insel 1990), prolactin (Canavan et al. 2011, Pi & Grattan 1999), and vasopressin (Bamshad et al. 1993) (**Figure 1**). Increases were also measured in levels of γ-aminobutyric acid (GABA) and glutamate signaling factors (Arriaga-Avila et al. 2014, Zhao et al. 2012), as well as in signaling factors of monoamines (Macbeth et al. 2008), especially DA (Arriaga-Avila et al. 2014, de Moura et al. 2015, Matsushita et al. 2015).

Changes in DA signaling correspond to increased activation in the NAc and VTA (Gammie et al. 2005, Matsushita et al. 2015). In addition, these findings of increased activity in the dopaminergic reward system are in line with a large body of evidence demonstrating the robust salience of pup reward for lactating dams. Pup reward was even higher than artificial drug reward (Febo 2011, Ferris et al. 2005, Hauser & Gandelman 1985) or other natural rewards such as food (Fleming et al. 1994).

As in the case of pregnancy-induced changes, the vast majority of adaptations in the postpartum maternal brain were documented in the hypothalamus, especially in the MPOA and the adjacent

Supplemental Material

regions sending and receiving inputs from it (see **Supplemental Table 1** for more details). A recent study has highlighted a novel region within the hypothalamus that is sexually dimorphic and carries a crucial role in maternal care: the anteroventral periventricular nucleus (AVPV) (Scott et al. 2015). Tyrosine-hydroxylase (TH) dopaminergic neurons within this region present a high female bias in sexually naive mice and increase substantially in number in lactating females (**Figure 2**). By contrast, this neural structure is unchanged in parental male mice and is not involved in the control of paternal care (Scott et al. 2015) (**Figure 2**).

Modifications that do occur in the male paternal brain (see **Figure 1** and **Supplemental Table 1** for more details) should be distinguished between uniparental and biparental species. In
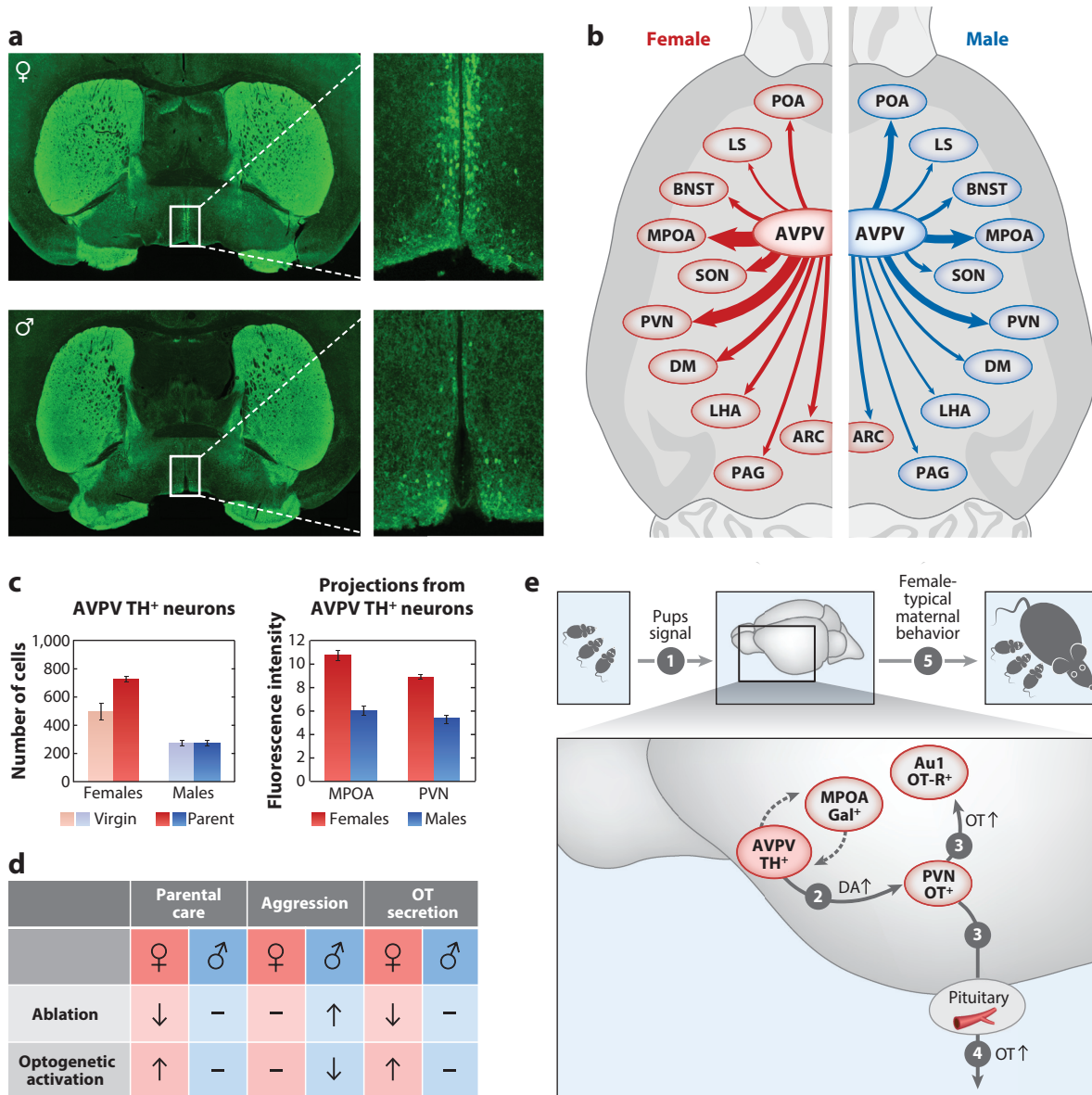
biparental prairie voles and California mice (*Peromyscus californicus*), neurogenesis is reduced in the hippocampus of fathers (Glasper et al. 2011, Lieberwirth et al. 2013), similar to the effect found in parental females. By contrast, in male laboratory mice, hippocampal neurogenesis is increased in fathers compared to sexually naive males (Mak & Weiss 2010). Increased neurogenesis has also been observed in the olfactory bulbs of parental male mice (Mak & Weiss 2010) but not in biparental male rodents (Glasper et al. 2011, Lieberwirth et al. 2013). Finally, analysis of the molecular differences discovered between fathers and sexually naive males showed that OT and oxytocin receptor (OT-R) expression is increased in various brain regions (Kenkel et al. 2014, Parker et al. 2001, Song et al. 2010, Wang et al. 2015) and in a similar manner in females and males of both uniparental and biparental males. In the bed nucleus of the stria terminalis (BNST), however, the number of OT cells in biparental prairie voles (Kenkel et al. 2014) and OT-R levels in biparental California mice are both reduced (Perea-Rodriguez et al. 2015) compared to virgin males. In contrast, fathers of uniparental meadow voles (*Microtus pennsylvanicus*) showed an increase in OT binding in the BNST region (Parker et al. 2001), which resembled the increase found in lactating female rats (Bosch et al. 2010). A parallel dichotomy in the BNST was found in expression of AVP, with reduced expression in biparental California mice fathers (Perea-Rodriguez et al. 2015) and increased expression in fathers of uniparental common deer mice (Lambert et al. 2011) and in mother rats (Bosch & Neumann 2010). Additional modifications in the male paternal brain are detailed in **Supplemental Table 1**.

▶ Supplemental Material

Taken together, it appears that several components of the maternal brain are found also in the paternal brain, such as increases in OT signaling; however, most of the modifications are female-exclusive, similar to the behavioral patterns of parental care. Moreover, the paternal brain in biparental species is differently structured compared to paternal brains of uniparental species and seems to resemble more closely the maternal brain. This implies the existence of conserved brain regions regulating parental care in both sexes across mammalian species.

The Preexisting Components of the Maternal Brain

Nulliparous females can also display maternal care (termed allomaternal), and this has been demonstrated in many mammals, including dolphins (Mann & Smuts 1998), elephants (Lee 1987), and monkeys (Förster & Cords 2005). Yet perhaps the most studied form of allomaternal care, which even includes arching over nest-retrieved pups in a lactating-like posture without actual milk

←——

Figure 2

Sexual dimorphism in the brain controls female-specific parental care: AVPV TH$^+$ neurons govern maternal behavior and OT secretion in female mice. (*a*) Immunostaining for TH, displaying a female-biased sexual dimorphism in the AVPV. Left panels show the whole brain, and right panels show enlargement of the AVPV region (indicated by *white boxes*). (*b*) Schematic of the sexually dimorphic projections from TH$^+$ AVPV neurons in adult males and females. The arrow thickness indicates projection density. (*c*) Quantification of TH$^+$ cells in the AVPV showing a female-exclusive increase in parental mice (*left*). Quantification of axonal projections from the TH$^+$ AVPV neurons to the MPOA and PVN regions revealing a female-biased dimorphism (*right*). (*d*) Summary of behavioral and endocrine phenotype following specific ablation or optogenetic activation of AVPV TH$^+$ cells in females and males. (*e*) Suggested model integrating recent cell-specific investigations into the neural basis of maternal behavior: ❶ Sensory signals from pups induce activation of TH$^+$ AVPV neurons, possibly in a cross talk with galanin-expressing MPOA neurons (Wu et al. 2014); ❷ activated TH$^+$ AVPV neurons stimulate OT-expressing PVN neurons; ❸ OT neurons in the PVN activate OT receptor–expressing neurons in the left auditory cortex (Marlin et al. 2015) and ❹ secrete OT into the blood; ❺ maternal behavior is facilitated. Figure adapted with permission from Scott et al. (2015). Abbreviations: ARC, arcuate nucleus; Au1, primary auditory cortex; AVPV, anteroventral periventricular nucleus; BNST, bed nucleus of the stria terminalis; DA, dopamine; DM, dorsomedial nucleus; Gal, galanin; LHA, lateral hypothalamic area; LS, lateral septum; MPOA, medial preoptic area; OT, oxytocin; OT-R, oxytocin receptor; PAG, periaqueductal gray; POA, preoptic area; PVN, paraventricular nucleus; SON, supraoptic nucleus; TH, tyrosine hydroxylase.

production (Lonstein et al. 1999), is found in laboratory mice and rats (Lonstein et al. 2015, Rosenblatt 1967). Sexually naive female rats might ignore pups upon the first encounter; however, repeated exposure (termed parental sensitization) will induce maternal care even in the absence of any hormonal or other physiological manipulations (Bridges et al. 1972). Similarly, wild, sexually naive female mice will typically ignore or attack foster pups (Jakubowski & Terkel 1982, Soroker & Terkel 1988), but prolonged exposure to pups with their parents can shift their behavior toward parental care (Jakubowski & Terkel 1982). In contrast, female laboratory mice, artificially selected to present high maternal performance and reduced aggression (Harper 2008) (see the section titled Methodological Issues in Studying Parental Care Using Animal Models), are usually spontaneously maternal. In fact, sexually naive female laboratory mice might present a high degree of maternal behavior even in the first encounter with foster pups (Chalfin et al. 2014, Kuroda et al. 2011, Scott et al. 2015). Evidence suggests that alloparenting behavior is not dependent on hormonal factors, as it was also demonstrated in female rats following removal of the gonads, adrenal gland, or pituitary gland (Rosenblatt 1967) and in estrogen-deficient (Stolzenberg & Rissman 2011) or hypophysectomized mice (Leblond & Nelson 1937).

These behavioral findings could indicate the existence of some innate components of the maternal brain that are not dependent on postfertilization events and hormonal modulation and might be activated upon pup exposure. Such sensitization-induced maternal care in sexually naive female rats was accompanied by increased activity in several regions identified as components of the maternal brain in postpartum females, as measured by c-Fos immunoreactivity, including the MPOA, BNST, cortical amygdala, and LH (Kalinichev et al. 2000, Numan & Numan 1994). Similar patterns of immediate early gene expression following pup exposure were also found in sexually naive female prairie voles, in which c-Fos expression was increased following pup exposure in the anterior olfactory bulbs, MPOA, medial amygdala (MeA), LS, and BNST (Kirkpatrick et al. 1994). In the MPOA of sexually naive female mice, Wu et al. (2014) identified similar activation of galanin-expressing neurons in postpartum and sexually naive females following pup exposure. Recently, a novel sexually dimorphic female-biased region was identified in the striohypothalamic nucleus of mice. The number of c-Fos immunoreactive cells in this region is reduced in virgin female mice following pup exposure, similar to what is observed in postpartum females (Moe et al. 2016).

However, most neural adaptations found in postpartum females are not found in maternally behaving virgin females and in some cases are even opposite in the latter, as in the case of hippocampal neurogenesis, which is reduced in postpartum female rats but elevated in virgin females following pup exposure (Pawluski & Galea 2007). Sensitization-induced or even hormonally primed allomaternal care in virgin females is still substantially inferior to that of postpartum females (Lonstein et al. 2015). In addition, allomaternal care usually does not contain a meaningful aggressive element in defense of foster pups (Ferreira et al. 2002, Martín-Sánchez et al. 2015). So, at least some of the components integrating the maternal brain apparently do not preexist in the virgin female brain but are rather forged during pregnancy, parturition, and lactation. Also, the maternal behavior of virgin females in response to pup exposure may be partly mediated through a different neural circuit that does not regulate maternal behavior in postpartum females. For example, maternally sensitized virgin rats show elevations in the number of c-Fos immunoreactive cells in the lateral preoptic area and cortical amygdala following pup exposure, whereas postpartum rats do not (Numan & Numan 1994).

In rodent males, researchers have also reported sensitization-induced paternal behavior of sexually naive individuals (Rosenblatt 1967). However, for wild mice, it seems to require prolonged exposure to a social environment in which the males cohabit with other parents and their pups and are exposed to both pup sensory cues and parental behavior displayed by fathers and mothers (Jakubowski & Terkel 1982). In laboratory rats, the duration of sensitization required was similar

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Parental sensitization: a procedure of repeated pup exposure, designed to induce parental care in nonparental individuals

in males and females; however, males did not reach the same level of parental performance as females (Rosenblatt 1967, Samuels & Bridges 1983). In addition, acute forced-swim stress has been shown to facilitate alloparental care in virgin male prairie voles but had no effect on virgin females (Bales et al. 2006). In contrast, allomaternal care of virgin female rats was associated with reduced levels of stress (Agrati et al. 2008, Ferreira et al. 2002). Unfortunately, the neural mechanism underlying this behavioral transformation in males has been very poorly examined and requires additional extensive research.

BRAIN SEXUAL DIMORPHISM IN PARENTAL CARE

The roles of males and females in parental care might often be substantially different (Dewsbury 1985); therefore, it is essential to examine to what extent the underlying mechanisms regulating this behavior are indeed sex specific. In this section, we examine the known elements in the neural regulation of parental care, focusing on sexually dimorphic components and their interaction with other factors controlling offspring-directed behavior (also see the sidebar titled Sexual Dimorphism in the Brain).

Brain Structures

Sexual dimorphism in morphology has been described in several brain regions involved in the pathway receiving inputs from the vomeronasal organ (VNO) (Beny & Kimchi 2014), which processes pup-related olfactory cues and regulates pup-directed aggression (de Vries & Villalba 1997). These include the accessory olfactory bulb (Segovia et al. 1984), bed nucleus of the olfactory tract (Collado et al. 1990), MeA (Hines et al. 1992), and medial BNST (del Abril et al. 1987, Hines et al. 1992); all are larger in males, and the differences are all dependent on sex-specific

Alloparental care: care of young presented by individuals other than their biological parents

Sexual dimorphism: a morphological, physiological, or behavioral difference between males and females of the same species

SEXUAL DIMORPHISM IN THE BRAIN

Sexual dimorphism in the brain can be found at the level of morphology, circuit connectivity, and molecular expression (Yang & Shah 2014). For example, morphological differences are found in songbirds, in which three out of four brain regions regulating vocal control are substantially larger in males than in females (Nottebohm & Arnold 1976). Morphological sexual dimorphism was also described in postmortem human studies, such as the sexually dimorphic nucleus in the hypothalamus (Swaab & Fliers 1985), which has been linked to sexual behavior and sexual orientation (Swaab & Bao 2013). An interesting example for dimorphism in circuit connectivity is found in *Drosophila*, in which researchers have identified a male-specific neural circuit including sensory, central, and motor neurons controlling male courtship behavior (Kohl et al. 2013, Stockinger et al. 2005, Stowers & Logan 2010, von Philipsborn et al. 2014). Recently, Oren-Suissa et al. (2016) elegantly demonstrated a female-specific mechanism of projections pruning in *Caenorhabditis elegans*. This developmental process forms a sexually dimorphic connectome between neurons found in both sexes, establishing the neural circuitry regulating sex-specific mating behaviors. In males of *C. elegans*, sex-specific interneurons derived from glial cells integrate into sex-shared neural circuits and thus mediate sexual associative learning (Sammut et al. 2015). At the molecular level, numerous studies describe sexually dimorphic patterns of gene expression in specific brain regions (Dewing et al. 2003, Werling et al. 2016, Yang et al. 2006). One of the comprehensive studies performed in this regard compared gene expression patterns between male and female brains in mice and revealed 16 novel genes that are regulated by sex hormones and present dimorphic expression in different brain regions. Through the use of knockout mice, four of these genes were shown to be crucial for sex-specific behaviors (Xu et al. 2012).

hormonal regulation during early development. Disruption of this pathway leads to inhibition of infanticide in male rats (Izquierdo et al. 1992, Mennella & Moltz 1988) and mice (Tachikawa et al. 2013, Wu et al. 2014) and in female wild mice (Chalfin et al. 2014), and to initiation of parental behavior in rats and mice of both sexes (Del Cerro et al. 1991, Fleming et al. 1979, Izquierdo et al. 1992, Numan et al. 1993, Tachikawa et al. 2013, Wu et al. 2014). By contrast, under seminatural conditions, female postpartum mice with disrupted VNO-mediated pheromone signaling showed impairments in maternal care (Kimchi et al. 2007).

In contrast to these brain regions, a marked female-biased sexual dimorphism was discovered in the AVPV, which is one of the few brain regions found to be larger in volume in females compared to males (Bleier et al. 1982) and contains significantly more neurons in females (Hoffman et al. 2005). On top of the gross morphological sexual dimorphism, the AVPV contains about four-fold more TH cells in females compared to males (Simerly et al. 1985, 1997), and these have been recently demonstrated to play a crucial role in the regulation of maternal behavior (detailed in the next sections).

Neuronal Projections

At the level of innervations, very few studies have linked sexual dimorphism with parental behavior. Earliest findings were concerned with vasopressin projections to the LS, which are substantially greater in males compared to females of several species, including rats (de Vries et al. 1981), mice (de Vries et al. 2002), gerbils (Crenshaw et al. 1992), and prairie voles (Bamshad et al. 1993, de Vries & Miller 1999). In parental prairie voles, this sexual dimorphism was retained but significantly reduced, as vole fathers presented lower levels of vasopressin fibers compared to virgin males (Bamshad et al. 1993, 1994). The sexual dimorphism in the vasopressin input to the LS may reflect the dimorphism in parental behavior, and its attenuation may enable biparental males to display parental care in a manner similar to parental females (de Vries & Boyle 1998). Indeed, the effect was absent in the closely related uniparental species of montane voles (*Microtus montanus*), in which vasopressin fibers in the LS were higher in males compared to females, regardless of reproductive state (Wang et al. 1994b).

The male-biased AVP inputs to this region originate mainly from the BNST and MeA (de Vries & Miller 1999). Interestingly, another brain region receiving innervations from these two areas in a sexually dimorphic manner is the AVPV, which receives about ten-fold more projections from the BNST and amygdala in males compared to females (Hutton et al. 1998, Polston et al. 2004). The AVPV itself, as described above, is also sexually dimorphic, but in a female-biased direction, and sends substantial projections to other brain regions, such as the MPOA, paraventricular nucleus (PVN), and SON, in a female-biased pattern (Forger et al. 2004, Scott et al. 2015, Simerly 2002). Importantly, these brain regions that receive female-biased AVPV TH input are not sexually dimorphic themselves. They are involved in parental care and OT secretion, however, suggesting AVPV TH neurons play a key role in the circuit regulating maternal care and in the sexual dimorphism of parental care (Scott et al. 2015) (**Figure 2**).

Hormonal Regulation

One of the earliest molecules implicated in parental care was the neuropeptide OT (Klopfer 1971), which is highly conserved across the animal kingdom and has been characterized as an essential regulator of offspring care in many species (Rilling & Young 2014). In female mice, genetic deletion of OT (Nishimori et al. 1996, Ragnauth et al. 2005) or OT-R (Rich et al. 2014, Takayanagi et al. 2005) did not induce severe impairments in maternal care, except for inability to nurse. However,

genetic knockouts might represent various developmental or compensatory mechanisms unrelated to the regulation of parental care (Kohl et al. 2016). In contrast, maternal behavior was enhanced in sexually naive female mice and rats following intraperitoneal (Marlin et al. 2015, McCarthy 1990), subcutaneous (McCarthy et al. 1986), or intracerebroventricular (Fahrbach et al. 1984, Pedersen & Prange 1979, Pedersen et al. 1982) administration of OT. In addition, a recent study showed that direct infusion of OT to the left auditory cortex, as well as cell-specific optogenetic stimulation of OT neurons in the PVN, facilitates pup retrieval in virgin female mice (Marlin et al. 2015). Researchers later showed that these PVN OT neurons are directly innervated by TH dopaminergic neurons in the AVPV that regulate maternal care, and that regulation of OT secretion by AVPV TH neurons is female specific (Scott et al. 2015). Also, administration of OT antagonists either intracerebroventricularly (Bosch & Neumann 2008, Fahrbach et al. 1985, van Leengoed et al. 1987) or directly to the MPOA or the VTA (Pedersen et al. 1994) impairs maternal behavior in lactating dams. Very few studies have examined the effects of OT manipulations on parental behavior in males (Bales & Saltzman 2016). Central administration of OT antagonist to sexually naive male prairie voles did not impair parental behavior by itself but did so only in combination with an AVP antagonist (Bales et al. 2004).

As for the neuropeptide AVP itself, either central administration of AVP or overexpression of AVP V1a receptor in the MPOA promoted maternal behavior in lactating rats, whereas central administration of an AVP antagonist or local virally mediated downregulation of AVP in the MPOA impaired maternal care in these animals (Bosch & Neumann 2008). Central administration of an AVP receptor antagonist in lactating rats increased maternal aggression in defense of pups (Nephew & Bridges 2008). Yet, when administered into the CeA (Bosch & Neumann 2010) or BNST (Bosch et al. 2010) of lactating rats, an AVP antagonist reduced maternal aggression (i.e., aggression toward adult intruders in defense of pups), whereas AVP increased it. In virgin female rats, central administration of AVP enhances (Pedersen et al. 1982), and AVP antiserum inhibits (Pedersen et al. 1985), the initiation of allomaternal behavior. In males, AVP by itself failed to impair allopaternal behavior in virgin male prairie voles when administered intracerebroventricularly (Bales et al. 2004). However, when administered locally into the LS, an AVP antagonist did reduce, and AVP increased, allopaternal responses in these animals (Wang et al. 1994a). In contrast, in uniparental meadow voles, centrally infused AVP enhanced, and an AVP antagonist impaired, parental behavior in virgin males (Parker & Lee 2001). Hence, the degree of sexual dimorphism in the role of AVP in parental behavior may be related to the degree of behavioral dimorphism itself (de Vries & Södersten 2009).

Prolactin plays a key role in the regulation of parental behavior across the animal kingdom. Virgin as well as lactating female mice with a null mutation in the prolactin receptor gene display deficits in pup retrieval (Lucas et al. 1998), and most pups born to heterozygous primiparous females bearing only one intact copy of the prolactin receptor (*Prl-R*) gene did not survive (Ormandy et al. 1997). Systemic administration of prolactin to nulliparous steroid-primed female rats reduces the latency to display full maternal behavior (Bridges et al. 1985, 1990), and a similar antagonist infusion increases the latency (Bridges et al. 2001). Similar effects were shown when researchers administered prolactin or a prolactin antagonist directly into the MPOA (Bridges et al. 1990, 2001). In males, recent work in mice has shown that *Prl-R*-deficient mice did not distinguish their own offspring from unfamiliar pups, and this phenotype was rescued by systemic administration of luteinizing hormone (Mak & Weiss 2010).

In virgin laboratory mice, maternal behavior appears to be independent of hormonal priming or the estrus cycle (Scott et al. 2015, Wu et al. 2014). In female rats, the hormonal priming of the brain toward full maternal care, either during normal pregnancy or an artificial regimen mimicking pregnancy, comprises mainly estrogen and progesterone (Moltz et al. 1970).

Administration of estradiol either subcutaneously (Siegel & Rosenblatt 1975a,b) or directly into the MPOA (Fahrbach & Pfaff 1986, Numan et al. 1977) enhances the onset of maternal behavior in virgin and pregnant rats. Inhibition of estrogen receptor α (Esr1) signaling in the MPOA of post-partum female mice using small interfering RNA severely impaired maternal behavior (Ribeiro et al. 2012), similar to genetic deletion of *Esr1* (Ogawa et al. 1998). In contrast, elevation of Esr1 expression levels in the MeA of male prairie voles significantly decreased alloparental behavior (Cushing et al. 2008). As for progesterone, although it plays a key role in the priming of the maternal brain toward parental care (Bridges 2015), artificial administration of high levels of pro-gesterone throughout late pregnancy and postpartum impaired maternal behaviors of rats (Bridges et al. 1978, Sheehan & Numan 2002). Thus, the rapid reduction in progesterone levels just before delivery (termed progesterone withdrawal) is apparently also important for functional maternal care. In males, progesterone receptor knockout virgin mice showed less aggression and elevated paternal care toward foster pups (Schneider et al. 2003). Similarly, systemic chronic administration of a progesterone receptor antagonist increased parental behavior of males, whereas an agonist treatment enhanced pup-directed attack (Schneider et al. 2003). Notably, sexually naive male rats can be induced to present full maternal behavior following a similar pregnancy-mimicking hor-monal regimen of estradiol and progesterone, administered either systemically (Rosenblatt et al. 1996) or directly into the MPOA (Rosenblatt & Ceus 1998). Unlike in females, however, this pro-cedure also involves complete abolition of testosterone, achieved by gonadectomy. Circulating levels of testosterone decrease in many vertebrate fathers compared to virgins, including cichlid fish (O'Connell et al. 2012), California mice (Trainor et al. 2003), Djungarian hamsters (Reburn & Wynne-Edwards 1999), common marmosets (*Callithrix jacchus*) (Ziegler et al. 2009), and humans (Gettler et al. 2011). Moreover, castration leads to a reduction in infanticide in mice (Svare & Mann 1981) and rats (Rosenberg 1974), which can be reversed by testosterone replacement.

Finally, a striking sexual dimorphism is found in the role of the stress hormone corticosterone. Numerous studies have demonstrated a general reduction in the plasma levels of glucocorticoids and in the activity of the hypothalamic-pituitary-adrenal (HPA) axis in postpartum females (for a review, see Slattery & Hillerer 2016). This reduced stress has proved essential for many processes of plasticity in the maternal brain, such as alterations in dendritic spine densities and neurogenesis in the hippocampus (Hillerer et al. 2014). Activating the HPA axis in lactating mice by administration of corticotropin-releasing factor agonists either centrally (D'Anna et al. 2005, Gammie et al. 2004) or directly to the LS (D'Anna & Gammie 2009) impaired maternal aggression but did not affect pup retrieval. In contrast, studies in males found no differences in basal glucocorticoid levels between fathers and virgin animals, and manipulating their levels usually did not produce any meaningful effects on paternal behavior (Bales & Saltzman 2016, Campbell et al. 2009, Harris & Saltzman 2013). The one exception was found in biparental prairie voles, in which acute stress promoted male paternal behavior without affecting female maternal behavior (Bales et al. 2006).

Neurotransmitters

The most studied neurotransmitter in the context of parental behavior is DA. Systemic administra-tion of DA antagonists severely impaired maternal behavior of postpartum female rats (Byrnes et al. 2002, Hansen et al. 1991b, Silva et al. 2001), and the effect was reversed by a DA agonist (Giordano et al. 1990). Local disruption of DA signaling in the NAc, but not in other striatal re-gions, produced similar effects (Keer & Stern 1999, Numan et al. 2005a, Parada et al. 2008, Silva et al. 2003). Likewise, specific ablation of dopaminergic neurons by 6-hydroxydopamine admin-istration to the NAc (Hansen et al. 1991a) or to the VTA (Hansen et al. 1991b) also impaired pup care in lactating female rats, whereas disinhibition of VTA neurons promoted maternal behavior

in virgin female rats (Byrnes et al. 2011). Specific activation of DA receptor type 1 (D1-R) in the NAc or MPOA via a selective agonist shortened the latencies to full maternal behavior in late-pregnant female rats (Stolzenberg et al. 2007). Also, selective antagonism of D1-R, but not DA receptor type 2 (D2-R), in the MPOA of lactating rats impaired pup retrieval (Miller & Lonstein 2005). However, selective ablation of TH-expressing neurons, most probably dopaminergic, in the MPOA did not impair maternal care in female mice (Wu et al. 2014).

In contrast to the MPOA, specific ablation of TH cells in the adjacent AVPV region severely impaired pup retrieval, reduced the duration of maternal care, and reduced plasma OT levels in both virgin and postpartum female mice (Scott et al. 2015). Also, optogenetic activation of these cells enhances maternal behavior and OT secretion. Notably, manipulation of AVPV TH neurons does not affect paternal behavior of males, but rather regulates intermale aggression (Scott et al. 2015). These findings suggest that DA might play a sexually dimorphic role in relation to parental behavior. Indeed, although studies examining the direct role of DA in male paternal care are scarce, it has been shown that repeated systemic administration of a D2-R agonist did not affect male paternal behavior in Djungarian hamsters (Brooks et al. 2005) or marmosets (Almond et al. 2006). By contrast, administration of the DA antagonist haloperidol reduced parental responses in both male and female biparental prairie voles (Lonstein 2002).

Another neurotransmitter involved in parental care is serotonin [5-hydroxytryptamine (5-HT)]. Specific ablation of 5-HT neurons in the medial raphe nucleus of postpartum female rats impaired nursing and pup retrieval and increased infanticide (Barofsky et al. 1983). Likewise, pharmacological research demonstrated that clozapine hinders maternal behavior by blocking 5-HT, as a specific 5-HT agonist reversed clozapine effects in lactating rats (Zhao & Li 2009). In addition, in two mouse strains with genetic null mutations of *Pet-1* and *Tph-2*, in which 5-HT transmission is disrupted, pup retrieval was substantially impaired and infanticide was increased (Alenina et al. 2009, Lerch-Haner et al. 2008). In males, a single study performed in paternal California mice showed an increase in c-Fos reactivity, specifically in 5-HT neurons in the dorsal raphe nucleus, following exposure to pups (de Jong et al. 2010). However, further research is needed to determine whether 5-HT might play some role in paternal behavior of males and whether the involvement of this neurotransmitter in parental behavior is sexually dimorphic.

Considerably fewer studies examined the direct role of other neurotransmitters in parental care. Yet researchers have found maternal behavior deficiencies in lactating rats after administration of GABA agonists into several brain regions, including the periaqueductal gray (Salzberg et al. 2002), medial prefrontal cortex (mPFC) (Febo et al. 2010), MPOA (Arrati et al. 2006), and ventral pallidum (Numan et al. 2005b). Additionally, unilateral infusions of a GABA agonist into the VP combined with contralateral excitotoxic lesion to the MPOA produced similar effects, suggesting that the MPOA facilitates maternal care through its GABAergic inputs to the NAc (Numan et al. 2005b). Administration of a GABA$_A$ antagonist to the LS of lactating mice impaired maternal aggression without affecting care of pups (Lee & Gammie 2009). To the best of our knowledge, no research has been conducted to explore the direct role of GABA transmission in parental behavior of males. Notably, the majority of galanin-expressing neurons in the MPOA are GABAergic, and these galanin neurons have been shown to play a key role in regulating both maternal and paternal behavior (Wu et al. 2014). This specific neuronal population was activated in both male and female parental mice following pup exposure, and their targeted ablation resulted in impaired parental behavior of both sexes and even induction of pup-directed aggression in virgin females. By contrast, optogenetic activation of MPOA galanin-expressing neurons in virgin male mice inhibited pup-directed attacks and promoted parental care in both virgin males and fathers (Wu et al. 2014).

Finally, a study in sheep found that blocking the noradrenergic pathway in the olfactory bulb with a norepinephrine antagonist caused lactating mothers to lose the ability to recognize their

offspring (Lévy et al. 1990). A similar effect was seen in cesarean-sectioned rats, in which a nor-epinephrine antagonist impaired the facilitating effect of a brief pup exposure on maternal behavior (Moffat et al. 1993). Consistently, female mice completely lacking noradrenaline show marked deficits in maternal behavior (Thomas & Palmiter 1997). Conversely, increasing norepinephrine levels in the BNST and MPOA compromised maternal behavior of lactating rats (Smith et al. 2012), and lesioning noradrenergic projections to the hypothalamus produced only a partial impairment in nest building and lactation (Bridges et al. 1982). Similar to the limited research on GABA, we could not find any studies exploring the direct role of noradrenaline in the regulation of parental behavior in males.

The Parental Brain in Males and Females: Shared or Sex-Specific?

To elicit the maternal performance necessary for offspring survival, the female brain has to be forged into the maternal brain. Although some aspects underlying maternal care, as seen in allo-maternal females, are hardwired circuits that preexist in the female brain, some crucial elements in the maternal brain are shaped only through gestation, pup exposure, and lactation (Champagne & Curley 2016, Pereira 2016). Some of these components can also be found in parental males (Kohl et al. 2016, Leuner et al. 2010), as researchers have identified the involvement of regions such as the olfactory bulbs, MPOA, LS, BNST, amygdala, and PFC in both maternal and paternal behavior (de Jong et al. 2009, Gubernick et al. 1993, Kirkpatrick et al. 1994, Lee & Brown 2007, Parker et al. 2001, Wu et al. 2014). However, closer and more specific observations within these brain regions and others, allowed through advanced molecular techniques, revealed sex-specific features in the neurobiology of parental behaviors. For instance, optogenetic activation of galanin neurons in the MPOA elevated parental care in both male and female sexually naive mice; however, it induced pup retrieval only in the females (Wu et al. 2014). Moreover, similar activation of TH neurons in the AVPV induced maternal behavior and OT secretion in females but had no effect on either in males (Scott et al. 2015). Likewise, specific silencing of OT signaling in the mPFC impaired social behaviors of female but not male mice (Nakajima et al. 2014), whereas specific activation produced anxiolytic effects in males alone (Li et al. 2016). These findings suggest that both the specific wiring of the parental circuitry and its regulation are at least partly different between males and females, allowing sex-specific behaviors (**Figure 1**, **Supplemental Table 1**). Whereas many of the brain regions and circuits are shared by male and female parents, most of the factors regulating them, especially sex hormones, modulate sex-specific behaviors.

Nevertheless, we emphasize that one of the key problems with identifying sexual dimorphism in the neural circuitry underlying parental behavior is methodological, as the vast majority of studies in this field were performed only in females (Zilkha et al. 2016). Furthermore, most of the research on parental care in males focused on biparental species (Bales & Saltzman 2016) (see **Supplemental Table 1**), which do not reflect typical sexual dimorphism as it usually appears in most mammalian species (Bamshad et al. 1993, Lambert et al. 2011, Reburn & Wynne-Edwards 1999). Thus, in many cases, it is unclear whether a neural circuit governing parental behavior is truly female-exclusive or has simply never been examined in uniparental males. A recent study that did examine both sexes of a uniparental species showed that a crucial circuit governing maternal care in female mice—TH neurons in the AVPV—has no effect on male paternal behavior (Scott et al. 2015).

METHODOLOGICAL ISSUES IN STUDYING PARENTAL CARE USING ANIMAL MODELS

The modern scientific examination of parental care was established half a century ago by Jay Rosenblatt (1967) and his colleagues, who showed that prolonged and repeated exposure of virgin

female rats to unfamiliar pups induces behaviors of maternal care, in a process termed maternal sensitization. These scientists then discovered the hormonal regulation of maternal care by transferring blood transfusions from lactating dams to sexually naive females or administrating various female hormones to ovariectomized rats, which also resulted in induction of maternal behavior (Moltz et al. 1970, Terkel & Rosenblatt 1968).

Current behavioral neuroscientists use molecular and tissue-specific approaches such as optogenetics and calcium imaging to study specific neuronal populations, which have already led to novel discoveries. These include, for instance, the role of aromatase-expressing neurons in the MeA of female mice in maternal aggression (Unger et al. 2015) or the mediation of response to pups by OT-R neurons in the left auditory cortex (Marlin et al. 2015) and by newly born neurons in the olfactory bulbs (Kopel et al. 2012). Nonetheless, the questions that must be raised are whether standard laboratory methodologies actually represent real-life parental care and whether they are the most appropriate for examining the neurobiology of reproductive behaviors, especially parental care.

Studying Parental Care in the New Era: Are We Doing It Right?

As detailed in the preceding sections, the vast majority of scientific data in the field of parental behavior was collected using a limited reservoir of animal models, mostly domesticated rats and mice, tested under standardized laboratory conditions. These studies are severely biased in three key elements: the examined sex (Beery & Zucker 2011), the chosen animal model (Brenowitz & Zakon 2015), and the environmental setup (Peters et al. 2015, Spruijt et al. 2014). The influence of these biases in the research of social and reproductive behaviors has been reviewed recently elsewhere (Zilkha et al. 2016). For the purpose of this review, we focus only on the elements relevant to the methodology of investigating parental care.

The first bias in parental behavior research, that of the examined sex, is discussed in the previous section. Here we discuss bias in the chosen animal model. In the first few decades of research, almost all the empirical research of parental care employed female rats, either lactating or virgins undergoing hormonal priming or repeated pup sensitization (Bridges 2015). In recent years, the introduction of advanced genetic tools such as developmental knockouts and, later, conditional gene expression shifted some research efforts into laboratory mice (Brenowitz & Zakon 2015). Yet the focus on these two rodent strains profoundly reduces the potential behavioral repertoire that can be examined to that typically presented by these model animals. This effect is quite noticeable in the field of parental care, which is considerably varied across the animal kingdom and even within the mammalian class (Dulac et al. 2014, Royle et al. 2012). For example, rats and mice cannot be used to examine the neurobiology of biparental care of offspring, found in approximately 5% of mammalian species (Numan & Young 2016) and in much higher proportions in other classes (Lynn 2016, Roland & O'Connell 2015). Rats and mice are also unsuitable models to study aspects of selective parent-offspring bonding found in herding animals such as sheep (Nowak et al. 2011) or parent-offspring exclusive attachment found in some primates, including humans (Feldman 2016). Moreover, laboratory rats and especially mice have undergone considerable processes of domestication and selective inbreeding, which have transformed their social communication traits (Hurst et al. 2001, Thoß et al. 2016) and abolished many behavioral traits encompassing the core behavioral repertoire of parenting and pup-directed responses (Price 1999, Thoß et al. 2011). First, laboratory mice present early sexual maturation and produce substantially larger litters than their ancestral wild mice (Harper 2008, Miller et al. 2002). Second, domestication and inbreeding processes have robustly diminished the natural circulating levels of glucocorticoids (Chalfin et al. 2014) and the heightened stress responses (Fonio et al. 2012, Takahashi et al. 2008) found in wild mice and affect pup-directed behavior substantially (Slattery & Hillerer 2016). Importantly,

Domestication:
the process by which captive animals adapt to humans and the environment they provide

laboratory mice of both sexes are significantly less aggressive than wild mice (Blanchard et al. 1998), and this effect is even more pronounced in females, as naive female laboratory mice typically do not show any aggression toward conspecifics, males or females (Chalfin et al. 2014). Thus, unlike virgin female laboratory mice, which typically display spontaneous parental care toward unfamiliar pups, virgin wild females attack unfamiliar pups, similarly to male mice (Jakubowski & Terkel 1982, McCarthy & Vom Saal 1985). Moreover, in wild mice, sexual dimorphism is manifested in the plasticity of pup-directed behavior: Whereas male wild mice gradually transfer from infanticide to parental behavior following mating (Perrigo et al. 1989, Vom Saal 1985), or cohabitation with parentally behaving males (Jakubowski & Terkel 1982), female wild mice switch rapidly to maternal behavior only following their own parturition (McCarthy & Vom Saal 1985, Soroker & Terkel 1988) and resume infanticidal behavior following the weaning of their own offspring (Soroker & Terkel 1988). Finally, inbred laboratory animals present an unvaried homologous genetic background, unlike wild animals and humans (Guénet & Bonhomme 2003). Therefore, investigating the underlying mechanism of parental behavior and related pathologies such as postpartum depression using laboratory rodents might harbor serious limitations and inhibit the discovery of novel genes or circuits involved (Harper 2008, Turner & Paterson 2013).

The third bias in the typical research of parental behavior lies in the experimental setup. The majority of studies, especially in recent years, have typically been performed in the standard shoe-box home cage of the tested animal by introducing a fixed number of pups for a predefined duration of about 10–30 min (Numan & Insel 2003). In addition, the behavioral assays are performed without the presence of conspecific animals, males or females (Tanaeva et al. 2014). In contrast, real parental care in nature occurs in various familial and communal designs, and several patterns of offspring rearing can appear in the same species under different environmental conditions (Hayes 2000). For example, female wild mice can form communal nests and even nurse pups communally when nesting in the territory of the same male, and joined nests are shown to reduce the risk of infanticide for their pups (Manning et al. 1995). In single nests, the complexity of the brood nest built by a pregnant female wild mouse depends on climate conditions, with the most complex nests built in cold climates (Wolfe & Barnett 1977). In montane voles, higher population density induced the creation of extended families, in which dams rear old and new litters together instead of abandoning their litter 15 days postpartum, which occurs under conditions of low density (Jannett 1978). All these diverse familial systems are not represented in current laboratory studies. However, the expansion of research boundaries to include such systems might bring us closer to discovering the neural mechanisms underlying parental care. Another major difference between natural and laboratory parenting lies in the fact that diverse social behaviors in nature are carried out in large open spaces, as even mothers who spend most of their time in the nest leave it to forage for food (Auclair et al. 2014, Klug & Barclay 2013). Therefore, the constant and secure availability of food and water in the laboratory home cage, alongside the lack of necessity (or ability) to leave the nest, may also influence features of the parental care displayed by the lactating mice or rats (Meehan 1984). Indeed, numerous studies have demonstrated that various social behaviors are qualitatively different in isolated and confined small experimental setups (Fone & Porkess 2008, Gross et al. 2012, Spruijt et al. 2014, Würbel 2001). Thus, limiting the scope of research on social parental behavior to standard laboratory conditions might also restrict the variety of behavioral phenotypes expressed in response to various manipulations. As a result, the potential to discover the neural mechanisms regulating parental behaviors would also be limited.

Combining Ethologically Relevant Methods with Advanced Laboratory Tools

In an attempt to emulate wild life, several research groups have developed seminatural enclosures, in which several animals are cohabitated in complex enriched large environments and their

behavior is quantified automatically for prolonged durations (Blanchard et al. 1995, Ohayon et al. 2013, Shemesh et al. 2013, Thoß et al. 2011, Weissbrod et al. 2013, Zilkha et al. 2016). Under these conditions, scientists can examine parental behavior more similarly to how it occurs in reality, with the presence of other conspecifics (males, females, or both) and the opportunity to establish communal nests, with or without limited availability of food. Such enclosures revealed the formation of communal breeding nests in wild-type laboratory mice, alongside severe impairments in maternal behavior of TrpC2 knockout female mice (Kimchi et al. 2007). In addition, OT knockout female mice placed under seminatural conditions displayed infanticidal behavior (Ragnauth et al. 2005). None of these phenotypes were observed in the standard maternal behavior tests performed in these mice (Hasen & Gammie 2009, Kimchi et al. 2007, Nishimori et al. 1996).

Other groups have used similar seminatural enclosures to compare patterns of maternal behavior between primiparous and multiparous woodrat (*Neotoma floridana smalli*) females (Alligood et al. 2008) and to monitor the effects of an immune state and genetic diversity on the reproductive success of male wild mice (Thonhauser et al. 2014, Zala et al. 2015). Scientists investigating laboratory mice can find great advantages in using wild or wild-derived mice, which are the ancestors of the laboratory mice we use today (Crawley 2007). These mice present complex genetic heterogeneity and display important behavioral features that were lost in laboratory mice, such as infanticide in virgin females (Jakubowski & Terkel 1982). A recent study has shown that both interfemale aggression and infanticide in female wild-derived mice are mediated by pheromone signaling through the VNO, as *TrpC2* knockout females with a wild-derived genetic background lacked these two behaviors (Chalfin et al. 2014). The molecular mechanism of such a phenotype could not have been examined in female laboratory mice, which have lost it completely. The traditional laboratory rats and mice are also not very useful in studying the mechanism underlying biparental care, found in rodents such as *M. ochrogaster* (Numan & Young 2016) or *P. californicus* (Bedford & Hoekstra 2015, Dewsbury 1985). Utilizing these unique rodent species, scientists discovered important roles for testosterone and vasopressin in the regulation of paternal behavior (Gleason & Marler 2013, Wang et al. 1994a). Biparental care can also be explored in nonmammalian species, such as poison frogs, in which closely related substrains display different parental styles, regardless of pair bonding (Roland & O'Connell 2015). Novel methodologies for gene editing can now enable scientists to employ specific manipulations of genes of interest in designated brain regions in many species beyond standard laboratory animals (Heidenreich & Zhang 2016). The extensive research in genetically modified mice and rats in the laboratory has led to enormous progress in understanding the mechanisms underlying parental behavior. Now, we and others propose to expand the research toolbox by using nondomesticated rodents and other species and employing ethologically relevant methods, in combination with current advanced genetic tools (i.e., optogenetics, pharmacogenetics, viral tracing). This will readily allow more and more unique behavioral phenotypes and parental styles to be investigated and pave the way for new discoveries.

CONCLUSIONS AND FUTURE PROSPECTS

The most robust transformations in the adult mammalian brain occur in females during the transition to motherhood to form the maternal brain. These neurobiological mechanisms driving maternal care are so intense and conserved that only simultaneous eradication of three major senses (vision, olfaction, and touch) could cause a severe impairment of maternal care in postpartum rats. Debilitation of one or even two of these senses did not substantially slow down pup retrieval (Beach & Jaynes 1956). The paternal brain contains some of the adaptations seen in maternal females; however, it seems that males cannot reach a fully active maternal brain as females do, and manipulations on adult males do not produce parental performance that can equal parous

females. This appears to be due to the sexual dimorphism that configures different male and female brains according to their different reproductive roles (Yang & Shah 2014). One of the common hypotheses suggests that the sexual differentiation of the brain happens mostly during early development (MacLusky & Naftolin 1981), and when the animal reaches adulthood, these sex-specific neural circuits are already hardwired. Therefore, any local manipulation of the adult brain can shape the behavior only within sex-specific boundaries and cannot induce female-specific behavior, namely full maternal behavior, in males (Scott et al. 2015). Within these boundaries, recent evidence suggests that even a supposedly innate preference of males to female stimuli can be manipulated into aversion through a learning process (Beny & Kimchi 2016). Thus, it would be interesting to examine whether postpartum wild-type females can be trained, for example, to avoid their own offspring. On a final note, biparental rodent species have presented a useful tool in the scientific research of male paternal care in the past few decades. However, to fully understand the sexual dimorphism of the neural circuits regulating offspring-directed behavior, it is crucial that future studies examine and compare males and females of both biparental and the more common uniparental species.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

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