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Common and divergent psychobiological mechanisms underlying maternal behaviors in non-human and human mammals

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Abstract

Maternal interactions with young occupy most of the reproductive period for female mammals and are absolutely essential for offspring survival and development. The hormonal, sensory, reward-related, emotional, cognitive and neurobiological regulators of maternal caregiving behaviors have been well studied in numerous subprimate mammalian species, and some of the importance of this body of work is thought to be its relevance for understanding similar controls in humans. We here review many of the important biopsychological influences on maternal behaviors in the two best studied non-human animals, laboratory rats and sheep, and directly examine how the conceptual framework established by some of the major discoveries in these animal "models" do or do not hold for our understanding of human mothering. We also explore some of the limits for extrapolating from non-human animals to humans. We conclude that there are many similarities between non-human and human mothers in the biological and psychological factors influencing their early maternal behavior and that many of the differences are due to species-characteristic features related to the role of hormones, the relative importance of each sensory system, flexibility in what behaviors are exhibited, the presence or absence of language, and the complexity of cortical function influencing the behavior.

Keywords

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I. Introduction

Mothering of offspring is a distinctive feature of the life of many adult female mammals. Although some form of maternal caregiving behavior is displayed in many vertebrates and even invertebrate taxa (Rosenblatt & Snowdon, 1996), only in mammals is mothering so rich in its behavioral complexity and protracted in its length. For example, only in mammals do we see lactation and the behavioral systems that permit transmission of milk from mother to offspring. Furthermore, when the offspring are born in litters, these feeding behaviors necessarily involve the mothers transporting young and gathering them together in a huddle before nursing can ensue. Even if there are only a few offspring or singletons, mothers must still adjust their bodies or the position of the young to facilitate attachment to teats and suckling. In all cases, mammalian mothers must also ensure that the young are protected from the elements, kept warm, and securely away from predators or threatening conspecifics. Behaviors that accomplish these functions are seen in most mammalian mothers, including humans. How these functions are accomplished in terms of behavioral topography or even who displays them (mother, father, alloparent, or all of them) varies across mammals, although most often the mother's ability to lactate and high maternal motivation initially results in her taking on this considerable mission.

Decades of scientific research on the psychobiology of mothering in non-human mammals have revealed that many of the endocrine, sensory and neural factors intrinsic to the physiology of pregnancy, parturition, and lactation are also fundamental for the display of mothering behaviors. Phylogenetic continuity between non-human mammals and humans suggests that this work in non-human animals is invaluable for our understanding of the psychobiology of human mothering. However, humans also are tremendously influenced by the probably unique contributions of culture and language. The resultant emphasis on the importance of experiential factors in studies of human parenting does not preclude a biology for these behaviors in our species, but simply permits greater environmental contributions to the process. These environmental contributions are themselves accomplished through such biological mechanisms as neural plasticity and epigenetics, which are now known to also influence parenting in non-human animals.

The central purpose of this review is to directly examine how the conceptual framework established by some of the major discoveries in our animal "models" do or do not hold for our understanding of human mothering, and to explore some of the limits for extrapolating from nonhuman animals to humans. We understand that drawing conclusions about the similarity and differences between non-human and human maternal phenomenology and regulatory mechanisms is constrained by the clear differences in the methodologies used to draw causal conclusions. When methods are similar across species, however, many analogies have been noted. For example, both animal and human studies involve observation of the mother's behavior with her offspring or in response to their cues in a variety of contexts and stimulus situations. Using direct observation, correlations have been established in both types of mothers between many aspects of psychological functioning (e.g., emotion, reward, executive function, sensory processing) and the details of their caregiving behaviors. Through observation, researchers have also been able to establish for both non-human and human mothers the importance of early-life experiences, maternal age,

postpartum experience, parity, contextual stress, nutrition, and stimulus characteristics of the young. Using the correlational approaches to understand the psychobiology of mothering one can learn a great deal about how brain or hormonal activity relates to maternal behavior under a range of environmental and experiential conditions in both non-humans and humans. Thus, the correlational approach with many statistical multilevel procedures at our disposal has permitted us to see both similarities and differences across species in the factors that are associated with mothers' behaviors.

In contrast to correlative or descriptive analyses, the study of basic mechanism requires an experimental approach. An experimental approach is the standard in non-human animal studies, where it is possible to use an extirpation-replacement strategy to test the causal role of a hormone, neurotransmitter, brain site or molecular-genetic mechanism in regulating behavior. Given present-day technologies, we are not yet at a point where these procedures can be safely applied to humans, which constitutes a major constraint in our understanding of the similar mechanisms in human mothers. However, through mechanistic analyses of non-human animals we can begin to generate hypotheses as to what might be occurring in humans and test those hypotheses using either non-invasive correlational approaches as described above or noninvasive experimental strategies. One could imagine the latter involving peripheral administration of centrally-acting drugs, which might eventually lead to treatments that could help ameliorate dysfunctional human mothering.

The laboratory rat is the best-studied mammal for the psychobiological analysis of mothering so, therefore, will receive the most attention in this review although we recognize that many other rodents (mice, hamsters, gerbils), lagomorphs (rabbits), cavy (guinea pigs), ungulates (sheep and goats), and non-human primates (marmosets, rhesus monkeys, gorillas) have also been studied and are discussed elsewhere (Barrett & Fleming, 2011; González-Mariscal & Melo, 2013; Lonstein, Pereira, Marler, & Morrell, 2014; Numan, Fleming, & Lévy, 2006; Olazábal, Pereira, Agrati, Ferreira, Fleming, González-Mariscal, Lévy, Lucion, Morrell, Numan, & Uriarte, 2013a; 2013b). Given this focus on laboratory rats, much of the work discussed in the present review finds its conceptual origins in the thinking and writings of the late Jay S. Rosenblatt, whose early work laid the foundation for the modern study of the psychobiology of parenting. Hence, we will also herein provide the basic background for much of the current research on the psychobiology of parenting that will be featured in an upcoming Special Issue on Parental Behavior dedicated to Jay Rosenblatt that will be published in *Hormones and Behavior* later in 2015.

The organization of this review involves direct comparisons and contrasts between studies examining the regulation of maternal behavior in selected non-human mothers and human mothers. We will begin with a description of the initial onset of maternal behavior during the parturitional period and its expression through its early maintenance. We also discuss other salient behavioral changes occurring across this period that contribute to mothers' ability to respond to her young, and how the hormonal, neurochemical, and neural systems underlying mothering also contribute to, and are in turn affected by, systems that regulate these other behaviors. Included in these are the systems regulating reward, emotion, learning, and executive functions. Without involvement of these systems, mothers would not show behavior towards young that is temporally appropriate, relevant, or synchronous. In

each section of the review we first describe the non-human animal work, followed by the most relevant and potentially analogous work in humans. In the overall discussion we compare and contrast findings in the animal models that have informed the human research, noting their similarities and differences. We also highlight some topics that remain understudied. There are a number of productive areas of research that are intentionally not included in the present review, but which are important to a more complete understanding of maternal biology. These include the study of the ontogeny of mothering and effects of early social experiences, the study of the genetics and epigenetics of parenting, a comparable analysis of fathering, and discussions of the evolution of parenting from a truly comparative perspective. We also do not discuss extreme pathology in mothering, such as offspring abuse and neglect. These topics are discussed in other recent reviews or volumes (Barrett & Fleming, 2011; Black, Heyman, & Smith Slep, 2001; Gudsnuk & Champagne, 2011; Lonstein et al., 2014; Numan, 2015; Rosenblatt & Snowdon, 1996; Saltzman & Ziegler, 2014) and many of these topics will receive considerable attention in the upcoming Special Issue.

II. Behavioral characteristics of mothering

Non-human mammals

In mammals where mothering has been studied, caregiving behaviors are most reliably observed right when the female gives birth. In laboratory animals, mothering seems to occur fully-formed as soon as the young emerge from the birth canal, even in previously inexperienced primiparous females (Lonstein et al., 2014; Numan et al., 2006; Rosenblatt & Lehrman, 1963; Wiesner & Sheard, 1933). Changes in the quality and predictability of maternal behaviors occur as experience is gained across successive births (discussed below), but in the laboratory rat, these changes are relatively subtle because the behaviors are usually so characteristic and dependable even in first-time mothers (Fleming & Rosenblatt, 1974a; Numan et al., 2006).

Female laboratory rats and other female rodents use their mouths as a primary instrument for mothering. They clean the pups as they emerge from the birth canal by eating their amniotic sacs and placentae, lick the pups from head to toe, orally gather the offspring within the nest prepared during late pregnancy, and actively hover over the wriggling huddle to provide them opportunities to attach to a nipple and provide the suckling that elicits the mother's quiescent nursing. This set of observable behaviors that can be objectively quantified in terms of their frequency and duration - nest-building, retrieval, body and anogenital licking, hovering over and nursing - comprises the behavioral repertoire of animals tested in a highly controlled laboratory setting (Numan et al., 2006; Rosenblatt & Lehrman, 1963). Importantly, one must be aware that this ethogram for rat mothering does not necessarily extend to all rodents and other small mammals. For example, prairie voles do not readily retrieve pups, probably because their pups are born with teeth that keep them latched on to their mothers even if the nest site is tremendously disturbed (Salo, Shapiro, & Dewsbury, 1994). Rabbits also do not often retrieve or lick their young, and only nurse them once a day during a very brief but apparently highly effective nursing bout (González-Mariscal, 2007).

Pre-parturient female ungulates, like sheep or goats, do not build a nest and tend to isolate themselves from their social group. Indeed, while non-maternal female ungulates show very strong behavioral responses when isolated from conspecifics indicative of agitation and stress, such distress reactions vanish around parturition. Isolation is an important preliminary step in the formation of the mother-young bond, as it protects the offspring from disturbances by congeners and predators, and facilitates early interactions with the mother. Similar to rodents, sheep mothers are attracted to amniotic fluids right at parturition and usually eat placenta. They also lick the newborn after birth, but licking does not last more than two hours until the lamb is dry. While licking and grooming the young, sheep mothers emit characteristic vocalizations of low amplitude and frequency that are called low-pith bleats. These vocalizations are mainly emitted around parturition and later on during nursing. These calls are very attractive to neonates and have soothing properties for the young. The first suckling attempts occur within hour after the lamb's birth, and nursing mothers move themselves into a parallel-inverse position with their young, which allows them to identify the offspring. Maternal care then quickly becomes exclusive: only the familiar lamb is accepted at the teats and the mother often violently rejects any alien lamb that may try to suckle. In most studies it is this licking, emission of maternal bleats, nursing, and aggression that are the main behaviors taken into account to characterize maternal responses in female sheep (Poindron & LeNeindre, 1980).

Humans

Unlike mothering by rodents or even sheep, in which caregiving involves a collection of often highly predictable behaviors in their form and sequence, there are very large variations in the form that human mothering behavior takes and this depends on her culture, social and/or economic status, age, parity, and early experiences in her own family of origin. Despite the large differences in the time that human mothers spend with their infants each day, the amount and type of infant carrying they do, whether they talk to their infants directly, look at them '*en face*', sleep with them, and/or nurse or bottle feed, there are certain functions mothers fulfill that in one way or another may be universal (Bornstein, 2012; see Corter & Fleming, 2002). Across all cultures, mothers have to insure that the newborn infants' basic needs are met by engaging in behaviors that allow the young to eat, sleep, and be protected from environmental extremes and other dangers. Thus, regardless of the specific cues or behaviors, effective caregivers have to be motivated to engage with the infant; be at least minimally attentive to the infant and respond to the infants' cues in a timely fashion; provide stimulation and training so that the infant can develop motorically, perceptually, and cognitively; show 'sensitivity' so the infant can develop appropriate expectations, engage socially and regulate their emotions as appropriate to their cultures. Through their interactions with the baby, human caregivers in all cultures are in a position to promote healthy development of their infant's brain and physiology (see Fleming, Grusec, & Haley, 2012; Hrdy, 1999; 2009).

The relative emphasis that different cultures give to each of these functions, and the form of the behaviors exhibited, varies both across and within cultures and depends on whether the culture emphasizes independence, individuality and autonomy (as in many urban Western cultures) or collectivity, relatedness, and interdependence (as in many Asian, African, and

rural cultures). Sometimes one can find a combination of the two, in cultures that are in flux as a result of increasing globalization (e.g., Costa Rica) (Bornstein, 2012; 2013; Keller, Lamm, Abels, & Yovsi, 2006; Lamm & Keller, 2007). Regardless of the culture, mothering also depends on what else the mother must do, which is dictated by whether she is alone or has a partner, how many children she has, what her other societal and economic roles are, and whether she and her family live in a social environment involving many relatives and friends or one that is more isolated and socially restricted (see Fleming et al., 2012).

While most of the studies discussed herein have been done in Western societies (usually the United States, Canada and Europe) where the bulk of the research on mothering currently occurs, it is essential to keep in mind the cultural and situational contexts that produce variability in behavior and how they constrain generalizability of results. To assess mothering in the studies described below, a number of questionnaires and procedures have been developed and normed on homogeneous populations. These constitute the primary dependent measures in the analyses of psychological, sensory, hormonal, and brain mechanisms regulating mothering. Included in these are observational studies that are in some ways similar to observational studies common for non-human mothering. In both cases, mother-offspring interactions are assessed in a variety of contexts and are then coded for particular behaviors, often in humans involving the mother's contingent responding that are thought to reflect cooperativeness, intrusiveness, availability and sensitivity (Ainsworth, 1969), as well as their punitiveness and warmth (Moss et al., 2011). In addition, and obviously unlike studies of non-humans, womens' attitudes about mothering and motivation to interact with infants can be assessed by using normed questionnaires such as the Child Attitude Questionnaire (CAQ) (Ruble et al., 1990) that probes mothers' about their feeling about their infants, other infants, and childcare activities as well as by assessing mothers subjective 'hedonic' responses to infant pictures, cries and/or odors (Barrett & Fleming, 2012; Stallings et al, 2001; Krpan et al., 2005; Fleming et al., 1997a; Fleming et al., 1997b). Other measures of human maternal responsiveness have commonly included scales assessing subjective responses, physiological measures of autonomic activity, and more recently functional magnetic resonance imaging (fMRI) responses to infant cries, odors, pictures, and films (see Barrett & Fleming, 2011; Bleichfeld & Moely, 1984).

III. Hormonal basis of mothering

Non-human animals

A framework originally conceptualized in studies of non-human animals by Jay Rosenblatt and others posits that the onset of maternal behavior depends first on the hormonal events occurring during pregnancy and parturition. This hormonal phase then gradually wanes, but by then has induced a maximal state of responsiveness to sensory stimulation from the young that then maintains maternal responsiveness for the duration of lactation and beyond (Rosenblatt, 1994).

The onset phase of mothering in recently parturient females involves a change in her responsiveness to pups from the negative or neutral reaction during pregnancy to a positive response just before or soon after giving birth. Hence, virgin or mid-pregnant rats will briefly sniff foster pups but then withdraw from, bury, or attack them (Fleming &

Rosenblatt, 1974a). If pups are placed into the non-parturient females' nesting areas, they will actively avoid the pups and reestablish their nests elsewhere (Fleming & Luebke, 1981). However, if inexperienced virgins are exposed daily to foster pups their avoidance declines and they begin to approach the pups and eventually show maternal behaviors, a process known as maternal *sensitization*. This process takes from 2 to 10 days depending on the strain of animal being assessed and numerous other experimental conditions (Rosenblatt, 1967).

The behavior of non-maternal females to pups can be contrasted to parturient mothers that do not recoil on their first exposure to them but instead approach and quickly engage in the very predictable set of behaviors described above (Fleming & Rosenblatt, 1974a; Numan & Insel, 2003). It is now well known that this shift in the new mothers' behavior at parturition has a blood-borne basis (Terkel & Rosenblatt, 1972) and comes about through the action of hormones (reviewed in Bridges, 1990; Lonstein et al., 2014; Numan et al., 2006; Numan & Insel, 2003) that both reduce the females' natural avoidance of some novel stimuli (Fleming, Cheung, Myhal, & Kessler, 1989) and specifically alters the salience of the offspring (Afonso, Shams, Jin, & Fleming, 2013; Fleming et al., 1989). Decades of research show that periparturitional hormones affect maternal behavior at different times in different species, and do so to different extents. Rats show a progressive effect of pregnancy, so show increasingly enhanced maternal responsiveness towards foster young even before giving birth (Siegel & Rosenblatt, 1975b). In other species, increasing responsiveness is not seen during pregnancy in inexperienced animals and maternal behavior appears for the first time at parturition. This is true for some strains of mice (Gandelman, Zarrow, & Denenberg, 1970), sheep (Poindron & Le Neindre, 1980), and marmosets (Pryce, 1993). Such endocrine effects are not thought to be involved in the onset of maternal care instilled through sensitization of virgin rats because sensitization is unaffected by ovariectomy or hypophysectomy (Rosenblatt, 1969). Instead, the sensory stimulation from pups seems to exert similar effects on the brain and neurochemistry to what has been reported for new mothers independent of significant endocrine changes (Afonso, Grella, Chatterjee, & Fleming, 2008).

The first striking piece of modern evidence for a blood-borne effect on mothering was Terkel and Rosenblatt's (1972) report that if inexperienced virgin rats share a blood supply with new mother rats and are presented with foster pups, they quickly begin to respond maternally. This early study was followed soon thereafter by studies identifying the specific hormones that activate mothering and it is now known that a number of endocrine changes occur around the time of parturition to enhance maternal behavior in rats and many other species. First, the very high levels of progesterone characteristic of pregnancy decline around the time of parturition. Second, estrogens increase during the latter third of pregnancy and peak at parturition. Third, in response to these estrogens there is peripheral release of prolactin (PRL) and oxytocin (OT), which can then either cross the blood-brain-barrier in significant amounts (PRL) or are simultaneously released intracerebrally (PRL and OT) to affect the maternal brain (Lonstein et al., 2014; Numan et al., 2006). This cocktail of endocrine changes potently increases females' positive appraisal of offspring cues and activates their nurturant behaviors toward the young.

Some early studies leading to this conclusion include the work by Siegel and Rosenblatt showing that by removing the usual sources of progesterone and estrogens in late-pregnant rats via ovariectomy and/or hysterectomy and replacing estrogens in some animals but not others, only the animals given estrogen replacement exhibited mothering (Siegel & Rosenblatt, 1975a; 1978). The induced decline in progesterone alone was inadequate to activate mothering. Work performed soon thereafter found that a regimen of progesterone and estrogens designed to simulate late pregnancy and parturition could produce a similar onset of maternal behaviors in virgin rats (Bridges, 1984; also Moltz et al., 1970). Furthermore, estrogens cannot act alone to produce these stimulatory effects, but must act against a background during the latter half of pregnancy of declining progesterone because maternal behaviors do not emerge if progesterone remains high despite high circulating estradiol (Bridges, 1975; Bridges, Rosenblatt, & Feder, 1978a; 1978b). Importantly, this increase in estrogens stimulates the release of and sensitivity to centrally acting PRL and OT to further promote maternal interest in pups (Bridges & Mann, 1994; Bridges, DiBiase, Loundes, & Doher1985; Bridges, Numan, Ronsheim, Mann, & Lupini, 1990; Pedersen, 1997; Pedersen & Prange, 1979; Pedersen, Ascher, Monroe, & Prange, 1982). The particular configuration of estrogens, progesterone, PRL, and OT that can stimulate maternal behavior may vary species, but the effects of these hormones have been demonstrated time and time again, including in rabbits, some ungulates, and some primates (González-Mariscal & Melo, 2013; González-Mariscal, Melo, Jiménez, Beyer, & Rosenblatt, 1996; Keverne & Kendrick, 1994; Lévy, Kendrick, Keverne, Piketty, & Poindron, 1992; Lonstein et al., 2014; Numan et al., 2006).

Although hormones are unnecessary for maintaining maternal behavior after its peripartum establishment, they are not completely irrelevant for modulating its ongoing display. For example, relatively recent work has revealed that while adrenalectomy does not eliminate maternal behavior, exogenous corticosterone enhances maternal licking in postpartum rats, but inhibits it in sensitized virgins (Rees, Panesar, Steiner, & Fleming, 2004; 2006). Furthermore, postpartum ovariectomy reduces the frequency that mothers lick their pups when assessed between postpartum days 2–7 (de Sousa et al., 2010), but increases hovering over the pups and licking them while reducing some non-pup-directed behaviors when measured from days 7–18 postpartum (Grieb, Tierney and Lonstein, in preparation). Lastly, central antagonism of OT receptors in postpartum rats reduces, but does not eliminate, pup licking and nursing (Pedersen & Boccia, 2003), which is consistent with the finding that central OT receptor expression is positively correlated with the frequency of maternal licking in early postpartum rats (Champagne, Diorio, Sharma, & Meaney, 2001).

How do these hormones act for the onset or continuation of maternal behaviors? What makes them effective? Are they deterministic in their effects? These are all important questions and partial answers to them exist. There are at least two complementary ways to answer the question how hormones exert their effects on mothering. First, one can directly examine at systems, cellular, or molecular levels the hormone-induced chemical, structural and functional modifications that occur in the neural network necessary for motherhood. The other focuses initially on more general behavioral effects of hormones and asks what classes of behavior are activated by hormones that could indirectly affect mothering. That is, in what ways do the hormones that activate mothering also affect: 1) mothers' processing of

and attraction to infant cues to young, 2) mother's ability to attend to the environment and readily shift her attention in ways necessary for appropriate and sensitive mothering, and 3) mothers' ability to learn about the offspring and thus become more efficient at caregiving? As will be seen below, hormone-induced changes in the neural systems involved in hedonics, emotions, attention and memory are integral for the onset of mothering and interface with the neural network necessary for the expression of specific maternal behaviors.

While maternal behavior is most rapidly activated by the hormonal changes associated with the end of pregnancy and parturition, hormones are not necessary for the expression of maternal behavior under all conditions. As mentioned above, nulliparous adult rats and juveniles that do not experience the hormonal changes of pregnancy and parturition will show nurturant behavior towards young pups if they receive extensive contact with them (Rosenblatt, 1967). This maternal sensitization process makes ecologic sense since many mammals in natural environments live in large social groups and have frequent opportunities as juveniles to interact with their younger siblings or even non-siblings (Calhoun, 1963). This early alloparental experience produces a long-term enhancement of later parental responding in some species (Gray & Chesley, 1984; Rees & Fleming, 2001; Stern & Rogers, 1988; Uriarte, Ferreira, Rosa, Sebben, & Lucion, 2008), including monkeys (Pryce, 1993). It should also be remembered that hormones are similarly less relevant for maternal behavior in species that are spontaneously parental as adults even in the absence of early experience, including many strains of laboratory mice (Gandelman et al., 1970).

Humans

Pregnant womens' feelings of attachment to the fetus grow across trimesters, an effect that, unlike maternal responsiveness in laboratory rats, is not related to changes in the absolute levels of ovarian hormones during pregnancy. Nonetheless, mothers who experienced greater attachment to their new babies after the birth underwent an increase from early to late pregnancy in their estradiol:progesterone ratio whereas those with low attachment experienced a decrease in their estradiol:progesterone ratio over this same time period (Fleming, Ruble, Krieger, & Wong, 1997a). Interestingly, this same change in hormonal profile was also associated with mothers' affective state; mothers with a greater shift in the estradiol:progesterone ratio across pregnancy also experienced greater postpartum well-being. These data suggest that mothers' hormones are related to attachment with the infant directly and, indirectly, by altering the mothers' well-being (Fleming, Ruble, Krieger, & Wong, 1997a). Unfortunately, the Fleming et al. (1997) study did not assess concentrations of PRL or OT, which animal studies indicate are also related to mothering. OT is particularly associated with general affiliation in humans (Carter, 2014; Feldman et al., 2012) and more specifically mothers with the highest plasma OT levels exhibit the most affectionate contact and social gaze during a recorded 10-minute interaction with their 4–6 month old infants (Apter-Levi, Zagoory-Sharon, & Feldman, 2014). Mothers with the greatest increase in circulating OT across pregnancy also showed higher levels of maternal bonding behaviors when with their infants (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). More recent work by MacKinnon et al. (2014) further suggests that levels of circulating OT during late pregnancy are related to a measure of the mothers' postpartum

theory of mind (i.e., ability to use facial cues to perceive what others are feeling or thinking), which in turn relates to the quality of their mothering behavior, perhaps by affecting sensitivity to infant social cues. Finally, there is recent evidence suggesting that mothers' OT levels are related to both her child's OT levels and to synchrony in their behavioral interactions (Feldman et al., 2012). Although most studies in mothers suggest a positive relationship between measures of mothering and OT, not all do; a recent study indicates an inverse relation between OT levels and high maternal sensitivity (Elmadih et al., 2014).

In addition to circulating hormones during pregnancy, early postpartum concentrations of cortisol - which are extraordinarily high at baseline and show relatively little additional rise in response to many stressors (Tu et al., 2006) - are positively associated with many positive features of early human mothering. During the first postpartum week, mothers with higher levels of cortisol engage in more contact with their babies, find baby odors more attractive, are better able to recognize their babies based on their odors, are more sympathetic when exposed to infant cries, and show heightened feelings of wellbeing (Corter & Fleming, 2002; Fleming, Ruble, Krieger, & Wong, 1997a; Fleming, Steiner, & Corter, 1997b; Giardino, Gonzalez, Steiner, & Fleming, 2008; Krpan, Coombs, Zinga, Steiner, & Fleming, 2005; Numan et al., 2006; Stallings, Fleming, Corter, Worthman, & Steiner, 2001). However, later in the postpartum period, when the priming effects of childbirth hormones are no longer present, high cortisol is either not related to mothering or is inversely related (Gonzalez, Jenkins, Steiner, & Fleming, 2012; Krpan et al., 2005). This bimodal effect of cortisol has been demonstrated in a variety of contexts and suggests that a certain level may be necessary for alertness and adequate attention to the young, especially if it is acting within the context of other hormonal priming (e.g., by progesterone and estrogen).

IV. Stimulus salience related to maternal responsiveness, offspring recognition, and offspring reward

Non-human animals

It was discussed above that the regulation of maternal behavior can be divided into a hormone-dependent onset phase and a relatively hormone-independent maintenance phase. The onset phase induces a maximal state of responsiveness to the sensory cues emanating from young, which thereafter maintains maternal responsiveness (Rosenblatt & Lehrman, 1963). The latter point is gleaned from the fact that females gradually lose their maternal responsiveness if the young are removed during this period. In addition to a role in maintaining maternal interest and behavior, offspring cues enable the mother to collectively or individually recognize the young. In rodents and probably other polytocous species, this recognition results in a slight preference for, but not an exclusive interest in, mothering one's own offspring. In contrast, this recognition in some ungulates involves a very specific and exclusive attachment to their singletons or twins.

Offspring emit a variety of sensory stimuli that mothers use to respond appropriately to the young, but the relative importance of these sensory cues differs across mammals according to how these cues are utilized more broadly in their social lives and in the nature of the

mother-young relationship. We describe below the importance of both proximal communication provided by olfactory and somatosensory cues, and distal communication provided by visual and auditory cues, for maternal responsiveness and individual recognition of the young in laboratory rodents and ungulates. We also provide examples of how mothers' response to sensory cues from their young undergoes a shift in salience and rewarding properties from before parturition to the postpartum state.

Olfactory cues—For most mammals, olfaction is their dominant sense and heavily influences their social interactions. While the precise role and relative importance of maternal olfaction varies from one mammalian species to another, olfactory cues play a part in many aspects of parental care. In most parturient females, the odor of amniotic fluid is highly attractive and is a potent stimulus involved in the normal development of mothering. This attraction is not present in most females before or during earlier pregnancy and is only temporary (Lévy, Poindron, & Le Neindre, 1983; Melo & González-Mariscal, 2003; Numan et al., 2006). Mothers also consume placenta at parturition, which in rats induces analgesia and may facilitate their onset of maternal behavior (Kristal, 1980; Kristal & Graber, 1976). Such a rapid change of preference for amniotic fluid and placenta at parturition is regulated by stimuli processed by the main olfactory system (Lévy et al., 1983; Lévy, Locatelli, Piketty, Tillet, & Poindron, 1995) and, in some species, by hormones (Kristal, DiPirro, & Thompson, 2012).

After parturition, the odors of the pups themselves become the relevant regulators of maternal behaviors. The laboratory mouse is a model in which olfaction plays a central positive role in the onset of maternal behavior, with removal of the olfactory bulb (olfactory bulbe ctomy) preventing nest building, reducing nursing, and inducing cannibalism (Gandelman, Zarrow, & Denenberg, 1971a; Gandelman, Zarrow, Denenberg, & Myers, 1971b; Sato, Nakagawasai, Tan-No, Onogi, Niijima, & Tadano, 2010b; Vandenbergh, 1973). The fact that the deletion of genes involved in olfactory signal transduction (SCN9A or Cnga2) in the main olfactory epithelium results in deficits in pup retrieval but not cannibalism (Fraser & Shah, 2014; Weiss et al., 2011), suggests that cannibalism is probably a side effect of the bulbectomy surgery and not directly related to the anosmia. On the other hand, removing the vomeronasal organ which mediates accessory olfactory functioning or deleting *Trpc2* (gene coding for ion channels in the vomeronasal organ) does not greatly interfere with the expression of maternal behavior in mice (Fraser & Shah, 2014; Hasen and Gammie, 2009; Lepri, Wysocki, & Vandenbergh, 1985). However, the importance of main olfactory cues for mouse mothering is diminished in experienced mothers, who can apparently compensate for a loss of olfactory function by using other sensory information (Dickinson & Keverne, 1988; Seegal & Denenberg, 1974).

The onset of maternal behavior primarily on olfaction not only in some altricial mammals like laboratory mice, but also in precocial ungulates like sheep. Primiparous ewes rendered anosmic before parturition show reduced maternal behavior, with the onset of licking and suckling delayed and licking times and maternal bleats reduced (Lévy et al., 1995). Such disturbances were not observed in multiparous anosmic ewes, indicating that experience can compensate for the loss of olfactory information, as was found in mice (Dickinson & Keverne, 1988; Seegal & Denenberg, 1974). Also similar to mice, inexperienced ewes with

lesions of the vomeronasal organ show little disturbance in maternal care. The olfactory cues that attract ewes to any newborn lamb are linked to amniotic fluid. Removing amniotic fluid from the neonate's coat reduces maternal licking and, in primiparous ewes, prevents acceptance behavior while increasing aggression (Lévy & Poindron, 1987). In experienced mothers, coating lambs in amniotic fluid alone is sufficient to induce maternal acceptance (Basiouni & Gonyou, 1988; Lévy & Poindron, 1984). Thus, olfactory cues provided by amniotic fluid ensure appropriate maternal behavior at parturition in sheep, especially in inexperienced mothers. The effects of anosmia, especially on licking behavior, are less pronounced and do not impede the mothers to display maternal behavior, contrary to what is found after removing amniotic fluids from the lamb's coat in intact dams. This indicates that anosmia performed before parturition can be compensated for by other sensory cues. In contrast, such a process does not take place if the olfactory system is intact but the lamb's relevant olfactory cues are removed. Therefore, the effects of anosmia on maternal responsiveness in ewes probably do not reflect the actual role of this sensory channel in intact mothers and the results of studies using olfactory cue manipulations in intact mothers seem more relevant. Given this, the effects of removing infantile olfactory cues from mouse pups have not been examined and such studies could help determine the importance of olfaction in maternal behavior in postpartum mice.

In stark contrast to mice and sheep, neither the main nor accessory olfactory systems are required for mothering in laboratory rats. Following destruction of the olfactory mucosa, a normal onset of maternal behavior occurs in primiparous females (Benuck & Rowe, 1975; Jirik-Babb, Manaker, Tucker, & Hofer, 1984; Kolunie & Stern, 1995), even though retrieval may be delayed because anosmic dams take longer to locate pups (Benuck & Rowe, 1975; Kolunie & Stern, 1995). Similarly, no deficit in maternal behavior is observed after removing the vomeronasal organ or cutting the vomeronasal nerves (Fleming, Gavarth, & Sarker, 1992; Jirik-Babb et al., 1984; Kolunie & Stern, 1995). Interestingly, the latency to begin retrieving pups is unaffected in these females, suggesting that the accessory olfactory system is not even critical for locating pups. Inconsistent results on maternal behaviors have been reported using bilateral bulbectomy ranging from profound disturbances and/or cannibalism (Benuck & Rowe, 1975; Fleming & Rosenblatt, 1974b; Kolunie & Stern, 1995; Schwartz & Rowe, 1976) to lack of deficits (Beach & Jaynes, 1956; Fleming, Kuchera, Lee, & Winocur, 1994b; Numan & Numan, 1994); however, peripherally induced anosmia by zinc sulfate does reduce licking by new mothers rats (Fleming & Rosenblatt, 1974c). Thus, as in mice, much of the bulbectomy effect when found in rats is probably due to the non-sensory consequences of the procedure. The minor role of olfaction for rat maternal behavior also seems to be the case in rabbits (Chirino, González-Mariscal, & Beyer, 1999).

In contrast to postpartum rats, the induction of anosmia disinhibits maternal behavior in virgin rats. That is, olfactory cues associated with afterbirth and pups prevent nulliparous female rats from being maternal. Virgin or non-pregnant female rats are simply repelled by placenta, amniotic fluid, and pup odor (Kristal, 1980) but anosmia eliminates these aversive properties and results in a rapid onset of maternal behavior (Carretero, Segovia, Gomez, & Del Cerro, 2003; Fleming & Rosenblatt, 1974b; Fleming, Vaccarino, Tambosso, & Chee, 1979). These inhibitory effects seem to be mediated by both the main and accessory systems and occur in a number of species (rat: Fleming et al., 1979; rabbit: González-Mariscal,

Chirino, & Beyer, 2004; Chirino, Beyer, & González-Mariscal, 2007; hamsters: Marques, 1979), although of course this is not the case in many strains of mice, which as discussed above require olfaction for their maternal behavior. Yet another pattern is shown in nulliparous ewes, which are also repulsed by amniotic fluids and anosmia prevents this response (Lévy et al., 1983; 1995). Unlike rats, however, anosmia alone is insufficient to induce full maternal behavior in nulliparous sheep and hormonal priming is also necessary (Poindron, Lévy, & Krehbiel, 1988).

In maternally discriminating species like some ungulates that recognize their young and allow them to suckle while rejecting others, olfaction is key (Lévy et al., 1995; Pitcher, Harcourt, & Charrier, 2010; Romeyer et al., 1993). Inducing anosmia in ewes before parturition prevents recognition of their own lambs and any young is accepted to suckle (Baldwin & Shillito, 1974; Bouissou, 1968; Lévy et al., 1995; Poindron, 1976; Romeyer, Poindron, & Orgeur, 1994). In this case, the main but not accessory olfactory system is involved (Lévy et al., 1995). In contrast, goat mothers require close contact with their kids for recognition and selective care to develop, suggesting a role for the vomeronasal system in this species; depriving goat mothers of physical contact with the kid for the first four hours postpartum even in the presence of their other stimuli leads to rejection of the young in some mothers (Romeyer et al., 1993). There is no evidence that polytocous species such as rodents show any type of individual recognition of their many pups, and will even nurse alien litters. Nonetheless, rat and degus mothers can still discriminate between their own and alien litters based on their odors and it has some small effects on how quickly they respond to the pups (Ebensperger, Hurtado, & Valdivia, 2006; Jesseau, Holmes, & Lee, 2008; Shah, Oxley, Lovic, & Fleming, 2002).

Somatosensory cues—Once the mother gives birth and begins interacting with her young, she receives numerous types of somatosensory stimulation from them. Numerous studies from Stern and colleagues and others have described how perioral and ventral somatosensory cues are essential for both the onset and maintenance of maternal responsiveness in rats (Stern, 1996a). For example, encouraging physical contact between nulliparous females and pups by placing them together in a small cage reduces the latency to become maternal (Stern, 1997; Terkel & Rosenblatt, 1971). This is supported by detailed behavioral observations showing that pup avoidance in virgins rats is first replaced by increasing tolerance of physical contact from pups, followed by mouthing and licking them, then retrieval and hovering over (Stern, 1997). In mated rats, prepartum infraorbital denervation eliminating tactile inputs to the perioral region disrupts the onset of maternal behavior at parturition (Stern, 1996b), and when infraorbital anaesthesia is combined with ventral anesthesia, maintenance of maternal responsiveness beyond parturition is also prevented (Morgan, Fleming, & Stern, 1992). These tactile inputs influence mothering, in part, by affecting maternal motivation as evidenced by the finding that anaesthetizing the perioral region disrupts dams' ability to learn a conditioned place preference based on interaction with pups (Magnusson & Fleming, 1995).

Even after maternal behavior is established, somatosensory cues contribute tremendously to ongoing maternal behavior. Reducing or eliminating tactile sensitivity of the dam's perioral region prevents both retrieval and licking (Kenyon, Cronin, & Keeble, 1981; Stern, 1996a).

Surprisingly, perioral tactile inputs are also involved in her quiescent nursing, because when licking does not occur due to perioral anaesthesia, nursing behavior is also not necessarily expressed (Stern & Johnson, 1990). As described by Stern (1996a) maternal licking, mouthing and nuzzling of pups are needed to induce her prolonged hovering over the pups, which eventually transitions to kyphosis (i.e., arched-back nursing) and other forms of nursing behavior. This transition from motorically active maternal behaviors such as licking and carrying to motorically quiescent nursing is regulated by the ventral stimulation provided by pups. In rats, this stimulation must come from at least four pups and they must be capable of suckling, as nursing by dams does not occur if the pups' mouths are sutured or anesthetized or if the nipples are surgically removed (Stern & Johnson, 1990; Stern, Dix, Bellomo, & Thramann, 1992).

Although such systematic experiments have not been performed in other mammals, studies in sheep indicate that preventing the ability to nurse the newborn lamb (but not lick it) by placing it in a wire mesh cage with its lid open for either 4 or 12 hours has little consequence on later maternal behavior even in primiparous females (Otal et al., 2009; Poindron & Le Neindre, 1980). Moreover, there is no indication that preventing only nursing impairs the recognition of one's own lamb in either primiparous or multiparous mothers (Otal et al., 2009). By contrast, deprivation of all physical contact with the newborn lamb had a drastically negative impact on the development of maternal responsiveness and selectivity in both sheep (Otal et al., 2009) and goats (Bordi et al., 1994; Romeyer et al., 1993). Whether these effects are caused by the lack of perioral stimulation, or by the absence of ingesting amniotic fluids and the impairment of some perception of olfactory cues from the young, is unknown. The latter possibility is likely given the important role of olfaction in maternal behavior of these ungulates.

Visual Cues—For mammals in which nurturance of pups most likely occurs in an underground burrow, vision is obviously not essential for maternal behavior. Blinding female rats by enucleating them before parturition does not induce deficits in any aspect of maternal behavior, and instead increases maternal licking and nursing (Herrenkohl & Rosenberg, 1972). Similarly, when visual deprivation is performed after parturition by eyelid suturing, maternal behavior remains intact and licking is enhanced (Kolunie, Stern, & Barfield, 1994). The importance of visual stimuli also does not appear essential for the normal development of maternal behavior in diurnal animals such as ungulates. Although preventing vision has not been performed in sheep, sight and sound of the neonate are not sufficient for ewes to remain maternal after parturition (Poindron & Le Neindre, 1980).

In already-maternal ungulates, visual stimuli from offspring allow localization of young from a distance of several meters. Mother sheep are able to distinguish between different colors of artificially colored lambs and approach those of the same color as their own lamb (Alexander & Shillito, 1978). Such visual recognition depends heavily on the cues from the lamb's head, because blackening the face of the young disturbs maternal recognition as much when the whole body of the lamb is blackened (Alexander & Shillito, 1977). More recent studies using photographs support the view that the lambs' faces are important for maternal recognition. Ewes can be trained to discriminate photographs of faces of unfamiliar

lambs (Ferreira, Keller, Saint-Dizier, Perrin, & Lévy, 2004), as well as familiar versus unfamiliar lambs (Kendrick, Atkins, Hinton, Heavens, & Keverne, 1996).

Auditory cues—Audition is crucial for distal communication, especially for bringing the mother and young together. It is, therefore, not surprising that it is unnecessary for the onset of maternal behavior at parturition when mother and young are already in close proximity or in laboratory rodents tested in a relatively small cage. Indeed, deaf postpartum rats express normal licking and nursing (Kolunie et al., 1994) and deaf nulliparous rats are just as likely to become maternally sensitized as hearing females (Stern, 1997). However, ultrasonic cries emitted when pups are displaced from the nest help their dams rapidly orient to them, increase the likelihood of transport to the nest (Stern, 1990) and help dams avoid accidentally stepping on the pups (Stern, 1997).

Detailed studies on auditory communication between mother and pups have been performed in laboratory mice (see Banerjee & Liu, 2013; Ehret, 2005) and show that playing recorded natural calls or synthesized model ultrasounds induce maternal approach. Lactating mice significantly prefer ultrasonic vocalizations and synthesized calls with certain acoustic properties over other ultrasounds (Ehret, 1992; Ehret & Haack, 1982) and can detect calling pups at least as far as 100 cm from the nest (Ehret, 2005). Pups also emit lower-frequency vocalizations with a particular inter-call interval when closer to the mother, known as wriggling calls, which cause her to adjust her nursing position or licking (Gaub & Ehret, 2005).

Similar to visual cues, auditory cues can convey information about the identity of the young. However, vocal recognition can take place at much greater distances than allowed by visual recognition or when mother and young cannot see each other. Numerous studies report that ewes are able to recognize the unique acoustic features of the bleats of their lamb (Poindron & Carrick, 1976; Searby & Jouventin, 2003; Sebe, Nowak, Poindron, & Aubin, 2007). This acoustic recognition develops later than olfactory recognition since it is fully functional only after 24 h of mother–young contact (Sebe et al., 2007). In goats, kid bleats show inter-individual differences as early as one day of age, suggesting possible coding for individual vocal signatures. Amazingly, mothers can discriminate kid bleat within two days postpartum (Terrazas, Serafin, Hernández, Nowak, & Poindron, 2003). Analysis of kid bleats over the first five days postpartum reveals changes in the vocal signature and raises the interesting question of how the mother builds and maintains an individual acoustic representation of her young. Certainly the need for efficient and long-term individual recognition is exacerbated in colonial species in which there are high risks of confusion due to population density and long mother-young separation. In pinnipeds, mothers can identify their offspring vocal cues within two days postpartum (Pitcher et al., 2010) and their pups' calls also change gradually over the rearing season, and presumably their mothers have the ability to notice such changes. Fur seal mothers can remember each version of their pup's calls from birth to seven months of age (Charrier, Mathevon, & Jouventin, 2003) and even six months after weaning (Insley, 2000)! These studies underline the strong memorization process occurring during maternal bonding with young in some species, and suggest adaptive significance for the ability to establish and store such auditory memories.

Pups and their sensory cues are rewarding—Using instrumental laboratory tasks, it is possible to demonstrate just how rewarding these offspring sensory cues are to new mothers. As described above, these cues from young act as 'triggers' for the expression of maternal behaviors, and as a group (and even in some cases, singly) these cues take on a positive valence for the mother (Bauer, 1983; Fleming et al., 1989; González-Mariscal & Chirino, 2011; Kinsley & Bridges, 1990; Lévy et al., 1983). Hence, at the time of parturition there is a shift within the mother's reward systems that is strengthed through her early physical interactions with the pups, resulting in the young becoming highly rewarding stimuli (Fleming, Korsmit, & Deller, 1994a; Lee, Clancy, & Fleming, 1999; Magnusson & Fleming, 1995; Mattson, Williams, Rosenblatt, & Morrell, 2001; Pereira, Seip, & Morrell, 2008; Wilsoncroft, 1969).

The powerfully rewarding effects of offspring are most clearly demonstrated by laboratory procedures that require mothers to learn a task using pups as a reinforcing stimulus. With very little experience interacting with young, new mother rats will develop a robust operant bar-press response when pups constitute the reinforcement and when females can retrieve pups from the hopper to a corner of the cage (Lee et al., 2000; Wilsoncroft, 1969). Similar effects are also seen in hormonally primed mice (Hauser & Gandelman, 1985). Simple exposure to pup cues in the absence of the ability to retrieve them is a less powerful reinforcer in rodents, indicating that the "consummatory" responses necessarily involving mother-offspring physical contact are particularly salient for the mother's perception of offspring as being rewarding (Lee et al., 2000; Wansaw, Pereira, & Morrell, 2008; Wilsoncroft, 1969). Rhesus monkeys will bar-press at high rates for the opportunity to simply see their infant, though (Pryce, 1993).

Other work using a conditioned place preference apparatus has found that new mother rats will also develop a preference for a unique environment that has been associated with pups over one previously associated food (Fleming, Korsmit, & Deller, 1994a) or with cocaine (Mattson et al., 2001; Seip et al., 2008). Consistent with the temporal course of mothering that emerges close to parturition and wanes as lactation progresses, late-pregnant and late-lactating (day 16) animals prefer the cocaine-associated chamber (Mattson, Williams, Rosenblatt, & Morrell, 2003; Seip et al., 2008). This phenomenon depends both on maternal and offspring factors, because late-postpartum dams will more readily establish a conditioned place preference for a pup-related chamber if young pups are used as the conditioned stimuli instead of older pups, or if the maternal motivation of late-postpartum dams is elevated by separating them from their older pups before conditioning (Wansaw et al., 2008).

Humans

Despite major species differences in the formation of bonds with infants, with humans forming very strong but not necessarily exclusive bonds with their infants, there are still considerable universals between non-human and human animals in the importance of infant cues in regulating maternal behavior. Human mothers receive multisensory stimulation right after delivery while they hold, look at and talk to their infants (Fleming, 1990). At this time, infant cues may help establish maternal behavior by increasing maternal arousal or by

producing motivational states that favor caregiving. For instance, mothers' responses to infant cues change in relation with hormonal changes occurring around parturition (Barrett & Fleming, 2011), and prenatal educational intervention for first-time mothers that includes information on how responding to the infant's cues induces beneficial effects on the quality of mother-infant interaction during the first 24 hours following birth (Leitch, 1999). Infant cues also induce specific maternal behavior patterns or inhibit behaviors incompatible with appropriate caregiving (Corter & Fleming, 2002). Finally, another function of infant stimuli that is in common with non–human mammals is that the infants provide salient cues that mothers can use to recognize their babies, which is necessary for mother-infant attachment to occur.

Olfactory cues—While olfaction is not the dominant sensory modality for human maternal care, odors nonetheless appear to be significant for early mother-infant interactions (Porter, 1991). Human new mothers are attracted to the body odors of their own (Porter, 1991; Porter, Cernoch, & McLaughlin, 1983) and other infants (Fleming, Ruble, Krieger, & Wong, 1997a). Mothers with more experience with infants exhibit both more attraction to infant odors and more positive maternal attitudes to infants and mothering (Fleming, Steiner, & Corter, 1997b). If mothers exhibit positive attitudes towards infant related odors, these cues could help mediate the earliest mother-infant interactions and establish successful breastfeeding.

Like other mammals that form an attachment to their own young, humans can discriminate their own infants and may show a preference for them. For example, olfactory identification of newborns has been demonstrated using soiled cotton vests (Schaal, 1986; Schaal et al., 1980) and early familiarization with infant odors facilitates this effects because mothers who have 30–40 minutes of contact with their neonate immediately after delivery show a greater proportion of correct choices than mothers who have less than 5 minutes of immediate exposure to their infant. Evidence for olfactory recognition of infants has been found in several subsequent studies (Corter & Fleming, 2002; Fleming, Steiner, & Corter, 1997b; Kaitz, Good, Rokem, & Eidelman, 1987; Porter et al., 1983; Porter, Cernoch, & Balogh, 1986; Russell, Mendelson, & Peeke, 1983), including a study showing that mothers who deliver by cesarean section and experienced limited (3 hours) pretest contact with their infants are still able to identify the shirt worn by them (Porter et al., 1983). Olfactory similarities between mothers and their children could account for this rapid identification and parents have been reported to mention that the scent of their baby reminded them of other family members (Porter et al., 1983; 1986). Furthermore, adult subjects are able to correctly match the body odors of mothers and their children (Porter, 1991; Porter, Cernoch, & Balogh, 1985), which could be mediated by shared portions of genomes between mothers and their children. Recognition performance is also related to hormones, as mothers with higher cortisol levels are better able to recognize their own infants' odors at two day postpartum (Fleming, Steiner, & Corter, 1997b). Interestingly, these mothers are also more attracted to their infant's body odor, suggesting that activation of the hypothalamic-pituitary adrenal axis could contribute to higher recognition performance by increasing maternal attraction to infant odors.

Somatosensory cues—Human mothers groom, stroke, and clean their newborns with their hands and fingers. They kiss and nuzzle with their mouths and faces. Thus, similar to nonhuman mothers, tactile stimulation is a primary component of most human caregiving behaviors. Touching is observed as soon as delivery ends, and during the first minutes after birth mothers are engaged in an intense tactile experience, spending more than 80% of the time touching the baby's skin first with the fingertips and then the palm (Klaus, Kennell, Plumb, & Zuehlke, 1970). While these observations suggest that mothers are highly attracted to tactile cues from their infant, one study found that approximately 50% of mothers did not even touch their infants when they were first presented (Carek & Cappelli, 1981). The intense tactile experience of mothers affords them the opportunity to learn the distinctive features of their infants' skin. Mothers recognize the tactile characteristics of the dorsal surface of their own infant's hands if they had been with their infant for just an hour or more since birth, but not less, indicating a rapid learning process taking place soon after giving birth (Kaitz, Lapidop, & Bronner, 1992).

Tactile stimulation also can come from breastfeeding, which can be intense because tactile sensitivity of the nipples and areolae is higher during the first few days postpartum compared to during pregnancy (Robinson & Short, 1977), and this heightened stimulation could be part of the mechanisms involved in attraction to the baby. In support, mothers who breastfeed display greater sensitivity to infant cues while interacting with them at three months postpartum (Britton, Britton, & Gronwaldt, 2006) and have a greater attentional engagement with infant distress signals compared to women who bottle feed (Pearson, Lightman, & Evans, 2010). One potential mechanism involved in these differences is the difference in the time these mothers spend interacting with their baby and thereby their sensitivity to infant cues. Of course, OT and PRL are potently released peripherally and probably intracerebrally during breastfeeding and so in these women may positively influence the brain regions involved in processing infant cues.

Visual Cues—Gaze is an important aspect of all primate behavior and mothers spend a great deal of time looking at their newborn infants (Bard, 1995). In humans, intense interest in establishing and maintaining eye-to-eye contact is observed just after delivery, with mothers spending more than 20% of their time "*en face*" with their infant (Klaus et al., 1970). A set of infantile features (e.g., large head, big eyes, protruding forehead; Lorenz, 1971) could contribute to the marked attraction to the baby's face. In fact, infant faces with artificially high baby schema are perceived as more cute and elicit stronger motivation for caretaking than the faces with low baby schema (Glocker et al., 2009). This baby schema can have other behavioral consequences. For example, photographs of infants ranked as most cute are looked at longest and those ranked least cute looked at for the shortest length of time (Hildebrandt & Fitzgerald, 1978). In addition, parturient mothers of infants with the most attractive faces, rated by a panel of judges, are engaged in more affectionate behavior with their babies than do mothers of unattractive infants. The latter mothers engage in more routine caregiving and can be more attentive to other people than to their infant (Langlois, Ritter, Casey, & Sawin, 1995). Infant's gaze can also evoke species-typical exaggerations in maternal vocalization, facial expression, and gaze during face-to-face play (Stern, 1974). Visual stimuli from the infant also induce emotional and physiological arousal. Faces of

babies are particularly capable of eliciting positive emotions in adults (Senese et al., 2013) and watching silent videotape of one's own baby evokes cardiac acceleration and large skin conductance responses in mothers (Wiesenfeld & Klorman, 1978).

Thus, similar to diurnal ungulates, facial characteristics are salient for the development of human mothers' attraction to the baby, which may facilitate the mother's capacity to rapidly recognize their neonate's face. Within 33 hours after delivery mothers are able to recognize photographs of their own baby faces (Porter, Cernoch, & Balogh, 1984), although one might suspect this recognition might occur earlier if a three-dimensional representation of the infant face is presented to the mothers. Physical resemblance between the infant and the mother, evaluated by judges, probably promotes this visual recognition (Porter et al., 1984). Given these effects of infant visual cues on maternal attraction to and recognition of the neonate, it is interesting that blind mothers most often communicate and interact very effectively with their infant by emphasizing the remaining available sensory cues, although disruption or delay in communication may sometimes occur (Adamson, Als, Tronick, & Brazelton, 1977).

Auditory cues—Right after birth the mother is exposed to her baby cries, which is most often a sign of a healthy baby. However, the significance of crying rapidly changes and evokes maternal arousal and hopefully approach behavior. In fact, crying is the most effective signal promoting proximity because it strongly elicits behaviors aimed at terminating the sound. The most common response to a crying infant is to pick it up and hold it, which is as effective as feeding to terminate crying (Bell & Ainsworth, 1972). Nevertheless, there is tremendous variability in maternal responsiveness to baby crying during the first year of life, with 4–97% of cries ignored by mothers. Maternal ignoring has consequences on vocal behavior of the baby and increases the likelihood that a baby will cry more frequently. More interestingly, those babies who show high duration and frequency of crying are low in facial and gestural communication, suggesting that maternal responsiveness to baby crying during the first year encourages the development of communication (Bell & Ainsworth, 1972).

Some studies suggest that mothers can recognize different types of cries. Gustafson and Harris (1990) found that women readily discriminated between the pain and hunger cries, possibly based on their differing fundamental frequencies (Wiesenfeld, Malatesta, & Deloach, 1981), but that intensity of distress was more salient than its cause. Furthermore, Stallings et al. (2001) reported that first-time mothers two days following delivery respond more sympathetically to pain than to the hunger cries. Not only do acoustic features of cries differ across types of cries, but infant cries also individually differ in their fundamental frequency and its modulation (Gustafsson, Levrero, Reby, & Mathevon, 2013), and this vocal signature supports recognition by mothers. Indeed, mothers distinguish between own infant's cries versus other infants' cries (Gustafsson et al., 2013; Morsbach & Bunting, 1979) within 48–72 hours after parturition (Formby, 1967). Factors positively affecting this recognition include the amount of time spent with the baby, whereas time spent with other babies has a negative effects on this learning of one's own baby cries (Gustafsson et al., 2013). This recognition is also accompanied by differential autonomic responses, with patterns of maternal heart rate change differing in response to audiotapes of own versus

other's baby cries. Additionally, heart rate acceleration follows hearing cries of one's own infant and is interpreted as arousal preparatory to active coping, whereas deceleration follows the cries of other infants and is interpreted as attention or passive coping (Giardino et al., 2008; Stallings et al., 2001; Wiesenfeld et al., 1981).

Infants and their sensory cues are rewarding—Human infants can be rewarding and activate regions of the adult brain that are associated with reward and pleasure (e.g., Kringelbach et al., 2008). Unlike the rat, however, where specific tasks are administered to test just how rewarding pups may be to the mother, much of the human literature that illustrates that the young are attractive and then rewarding depends on other indicators. These include the existence of associations between mothers' subjective evaluation about the 'pleasantness' of the young or their specific sensory cues (e.g., odors or cries), their subjective feelings of attachment to their infant, their behavior while interacting with infants and their attention and brain activation patterns in response to infant cues. Furthermore, infant cues can grab and/or disrupt adult attention (Dudek, Faress, Bornstein, & Haley, under review), depending on the valence of cues. For instance, adults are more distracted by infant cries than by infant laughs. As summarized above, studies show that after giving birth, mothers express heightened attraction to infant odors and sympathy to infant cries, and the extent of sympathy or attraction is associated with mothers' expressed maternal behavior and their heart-rate and cortisol responses to those cues (Fleming et al., 1993; Fleming, Steiner, & Corter, 1997b; Giardino et al., 2008; Porter, 1991; Porter et al., 1983; Stallings et al., 2001). Moreover, experience with salient infant cues enhances maternal attention to them, as illustrated in studies by Pearson and colleagues who examined attentional capture or bias by infant and adult faces in women during late pregnancy (Pearson, Lightman, & Evans, 2011). Their task involved measuring how rapidly mothers could detect a neutral stimulus presented in the peripheral field while they focused on distressed or non-distressed infant faces. Mothers were much less able to disengage from the distressed infant face than from the non-distressed infant face, and this result was related to later maternal self-reported postpartum bonding with their own infant. Also, in comparisons between parents and non-parents in their ERP responses to infant cues, Proverbio et al. (2006) reported that parents not only find infant cues more salient, but are also better able to discriminate amongst different infant emotional expressions, suggesting their heightened attention to discriminating features of the infants.

While too little attention bias to infant cues is clearly problematic for parenting, too much attention bias to infant cues can also interfere with parenting. Mothers who were overly distractible to infant cues and unable to selectively attend to a target task and ignore infant cries had greater insecure maternal attachment history (Haley & Ryan, under revision) and less emotion regulation as indexed by reduced control of their autonomic activity (Haley & Jabrayan, in preparation). Taken together, mothers showing moderate attention biases to infant cues - rather than too little or too much - exercise greater cognitive flexibility and selective attention, which may enhance parenting experiences with rewarding infant cues.

V. Emotion and mood regulation

The enhanced salience of infant cues seen in many new mothers is positive in valence and increases the rewarding properties of the relationship between mother and young. However, the early postpartum period has many other psychological effects on the mother. New mothers often undergo substantial changes in their emotional regulation and mood states that affect how they interact with their young. In humans, both anxiety and depression are well studied for their effects on mothering, and both have been modeled in postpartum laboratory rodents in order to more mechanistically study their causal factors in the mother and consequences for how she interact with the offspring.

Non-human mammals

Anxiety-like behaviors—Non-mother rats are often neophobic and display high levels of anxiety-related behaviors, as indicated by their cautious approach to and engagement with new stimuli and low exploration of novel environments (Fleming et al., 1989; Fleming & Luebke, 1981; Fleming, Vaccarino, & Luebke, 1980). In contrast, most mother rats are generally less neophobic, fearful or anxious. This change in emotional regulation in most mothers contributes to both the successful onset and maintenance of caregiving. One of the primary sensory systems that prevents non-mother rats (i.e., adult virgins) from responding maternally, is the olfactory system. Peripheral or central manipulations that prevent olfactory input from reaching emotion regulating regions of the brain, including the amygdala, reduces pup-related avoidance or anxiety-related behavior in virgin female rats (Fleming et al., 1980; Fleming & Rosenblatt, 1974c; Morgan, Watchus, Milgram, & Fleming, 1999; Numan et al, 1993).

It seems unclear whether the primary effects of olfactory manipulations that promote the onset of mothering, or the hormones of pregnancy and parturition that naturally accomplish this, do so by alleviating olfactory inhibition specifically of caregiving behaviors or by generally changing females' emotional state to allow their interaction with young. It may be the former situation. Female rats' interest in pups increases in the final few days of pregnancy (Rosenblatt & Siegel, 1975), but their anxiety-related behaviors in an open field or elevated plus-maze do not differ from that seen in cycling females (Neumann et al., 1998; Zuluaga et al., 2005). Furthermore, if a general rather than specific (i.e., pup-related) reduction in neophobia is the basis for the onset of maternal behavior, anxiolytic drugs would be expected to hasten the onset of mothering in sensitized nulliparous rats, but they apparently do not (Ferreira, Picazo, Uriarte, & Pereira, 2000). Lastly, while olfactory bulbectomy or peripheral anosmia increase maternal responsiveness they do not reduce anxiety-related behaviors (Mayer & Rosenblatt, 1977; 1993). One could conclude that inhibition of mothering in non-maternal animals may be more related to aversive pup-related cues, which can be distinguished from a more general reduction in aversion-related behaviors to a range of negatively-valenced stimuli.

Most studies find that such a general reduction in neophobia, fear, and anxiety does occur after most females give birth. In postpartum laboratory rats, this change can be found in many paradigms within 24 hours after parturition, lasts for a few days or up to about one week, and requires recent physical contact with the litter although suckling *per se* is

unnecessary (Lonstein, 2005; 2007). Some reduction in neophobia, fear, and anxiety even accompanies maternal state in sensitized nulliparous female rats (Agrati, Zuluaga, Fernandez-Guasti, Meikle, & Ferreira, 2008; Ferreira, Pereira, Agrati, Uriarte, & Fernandez-Guasti, 2002; Pereira, Uriarte, Agrati, Zuluaga, & Ferreira, 2005). This blunting of maternal emotional reactivity could have implications for many postpartum behaviors. For example, it could affect mothering behaviors by allowing dams to be better equipped to ignore relatively benign environmental threats and instead focus on the pups. Reduced anxiety postpartum may also be permissive for the elevated aggression that dams direct toward intruders to the nest (Lonstein & Gammie, 2002), and may compel lactating mothers to forage further and further from the nest in search of the caloric requirements necessary to maintain their high metabolism (Woodside, Budin, Wellman, & Abizaid, 2012). However, anxiety that is too low could also be problematic in some circumstances. Studies of the relationship between natural variation in anxiety and mothering in laboratory rodents find no significant relationship when tested under relatively benign conditions (Curley, Jensen, Franks, & Champagne, 2012), but mother rats genetically selected for very low anxiety are relatively ineffective in their ability to respond to pups under novel or otherwise challenging conditions that can interfere with maternal motivation (Neumann, Krömer, & Bosch, 2005). In fact, it has been suggested that a moderate level of anxiety that is neither too high (rendering dams over-reactive to threat) nor too low (rendering them naively under-reactive) is optimal for maternal ability to focus attention on the needs of the pups despite threats in the environment (Ragan & Lonstein, 2014). Furthermore, recent work shows that whereas there are individual differences in female rat trait anxiety outside the postpartum period, females' anxiety converges to a more homogeneous level after they give birth and the trait-related differences are eliminated. These effects depend on recent maternal contact with young because if mothers are separated from young a few hours before anxiety testing, trait differences reemerge (Ragan & Lonstein, 2014).

Depression-like behaviors—Studies using the forced swim and sucrose preference tests as indicators of a depressive-like phenotype have revealed no differences in depression-like behaviors between late-pregnant or early postpartum laboratory rodents and nulliparous females, although there may be a drop in such behaviors around days 14–17 of pregnancy (Craft, Kostick, Rogers, White, & Tsutsui, 2010; Frye & Walf, 2004a; Lavi-Avnon, Shayit, Yadid, Overstreet, & Weller, 2005a; Lavi-Avnon, Yadid, Overstreet, & Weller, 2005b; Maguire & Mody, 2008; Molina-Hernández & Téllez-Alcántara, 2001; Molina-Hernández, Contreras, & Téllez-Alcántara, 2000; Neumann et al., 1998; Pawluski, van den Hove, Rayen, Prickaerts, & Steinbusch, 2011). These negative results should be considered in light of the fact that these tests are probably sensitive to the changes in females' fat and lean body mass, food intake and metabolic demands that change across reproduction. In contrast to studies of peripartum rats, other studies examining ovariectomized virgin females given exogenous ovarian hormones to mimic late pregnancy followed by their abrupt withdrawal have often found an increase in depression-like behaviors (Beckley & Finn, 2007; Galea, Wide, & Barr, 2001; Green, Barr, & Galea, 2009; Schiller, O'Hara, Rubinow, & Johnson, 2013; Stoffel & Craft, 2004; Suda, Segi-Nishida, Newton, & Duman, 2008). Because late-pregnant and parturient rats generally show no changes in depression-like behaviors, these exogenous hormone withdrawal studies must be missing some meaningful facets of the

natural model that prevents these behaviors. These could include something about the precise patterns of natural ovarian hormone flux, other neurochemicals that are normally changing along with the ovarian hormones, or the litter contact that begins immediately postpartum.

Because stress is a major contributor to depression in humans, some recent studies have incorporated stress into their peripartum rodent models to increase face validity. Most find that physical and/or psychosocial stress imposed over many days of pregnancy increases the time that females spend immobile in the forced swim test when tested during lactation (Haim, Sherer, & Leuner, 2014; however see Hillerer, Reber, Neumann, & Slattery, 2011; Leuner, Fredericks, Nealer, & Albin-Brooks, 2014; Smith, Seckl, Evans, Costall, & Smythe, 2004). Stress-induced corticosterone release is not the only mechanism underlying this behavioral change, because injecting pregnant rats with corticosterone alone does not alter their postpartum forced-swim behavior compared to vehicle-treated controls (Brummelte & Galea, 2010). The increased depression-like behavior consequent to pregnancy stress can be associated with changes in postpartum mothering. These changes have included reduced time in the nest and nursing (Leuner et al., 2014; Smith et al., 2004), which is similar to what occurs when pregnant rats had been treated with corticosterone (Brummelte & Galea, 2010) or when stress is applied just postpartum (Nephew & Bridges, 2011), but at other times manifests as abnormally increased nursing (Hillerer et al., 2011) and still others have found no effects of pregnancy stress alone on later maternal behavior (Pardon, Gérardin, Joubert, Pérez-Diaz, & Cohen-Salmon, 2000; Pawluski et al., 2012). Clearly, more work is needed to clarify the relationship between depression-like behaviors and mothering in unstressed and stressed parturient laboratory rodents.

Humans

Anxiety—Sensitive responding to infants requires that mothers are affectively prepared to interact with them. Accordingly, maternal psychological well-being greatly impacts early human mothering. For many women, the first postpartum week is an exciting and positive experience, one that maps on to many changes in mothers' awareness of her new role and the experience of 'falling-in-love' with the baby. Studies of the normal changes in anxiety across the peripartum period and beyond in new mothers report mixed results, with some studies showing a decrease in anxiety (Figueiredo & Conde, 2011; Vesga-López et al., 2008), others showing an increase in anxiety (Britton, 2008), and yet others reporting no change (Leckman et al., 1999). These discrepancies may be due to different methodologies used for assessing anxiety or the postpartum time in which anxiety is evaluated. For instance, Figueiredo and Conde (2011) observed that compared to pregnancy, state anxiety remains high only during the first postpartum days, but then decreases across the first three months postpartum. A variety of hormones, neuropeptides, and other neurochemicals released or inhibited when human mothers receive suckling or other tactile inputs from their infants are presumed to contribute to a decrease in anxiety, although their mechanisms of action for this purpose in women are not particularly well studied. Some likely candidates are those known through experimental work to act centrally to affect anxiety in postpartum rodents, including OT, PRL, vasopressin, corticotropin releasing hormone, GABA, norepinephrine and serotoinin (see Altemus et al., 2004; Carter, Altemus, & Chrousos, 2001;

Heinrichs et al., 2001; Lonstein, 2007; Lonstein, Maguire, Meinlschmidt, and Neumann, 2014).

Regardless of the changes in anxiety that occur for postpartum women as a whole, there is still a subpopulation of mothers who experience a worsening of pre-existing anxiety symptoms or the new onset of an anxiety disorder. Diagnosis of generalized anxiety disorder is up to twice as high in pregnant or postpartum women when compared to the general population (4–8% vs. 3–4%; Ross & McLean, 2006). Because screening for anxiety in the peripartum population is rare, it is probably underreported to tremendous degree and it has been suggested that up to 20–30% of women are truly affected by high peripartum anxiety (Britton, 2005; 2008; Matthey, Barnett, Howie, & Kavanagh, 2003; Ross & McLean, 2006). Such differential susceptibility to anxiety in new mothers is partly driven by individual differences in a number of genetic and experiential factors (see Agrati and Lonstein, 2015 for examples) and certainly seems maladaptive because high anxiety has a particularly negative affect on maternal caregiving. Anxious mothers show less warmth, more disengagement, are more critical of their infants, and are prone to catastrophizing (Moore, Whaley, & Sigman, 2004; Whaley, Pinto, & Sigman, 1999; Woodruff-Borden, Morrow, Bourland, & Cambron, 2002). Akbari et al. (in preparation) recently showed that mothers who experienced higher levels of anxiety specifically in response to infant pain and hunger cries tended to be less attentive to their 4–6 month old infants during a free interaction. These characteristics of anxious mothers have detrimental consequences for infant cognitive and socioemotional development (Glasheen, Richardson, & Fabio, 2010). The factors generating such heterogeneity in peripartum anxiety are numerous and include a host of individual, social, and contextual variables. Some examples of these are a history of anxiety, socioeconomic status, social support, fatigue, physical exercise (Britton, 2008; Correia & Linhares, 2007; van Bussel, Spitz, & Demyttenaere, 2009; Vesga-López et al., 2008), and individual differences in women's genetic profile and physiology (Eley, 2007; Macbeth & Luine, 2010). Furthermore, similar to laboratory rats, physical contact with infants even without suckling transiently reduces anxiety (Heinrichs et al., 2001), so when postpartum women are assessed for anxiety relative to their last interaction with their infants becomes critical. Finally, womens' early-life experiences and temperament of their infants modulate postpartum anxiety. Agrati, Brown, Steiner, & Fleming al. (in press) recently evaluated the effect of early adversity in mothers' family of origin and infant temperament on the course of state anxiety in women during pregnancy and over the first two postpartum years. They found that greater early adversity was associated with higher pregnancy anxiety, followed by a marked decrease once the baby was born, and a subsequent increase during the later postpartum period. Moreover, women of children high in temperamental negative affectivity who also experienced greater early adversity had elevated and flat anxiety trajectories. These results show that maternal anxiety dynamically changes through the postpartum period with a course that is affected both by previous experience and experience related to the child's temperament. However, it is also likely that mothers' anxiety itself may affect infant temperament through anxiety-related alterations in maternal behavior and Jonas, Atkinson, Steiner, Meaney, Wanzana, & Fleming (in press, 2015) recently found that among mothers who did not breastfeed at 3 months, that mothers' anxiety predicted both reduced maternal sensitivity at 6 months and later elevations in infant negative affectivity over a year later.

That is, breastfeeding appeared to protect mothers from anxiety-related effects on later maternal behavior and infant negativity.

Depression—In addition to anxiety, a substantial number of women also experience depressive symptoms after giving birth (Friedman & Resnick, 2009; Gale & Harlow, 2003; Marcus, 2009). The very common, but fortunately transient, postpartum "blues" occurs in almost 85% of women but lasts less than 2–3 weeks after parturition (Gale & Harlow, 2003; Henshaw, Foreman, & Cox, 2004). Postpartum depression resembles other episodes of major depression that occur outside the postpartum period, with the exception of its unique time of onset and course of remission usually within 6–8 months. Postpartum depression is highest in the third month postpartum, but has a comparably high rate from mid-to-late pregnancy to the first few months postpartum, highlighting the reproductive period as a time of increased risk for the onset of depression (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Gavin et al., 2005). Many have suggested that there is a neuroendocrine basis for postpartum depression, one that involves withdrawal of hormones at parturition, but this is not necessarily the case because depression rates do not significantly differ between postpartum women and women who recently adopted infants or toddlers (Fields, Meuchel, Jaffe, Jha, & Payne, 2010; Mott, Schiller, Richards, O'Hara, & Stuart, 2011). Non-parturient humans do undergo changes in their endocrine systems after they become parents and interact with infants (Storey, Walsh, Quinton, & Wynne-Edwards, 2000), but one could assume such changes are less than what occurs in parturient women, so non-endocrine factors must be relevant for maternal depression (Goodman, 2004). Such factors include their history of depression, infant colic, seasonal factors, disrupted sleep, socioeconomic status, lack of social support, stressful recent life events, marital conflict, and early childhood adversity (Dennis, Heaman, & Vigod, 2012; Di Florio et al., 2013; Lancaster, Gold, Flynn, & Yoo, 2010; Milgrom et al., 2008; O'Hara & Swain, 1996; Viguera et al., 2011).

There have been many studies of the effects of postpartum depression on human maternal behavior. These studies show that mothers with postpartum depression tend to be more intrusive and irritated, and respond with less sensitivity and contingency to their babies. Depressed mothers are also likely than non-depression mothers to respond more negatively to their infant and have disrupted patterns of communication with them (Beebe et al., 2008; Chung, McCollum, Elo, Lee, & Culhane, 2004; Feldman & Eidelman, 2007; Herrera, Reissland, & Shepherd, 2004; Milgrom, Westley, & Gemmill, 2004; Paris, Bolton, & Weinberg, 2009; Righetti-Veltema, Conne-Perreard, Bousquet, & Manzano, 2002). Later during the postpartum period, depressed mother-infant dyads exhibit reduced mutual attentiveness, vocal and visual communications, touching interactions or smiling compared to postpartum non-depressed dyads (Field, 1990; Fleming, Ruble, Flett, & Shaul, 1988; Righetti-Veltema et al., 2002). In an excellent example of this work, Field and colleagues (Field et al., 2007) found that when compared to non-depressed mothers, mothers with postpartum depression were less interactive with their four-month-old infants at baseline before adopting a still face, as well as in the reunion period after the still face. The latter finding is especially telling because the main feature of the reunion period of the still-face paradigm is to attempt to reinstate more positive interaction or regulate the emotions of the

infant. More practical, but equally important, maternal activities such as breastfeeding, bedtime routines, medical care and safety practices, are also negatively affected by postpartum depression (see Field, Diego, & Hernandez-Reif, 2009).

VI. Postpartum learning, cognition, and executive function

In addition to the mothers' emotional state, their cognitive and executive functions also affect how new mothers cope with their environments and interact with their offspring. Mothers' behavior does not only involve the species-characteristic responses that were described above. Their behavior also involve more complex sequential ordering of responses, selectively inhibiting some responses and not others, an ability to shift attention between different young and between the young and other cues in the environment as relevant, showing flexibility in where and when to engage in different mothering behaviors depending on the social and physical context, and retaining earlier-acquired experiences. These properties of attention, flexibility, planning, and working memory are collectively known as 'higher-order' executive functions.

Non-human mammals

Because high maternal responsiveness persists long after parturition and is thought to be non-hormonally driven, processes involved in high-order cognitive processes including learning about the pups become relevant for the maintenance of maternal behavior (Bridges, 1975; 1977; Cohen & Bridges, 1981; Orpen & Fleming, 1987; Orpen, Furman, Wong, & Fleming, 1987). In comparison to rat mothers who are separated from young at parturition and whose responsiveness declines immediately, mothers with as little as one hour of interaction with offspring on the second postpartum day have high maternal responsiveness for up to 10 days, while mothers with 24 hours of experience are responsive for three weeks or longer (Bridges, 1975; 1977; Cohen & Bridges, 1981; Orpen et al., 1987; Orpen & Fleming, 1987). The processes underlying this 'maternal experience effect' involve learning and memory systems recruited when the mother interacts with her young (Morgan et al., 1992). The specific cues received that are necessary for this effect are tactile - exposure to only pup odors after parturition is insufficient for dams to sustain high responsiveness, whereas crouching over the litter and receiving somatosensory stimulation of the ventrum contribute to the learning process (Morgan et al., 1992).

Early postpartum learning also occurs in sheep, and this learning maintains their maternal responsiveness beyond the peri-partiuritional period (Lévy & Keller, 2008). However, maternal responsiveness fades rapidly. A 36–72 hour separation period that follows 4 hours of contact after parturition induces rejection of the familiar lamb (Keller, Meurisse, & Lévy, 2005; Lévy et al., 1991). This decline in maternal responsiveness cannot be compensated for by increasing initial mother–young contact because the reject is also observed when the separation is performed after a week of postpartum interaction (Keller et al., 2005). This result suggests that contrary to rodents, there is no long-term retention of maternal responsiveness and that continuous sensory stimulation coming from the young are necessary for its maintenance. However, the difference observed between rodents and sheep could instead be the result of the paradigms used. In rodents, the response often measured after a long-term separation is the latency of sensitization as maternal responsiveness can be

induced after prolonged contact with pups that could last several days, whereas in sheep the spontaneous response during a short presentation of the lamb (3 min) was measured. It is possible that at the time of the test, unresponsive ewes may become maternal if given a longer period of exposure to the lamb. That is, an increase in the observation period in sheep would be necessary to allow direct comparisons between rodents and ungulates. Maternal selectivity can, however, be strengthened over time. Although selective mothers exposed to the lamb for 4 hours just after birth are not able to retain selectivity after 24 or 36 hours of separation, memory of the lamb is maintained if ewes and their lambs have been in contact a week (Keller et al., 2005; Lévy et al., 1991). Hence, offspring recognition memory is labile and has a short duration during the initial postpartum period, whereas maternal selectivity strengthens over time, suggesting the involvement of consolidation processes for emergence of the latter.

Once mothers have initially expressed maternal behavior and consolidated the experience, the quality and intensity of the expressed behaviors depend heavily on how attentive mothers are to the relevant cues (Lovic & Fleming, 2004), how flexible they are in their behaviors (Lovic & Fleming, 2004), and how well they regulate their impulsivity (Lovic, Keen, Fletcher, & Fleming, 2011a; Lovic, Palombo, & Fleming, 2011b). These executive functions are largely mediated by the medial prefrontal cortex (Afonso, Sison, Lovic, & Fleming, 2007; Dalley, Cardinal, & Robbins, 2004) and meso-striatal-cortical dopamine systems (Dalley et al., 2004; Phillips, Vacca, & Ahn, 2008) (see below). The link between executive functions and mothering are indicated by data showing that rat mothers who make more errors on the attention set-shifting task or on the prepulse inhibition task show reduced maternal behavior (Lovic & Fleming, 2004). Moreover, orthogonal to these effects, mothers who lick their young more are also best at inhibiting responses to irrelevant environmental stimuli (Lovic & Fleming, 2004) and have reduced motor impulsivity (Lovic et al., 2011b). These effects of inhibition on mothering seem to be restricted to motor inhibition and not cognitive inhibition (Lovic et al., 2011b).

In addition to attentional and impulsivity systems, mothers exhibit improved learning and memory, and in some cases the effects are quite long-lasting. While there is no evidence that new mothers perform better on simple conditioning tasks (Leuner & Shors, 2006), there is evidence that new mothers are better than non-mothers on social learning and memory tasks (Fleming, Kuchera, Lee, & Winocur, 1994b) and in some studies on spatial learning and memory tasks (Kinsley et al., 1999; Pawluski, Walker, & Galea, 2006b). In paradigms that test spatial memory, parous rats that had weaned their pups days, weeks, or even months before acquisition make fewer reference and/or working memory errors compared to nulliparous females (Gatewood et al., 2005; Kinsley et al., 1999; Lemaire, Billard, & Dutar, 2006; Love et al., 2005; Pawluski, Vanderbyl, Ragan, & Galea, 2006a; Pawluski, Walker, & Galea, 2006b; but for opposite results see Bodensteiner, Cain, Ray, & Hamula, 2006; Darnaudéry et al., 2007). A combination of mothering experience and the hormones of reproduction appear to contribute to the enhanced memory results because: 1) it is unclear if learning or memory are enhanced in pregnant rats (Bodensteiner et al., 2006; Galea et al., 2000), 2) such effect are not found in females whose pups were removed soon after parturition (Pawluski, Vanderbyl, Ragan, & Galea, 2006a), and 3) while nulliparous sensitized females also show enhanced spatial memory if they are tested within a few days

after their final interaction with pups (Kinsley et al., 1999; Lambert et al., 2005), this enhancement does not persist as long as it does in female rats with both reproductive and maternal experience (Pawluski, Vanderbyl, Ragan, & Galea, 2006a).

Humans

Women depend on changes in executive functions including planning, organization, flexibility, and attention for their ability to appropriately respond to their babies and children. Mothers with disturbed attachments to their own caregivers (disorganized/ unresolved) and to their own infants (irrational fear of loss of the infant), and mothers of disorganized infants (infants whose attachment strategies collapse under stress), show attentional difficulties when assessed with emotional Stroop tasks (Atkinson et al., 2009). Furthermore, mothers with fewer errors on extra-dimensional shift and spatial working memory tasks at 2–6 months postpartum are more sensitive in their interactions with their infants and show more contingent responding to infant cues (Gonzalez et al., 2012). This is particularly the case with teenage mothers, who tend to respond less sensitively to their infants. Teenagers in general, but teenage mothers especially, tend also to show much poorer attention, executive function, and impulse control (Chico, Gonzalez, Ali, Steiner, & Fleming, 2014; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; McAnarney, 2008; Rubia, Hyde, Halari, Giampietro, & Smith, 2010; Sturman & Moghaddam, 2011; Van Leijenhorst et al., 2010).

As mothers gain experience with their infants during the first few postpartum months, most feel increasingly attached to them - they express more positive attitudes, become more efficient at tasks such as feeding (Thoman, Barnett, & Leiderman, 1971; Thoman, Turner, Leiderman, & Barnett, 1970), and are more attuned to their infant's signals (Sagi, 1981). In analyzing the importance of early experience in developing and maintaining maternal behavior, the effects of separation versus contact at birth on mothers' initial interactions with their babies is of interest. Gaulin-Kremer, Shaw, and Thoman (1977) looked at differences in mothers' first extended interactions and found that the closer to parturition the first extended contact occurred, the more mothers held, talked to, and caressed their infants before actually nursing them. In general, however, the first extended contact did not occur until some hours after birth, and beyond the time when contact is supposed to be most critical. A number of other studies also suggest that maternal behavior is elevated when there are shorter intervals between birth and the mother's first extended contact with the infant. For instance, there is an inverse relationship between the interval to the first contact during the first day and the duration of maternal approach behavior (contact, hugging, talking to) at 3–4 days postpartum, although not at 6 weeks postpartum (Fleming, Steiner, & Anderson, 1987). Short-term experience effects on early maternal responding have also been suggested by studies that vary the timing of mother-infant contact during the first postpartum days (e.g., Grossmann, Thane, & Grossmann, 1981; see also Fleming et al., 1988; Leerkes & Burney, 2007). Taken together, these studies indicate that additional contact may facilitate maternal behavior in first-time mothers of term infants, although the benefits appear to be short-lived and occur only in some women.

In contrast to the positive effects of motherhood on some aspects of learning and memory in laboratory rodents, pregnancy and the postpartum period have generally detrimental effects on some memory in women. A recent meta-analysis indicates that most pregnant women subjectively state that they experience high levels of memory impairment, and these perceptions are supported by over a dozen controlled studies comparing pregnant/ postpartum and control women on standard objective measures of memory (Henry & Rendell, 2007). The studies included in the meta-analysis found that pregnant or postpartum women showed significantly lower performance in standard measures of working memory, free recall, and delayed free recall. Short-term, implicit, and recognition memory were unaffected by reproductive state, however, suggesting that only memory tasks involving high-demand cognitive processing are affected by reproductive state. Most studies on this topic published since the meta-analysis generally support these conclusions (e.g., Cuttler, Graf, Pawluski, & Galea, 2011; Henry & Sherwin, 2012; Wilson et al., 2011; but see Logan, Hill, Jones, Holt-Lunstad, & Larson, 2014). Endocrine factors associated with these memory impairments include higher circulating progesterone and PRL during pregnancy (Henry & Sherwin, 2012; Wilson et al., 2011), lower dihydroestradiol acetate during pregnancy, relatively high or low corticosterone pre- and postpartum (Buckwalter et al., 1999; Henry & Sherwin, 2012), and high estradiol during both time periods (Glynn, 2010).

VII. Neural basis of mothering

As we have described, there are multiple behavioral and psychological processes involved in mothering in non-human animals. These are regulated by multiple neural networks that interface with a core neural system underlying the basic motivation to respond to the offspring and provide caregiving behaviors. It will be seen below that this system is highly conserved across mammals. Moreover, it is obvious that maternal behavior is not unitary but is comprised of a collection of individual behaviors that each have their own mediating neural mechanisms. We first discuss the core maternal system regulating the 'motivation' to mother and the expression of individual components of the behavior, and then the broader systems with which this core system interconnects to effect appropriate maternal behaviors.

Non-human mammals

Maternal motivation: basal forebrain activating system (mPOA/BSTv)—For at least 40 years, the focus of work on the brain mechanisms underlying the onset and expression of maternal behavior has been on cells of the hypothalamic medial preoptic area (mPOA) and the adjacent ventral bed nucleus of the stria terminalis (BSTv). These sites integrate the hormonal signals of pregnancy and lactation with every modality of sensory information from offspring to regulate maternal behavior. Through their widespread afferent and efferent projections to most other regions of the hypothalamus, the mesolimbic system, and cortical structures (Simerly & Swanson, 1987a; 1987b), this core mPOA/BSTv neural system for mothering interfaces with other neural systems that regulate stimulus salience and control, reward, emotion, and executive function (Figure 1).

Early studies by Numan (1974) and Numan et al., (1977) clearly established the critical role of the mPOA/BSTv in maternal behaviors in laboratory rats by demonstrating that prepartum or postpartum lesioning eliminated maternal retrieval of pups and nest building.

This finding has since been replicated by others and extended by many studies reviewed in great detail elsewhere (Lonstein et al., 2014; Numan et al., 2006; Numan & Insel, 2003). The importance of a functional mPOA/BSTv for offspring caregiving behaviors extends to female laboratory mice (Tsuneoka et al., 2013), female hamsters (Miceli & Malsbury, 1982), ewes (Perrin, Meurisse, & Lévy, 2007), male laboratory rats (Kalinichev, Rosenblatt, & Morrell, 2000; Rosenblatt, Hazelwood, & Poole, 1996), and both sexes of the biparental California mouse (*P. californicus*) (Lee & Brown, 2002).

An important point for the conceptualization of mothering as a supracategory containing a collection of individual behaviors, often with differing sensory and neural determinants, is that mPOA/BSTv lesions do not abolish all maternal behaviors. Lesioned dams continue to hastily approach and sniff pups, suggesting that the mothers remain attracted to offspring (Kalinichev et al., 2000; Numan, 1974; Terkel, Bridges, & Sawyer, 1979). However, walking across a small test cage to investigate pups takes little effort, so is not a very rigorous test of maternal motivation. In fact, when mPOA-lesioned dams are tested in an operant bar-pressing paradigm, they are unwilling to exert much effort to gain access to pups - suggesting that the mPOA/BSTv maintains maternal motivation as well as execution of some maternal behaviors (Lee et al., 2000). Licking the pups appears less affected than retrieval and nest building when it has been assessed after mPOA/BSTv lesions (Kalinichev et al., 2000; Lee et al., 2000; Lee & Brown, 2002; Terkel et al., 1979) and only mild or moderate deficits are found in nursing after these mPOA/BSTv manipulations (Lonstein et al., 2014; Numan & Insel, 2003). All behavioral components including licking are, however, disrupted after similar manipulations in parturient sheep (Perrin et al., 2007). When interest for the lamb is challenged by a separation/reunion lamb test ewes with mPOA inactivation exhibit little reaction after separation of their lambs and do not show any motivation to reunite with them indicating that, as in rats, the mPOA is key for expression of maternal behavior and motivation. The mPOA is also involved in the maintenance of maternal responsiveness beyond parturition because maternal ewes infused at two hours postpartum with lidocaine for a 12-hour period show deficits in maternal responding (Perrin et al., 2007).

In contrast to the detrimental effects of mPOA lesions on the expression of rat maternal behavior during early lactation, Pereira and Morrell (2009) recently found that temporary deactivation of the mPOA with an anesthetic during the second week of lactation in rats *increased* maternal behavior, which is a time when the behavior normally declines. These intriguing results suggest that the mPOA undergoes a functional reorganization across the postpartum period that changes in the mother's behavior in accordance with the needs of her aging offspring, and additional studies further examining this possibility will be a great contribution to the literature.

The neurochemical influences on the mPOA/BSTv for maternal behavior include steroid hormones, neuropeptides, and neurotransmitters. When applied directly to the mPOA/BSTv, estradiol induces a rapid onset of maternal retrieving in rats (Fahrbach & Pfaff, 1986; Matthews Felton, Linton, Rosenblatt, & Morrell, 1999; Numan et al., 1977) and nest building in rabbits (González-Mariscal, Chirino, Rosenblatt, & Beyer, 2005). Surprisingly, prepartum mPOA implantation of tamoxifen (an estrogen receptor modulator with

antagonist properties) in the mother rat does not greatly impair the onset of maternal behavior at parturition (Ahdieh, Mayer, & Rosenblatt, 1987), but short hairpin interference of estrogen receptor alpha mRNA in postpartum mice appears to prevent maternal behavior (Ribeiro et al., 2012). As discussed above, the maintenance of maternal behavior does not require hormones, but it has been proposed that activation of estrogen receptors in the mPOA/BSTv ligand independently by neurotransmitters released when postpartum mothers interact with pups may still contribute to the behavior (Lonstein & De Vries, 2000a). In addition to estradiol, PRL and placental lactogens in the mPOA/BSTv facilitate the ovarian-hormone induced onset of mothering in laboratory rats (Bridges et al., 1990; Bridges, Rigero, Byrnes, Yang, & Walker, 2001; Bridges et al., 1997). The mPOA/BSTv is also a site of action for the facilitatory effects of OT and vasopressin (Bosch & Neumann, 2008; Kendrick, Lévy, & Keverne, 1992; Pedersen, Caldwell, Walker, Ayers, & Mason, 1994), and the inhibitory effect of endogenous opioids (Rubin & Bridges, 1984), on mothering. In sheep, however, infusions of OT into the mPOA do not induce all components of the maternal response, but only reduce aggression towards lambs (Kendrick, 2000). Retrodialysis infusion of OT in the paraventricular nucleus of the hypothalamus does induce full maternal response, though (Da Costa, Guevara-Guzman, Ohkura, Goode, & Kendrick, 1996). With regards to the traditional neurotransmitter systems, mother rats have higher dopamine (DA) and serotonin turnover in the mPOA compared to nulliparous rats (Lonstein, Dominguez, Putnam, De Vries, & Hull, 2003; Olazabal, Abercrombie, Rosenblatt, & Morrell, 2004), and DA and gamma amino-butryic acid (GABA) are released into the mPOA when ewes interact with lambs (Kendrick et al., 1992). These findings are consistent with experiments demonstrating that DA, GABA or noradrenergic receptor modulators infused into the mPOA/BSTv can positively or negatively affect maternal behaviors (Arrati, Carmona, Dominguez, Beyer, & Rosenblatt, 2006; Miller & Lonstein, 2005; Smith, Holschbach, Olsewicz, & Lonstein, 2012; Stolzenberg et al., 2007). The neurochemicals emanating from the mPOA and released onto its afferents to positively control maternal behavior include GABA (Lonstein and DeVries, 2000c; Tsuneoka et al., 2013), OT (Shaharokh et al., 2010), and galanin (Wu et al., 2014).

Maternal selectivity: main olfactory bulb and associated structures—Mothers of precocial species acquire the ability to recognize their own young soon after birth and refuse to nurse alien offspring (see Section II). In sheep, such discrimination relies on olfaction. The neural substrates controlling olfactory memory process differ from the brain regions regulating maternal responsiveness. Recognition of the young is mediated by the main olfactory bulb coding information about the familiar lamb's odor (Kendrick et al., 1992). Noradrenergic inputs from the locus coeruleus to the olfactory bulb are, in part, responsible for the formation of this memory (Lévy, Gervais, Kindermann, Orgeur, & Piketty, 1990; Pissonnier, Thiery, Fabre-Nys, Poindron, & Keverne, 1985). Increased norepinephrine release at parturition, with the help of OT, activates olfactory bulbs cells; this potentiates the glutamate system by the retrograde messenger, nitric oxide (Kendrick et al., 1997; Lévy, Guevara-Guzman, Hinton, Kendrick, & Keverne, 1993). This enhances cellular activity in response to own-lamb odors. In this way, this output is decoded by subsequent olfactory processing regions, including the cortical and medial nuclei (MeA) of the amygdala. Inactivation of either of these nuclei does not affect maternal responsiveness, but prevents

mothers from learning to discriminate their own from an alien lamb (Keller, Perrin, Meurisse, Ferreira, & Lévy, 2004b). The fact that maternal care is not inhibited after inactivating these amygdala sites indicates that the neural network involved in olfactory recognition of the lamb differs from the one involved in controlling maternal responsiveness. Interestingly, the cortical and medial regions of the amygdala project to diencephalic structures involved in the control of maternal responsiveness such as the mPOA (Meurisse, Chaillou, & Lévy, 2009). The neural network involved in olfactory recognition of the lamb also includes additional brain structures. For example, the entorhinal and piriform cortex are activated during lamb odor memory formation (Da Costa, Broad, & Kendrick, 1997a; Keller, Meurisse, & Lévy, 2004a) and these structure are critical in olfactory recognition memory (Petrulis & Eichenbaum, 2003; Sánchez-Andrade, James, & Kendrick, 2005).

Reward and mothering: mesolimbic dopamine system—The mesolimbic DA system is well-known for its role in goal-directed, 'rewarding' and motivated behaviors (Berridge, 2004), and as such, has an integral role in salience and rewarding properties of young, and maternal caregiving. Taken together, studies of mesolimbic DA's role in maternal behavior indicate that elevated dopaminergic signaling is most involved in the motorically active components of maternal behavior such as retrieval while its inhibition promotes motorically inactive nursing (see Stern & Lonstein, 2001). The source of the mesolimbic system, the ventral tegmental area (VTA), receives projections from the hormone- and pup cue-primed mPOA/BSTv for the expression of maternal behaviors; impaired retrieval and nest building are found in postpartum rats with knifecuts that disconnect the VTA from the mPOA (Numan & Smith, 1984), lesions of the entire VTA (Numan & Smith, 1984) or after more selective lesions of just the VTA's monoaminergic cells and fibers (Hansen, Harthon, Wallin, Löfberg, & Svensson, 1991). Conversely, chemically disinhibiting the dopaminergic cells of the VTA promotes the onset of maternal responding in nulliparous rats during a maternal sensitization paradigm (Byrnes et al., 2011). The nature of the chemical message that the VTA receives from the mPOA to promote maternal behaviors is, at least in part, OTergic (Pedersen et al., 1994; Shahrokh, Zhang, Diorio, Gratton, & Meaney, 2010).

The nucleus accumbens (NAC) is a primary target of ascending DA cells from the VTA. DA release in the core and shell regions of the NAC rises in mother rats before and during interaction with pups (Afonso et al., 2013; Afonso, King, Novakov, Burton, & Fleming, 2011; Afonso, King, Chatterjee, & Fleming, 2009; Champagne & Chretien, 2004; Hansen, Bergvall, & Nyiredi, 1993; Lavi-Avnon et al., 2008; Pereira & Morrell, 2011). In mothers, but not in non-maternal virgins, the release of DA is considerably greater to pups than to food stimuli (Afonso et al., 2009; 2011) and in different studies relates to the duration of pup-sniffing and licking (Afonso et al., 2009; 2013). Furthermore, because the hormones of pregnancy reduce basal DA levels in the NA shell in female rats, the magnitude of pup-evoked increase in DA release is enhanced, possibly functioning to increase the saliency of the pups (Afonso et al., 2008; 2009; 2011; 2013). Blocking the resultant D1 receptor activity (but not D2 receptor activity) in the NAC greatly impairs maternal retrieval and licking of pups (Keer & Stern, 1999; Numan, Numan, Pliakou, et al., 2005a), whereas stimulating

NAC D1 receptors stimulates the behaviors in nulliparous rats (Stolzenberg et al., 2007). Interestingly, activation of the D1 but not D2 receptors in the mPOA is also necessary for maternal retrieval and licking in laboratory rats, reflecting differential importance of their specific intracellular cascades for these and other motivated behaviors (Miller & Lonstein, 2005; Stolzenberg et al., 2010). While the focus of striatal DA release for maternal behavior has focused on the NAC (*i.e.*, ventral striatum), recent work on mice with a genetic restriction of DA release only in the dorsal striatum indicates that this alone is sufficient for almost normal mothering (Henschen, Palmiter, & Darvas, 2013).

In contrast to the motorically active components of mothering such as retrieval and licking, if the pups are placed into the nest and retrieving is not required, the amount of time mothers spend with pups after damage to the mesolimbic system is often found to be no different from control mothers. In fact, mesolimbic DA disruptions can even facilitate quiescent nursing behavior (Miller & Lonstein, 2005; Stern & Lonstein, 2001), indicating that DA-deprived mothers remain interested in pups and willing to maintain physical contact with them. Furthermore, deficits in the maternal motivation of female rats with low DA release can be overridden if the dams and pups are separated from each other for a few hours (Hansen, 1994; Keer & Stern, 1999; Pereira & Ferreira, 2006). Moreover, DA also influences the consolidation of maternal responsiveness; infusion of a D1 and D2 antagonist into the NAC in new mothers when they are initially exposed to pups blocks the formation of the long-term maintenance of maternal behavior that is based on early experience with pups (Parada, King, Li, & Fleming, 2008). Under normal conditions that permit sufficient mesolimbic DA stimulation in response to offspring cues, the NAC then communicates through reciprocal GABAergic connections with ventral pallidum (VP) for the execution of pup retrieval and licking. Lesioning the VP or infusing a GABA$_A$ receptor agonist into it prevents these behaviors (Numan, 1988; Numan, Numan, Schwarz, et al., 2005b).

Inhibition of mothering and sites of emotion regulation: amygdala and hypothalamus—In rats the excitatory mPOA/BSTv system regulating maternal behaviors is strongly suppressed under conditions that do not warrant offspring caregiving (e.g., in virgin females, males) by a network of inhibitory systems that process potentially aversive olfactory cues emanating from young. Lesions of brain sites that process this information and transmit it to the mPOA disinhibit maternal responding in female rats. Most studies on this topic have targeted the MeA, which when lesioned or chemically inhibited results in tolerance of neonates, eventual maternal responding, and reduced anxiety or fear in a novel environment (Fleming et al., 1980; Numan, Numan, & English, 1993; Sheehan, Paul, Amaral, Numan, & Numan, 2001). On the other hand, electrically stimulating the MeA inhibits mothering in non-hormonally primed experienced mother rats (Morgan et al., 1999). It is important to realize that in animals that require olfaction for their spontaneous or postpartum maternal behavior, such as many strains of laboratory mice (Gandelman et al., 1971b), MeA lesions would be expected to decrease or abolish positive responses to pups, and would likely do so by preventing mesolimbic DA release in response to offspring (Sato, Nakagawasai, Tan-No, Onogi, Niijima, & Tadano, 2010a; 2010b).

It is important to recognize that not all regions of the amgydala necessarily have a negative influence on maternal behaviors. Studies have shown that lesioning the basolateral amygdala

(BLA) does not hasten maternal responding in nulliparous rats (Numan et al., 1993), and while numerous studies have found that lesioning or inactivating the BLA in pregnant or postpartum rodents and sheep has minor or transient effects on caregiving (Lee et al., 1999, 2000; Martel et al., 2008; Keller et al., 2004b), GABAA receptor antagonism in the BLA and adjacent basomedial nucleus do impair retrieval of pups (Numan et al., 2010). When the BLA does have effects on postpartum maternal behavior, it may do so by receiving sensory inputs from the young and potentiating activity of the mesolimbic system via projections to the nucleus accumbens and ventral palladum (Numan and Stolzenberg, 2009).

In addition to projecting to the mPOA, the MeA has dense connections with the dorsal hypothalamic/anterior hypothalamic area (DH/AHA) and the ventromedial nucleus (VMN) of the hypothalamus, which probably contribute to the MeA inhibition of maternal behavior. The MeA's projections to these sites are activated in non-maternal rats forced to be exposed to pups (Sheehan et al., 2001) and excitoxic DH/AHA or VMN lesions facilitate retrieval and other aspects of mothering in nulliparous rats (Bridges, Mann, & Coppeta, 1999; Sheehan et al., 2001). The DH/AHA and VMN are part of the neural network involved in defensive responses to aversive stimuli (Canteras & Graeff, 2014), and their involvement to this system could underlie avoidance of neonates in non-maternal animals. Other sites traditionally involved in aversive responding such as the septum, central amygdala and midbrain periaqueductal gray have also been suggested to mediate the aversion to pups in non-maternal animals (Numan et al., 2006), but research is required to establish this possibility. So far, the work on the periaqueductal gray suggests that it has both a positive and negative role in mothering. Lesions of the dorsal periaqueductal gray revealed that is it necessary for the efficiency of retrieval (Lonstein & Stern, 1997>) while lesions of the ventrocaudal periaqueductal gray lesions reveal that it is a site of sensorimotor integration for suckling-induced nursing behavior (Lonstein & Stern, 1997; 1998; Lonstein, Simmons, & Stern, 1998). Lesions of these regions also prevent predator odors from disrupting maternal behaviors (Sukikara, Mota-Ortiz, Baldo, Felicio, & Canteras, 2010) and generally reduce anxiety-related behavior in postpartum rats (Lonstein et al., 1998), so perhaps would also prevent aversive pup cues from inhibiting the behavior in nulliparous females. The neurochemicals alleviating the negative influences of the amygdala, hypothalamus, septum and PAG on maternal behavior are probably many the same that act positively on the mPOA/BSTv to promote mothering. All of these inhibitory sites are dense in ovarian steroid and neuropeptide receptors and stimulating these receptors in some of these sites reduces anxiety, fear, and other aversive behaviors in female rodents (e.g., Bale et al., 2001; Figuera et al., 2008; Frye and Walf, 2004b; Spiteri et al., 2010).

Executive function and mothering: cortical contributions—As the field studying postpartum behaviors in laboratory rodents has expanded beyond pup-directed behaviors to study the 'higher-order' cognitive system influencing mothering, interest in the cortical control of mothering in laboratory animals has surged. Given that, some of the very earliest work on the brain control of mothering was, in fact, on the cortex but this work indicated little site-specificity for cortical control of maternal behavior (Beach, 1937). More recent research on this topic, though, has found roles particularly for the medial prefrontal cortex (mPFC) in caregiving behaviors. The major subdivisions of the mPFC (cingulate, prelimbic

and infralimbic) together have considerable anatomical connections with the mPOA/BSTv, hypothalamus, amygdala, mesolimbic system, as well as with other cortical association, sensory, and motor areas (Floyd, Price, Ferry, Keay, & Bandler, 2001; Gabbott, Warner, Jays, Salway, & Busby, 2005; Hoover & Vertes, 2007; Vertes, 2004). Thus, the mPFC is well suited to act as a higher-order, experience-informed positive or negative regulator of the goal- and emotion-related behavior of mothering (Heidbreder & Groenewegen, 2003; Miller & Cohen, 2001).

Neurons of the postpartum rat mPFC respond electrophysiologically to nest odors (Hernández-González, Navarro-Meza, Prieto-Beracoechea, & Guevara, 2005) and snout contact with pups (Febo, 2012), and in sheep and rats have increased immediate-early gene activity after an interaction with offspring or cues associated with them (Broad, Hinton, Keverne, & Kendrick, 2002; Da Costa, Kampa, Windle, Ingram, & Lightman, 1997b; Fleming & Korsmit, 1996; Mattson & Morrell, 2005). The female rat mPFC also shows elevated fMRI activity in response to natural or artificial suckling (Febo, Numan, & Ferris, 2005; Febo et al., 2008; Ferris et al., 2005). The relevance of this cellular activity in the mPFC is indicated by the disrupted frequency and temporal patterning of retrieval after postpartum lesions impinging upon all three subregions of the mPFC; this disruption is also thought to be related to the dams' reduced ability to filter out irrelevant environmental stimuli (Afonso et al., 2007). Similar deficits in retrieval occur after transient chemical inactivation of the mPFC (Febo, Felix-Ortiz, & Johnson, 2010; Pereira & Morrell, 2011). The dorsal (cingulate) mPFC is probably most responsible for these disorganizing effects, because deactivating the ventral (infralimbic) mPFC produces much more severe effects, with mothers almost completely ignoring pups and instead spending their time eating and sleeping (Pereira & Morrell, 2011). Interestingly, as lactation progresses and the pups require less care, the role of the ventral mPFC for their mother's behavior decreases and the prelimbic region takes on a greater role that may reflect the more habitual nature of later, experienced mothering (Pereira & Morrell, 2011).

Humans

Obviously, unlike research animals in which individual brains sites can be experimentally manipulated to study their roles in mothering, studies of the human maternal brain must instead examine this question non-invasively. This has most often been achieved by using fMRI. Because fMRI requires immobilization of the subjects, this research cannot yet examine the metabolic activity of the brain while mothers are displaying caregiving behaviors. This makes direct comparisons with the non-human animal literature somewhat difficult. Even so, the fMRI work does provide particular insight into brain regions involved in the sensory, emotional, and cognitive aspects of mothering and their response to infant stimuli that are less easily studied in non-human animals. Fortunately, we can also draw upon findings from the existing fMRI literature with human subjects that have examined these domains using well-established and transferable basic paradigms in non-mothers (e.g., face processing, emotion perception, working memory tasks, etc.).

As mentioned above, infant cues affect the display of nurturant behaviors and these cues activate broad swaths of the adult brain, even in nulliparous women. For example, a recent

fMRI study found that infant faces that are more 'baby-like' (e.g., larger face width, forehead height, and eye size, smaller nose and and mouth width) are especially effective in activating women's brains compared to infant faces lower in such stimuli (Glocker et al., 2009). In parturient mothers, numerous studies using natural infant visual (faces) as well as auditory (cry) stimuli have examined their neural responses and the data most often indicate that for both modalities the maternal brain readily distinguishes between infant and non-infant cues, and that the cues from one's own infant elicits significantly greater activity compared to the stimuli of unfamiliar infants. We will here highlight some overall findings from this literature, but readers are referred to more comprehensive reviews for details and methodological considerations about such studies (Barrett & Fleming, 2011; Swain et al., 2014). Briefly, methodological considerations that can undermine easy resolution of this literature include differences among studies in the modality of the infant stimulus, very large differences in sample sizes, the postpartum stage of the mothers, and the analysis methods. In particular, the vast and growing array of study designs and approach to statistical analysis apparent in the fMRI literature should always be considered when comparing across studies (e.g., whole-brain vs. region-of-interest approach, baseline used (fixation or a contrast condition), activation vs. deactivation, etc.) Moreover, although we have organized relevant brain structures and systems as separate from one another, in fact most fMRI studies using whole brain analyses find activation in many brain regions simultaneously. Furthermore, there has been a dramatic shift in our understanding of seemingly spatially distinct brain regions as comprising neural systems or networks that are highly functionally interconnected. Simultaneous activation of many brain regions may reflect different aspects or components of the eliciting stimuli or the fact that individual brain structures connect with others and primary activations of one area can lead to simultaneous activation of others. For this reason ascribing one brain site to one psychological function, as we have sometimes done when talking about non-human neural mechanisms of mothering, is not appropriate in these human studies nor does it reflect the reality of how brain systems work. Here, our discussion of these brain regions as such is purely an organizational heuristic.

Basal Forebrain Activating System: Preoptic Area/BST/Hypothalamus—
Compared to what is exhibited by rats or sheep under most conditions, human mothering is less reflexive and preditable in its display, less dependent on steroid and peptide hormones for its display, and more reliant on higher-order and cognitive processes (see Curley & Keverne, 2005). Given this, one might predict that subcortical sites critical for mothering in nonhuman species, such as the hypothalamus, are relatively deemphasized in their importance for human mothering. A recent review of extant studies does indicate that the preoptic area/hypothalamic region of postpartum women is less consistently activated during exposure to infant stimuli (auditory or visual) compared to other responsive brain systems (Swain et al., 2014), but it is still notable that most studies that have looked at the hypothalamus do report increased blood oxygen-level dependent (BOLD) signaling there. Importantly, the hypothalamus is a small brain region, and the preoptic area is even smaller, so their involvement in mothering may be best studied by *a priori* hypothesis-driven region of interest approaches to statistical analysis, due to the highly stringent corrections for multiple comparisons employed in whole-brain approaches (informative in their own right, but less so with a clear theoretically driven hypothesis as to how a particular brain region is

expected to behave). Advances in fMRI resolution will also continue to allow researchers to examine smaller and smaller regions of interest, which will be necessary to pinpoint the preoptic area. It is also important from a theoretical perspective that many of the studies providing the negative findings were not restricted to infants and involved stimuli from children as old as toddlerhood. This may be analogous to the less dramatic effect of mPOA lesions on some aspects of maternal care in experienced multiparous vs. primiparous laboratory rats (Franz, Leo, Steuer, & Kristal, 1986). It also seems relevant for fMRI studies of the POA that much of its role in non-human animal mothers is related to goal-directed, offspring-seeking behaviors, so passive receipt of infant auditory or visual cues may not be optimal to alter its BOLD activity in women. Perhaps training subjects to make an operant response while in the fMRI scanner to modify the infant cues (e.g., change anger cries to cooing, or bring facial pictures closer or more in focus) would most reliably elicit preoptic area BOLD activity.

Interestingly, when hypothalamic fMRI activity is found in human mothers it partly depends on the mother's ability to establish secure attachment with other individuals, and is correlated with maternal levels of plasma OT after an interaction with the infant (Strathearn, Fonagy, Amico, & Montague, 2009). Thus, instead of being relatively emancipated from hypothalamic hormones, perhaps the most sensitive mothers have the greatest neuroendocrine influence on their behavior and vice-versa. In addition, fMRI activity in some non-hypothalamic sites is correlated with mothers' plasma OT (Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012), and exogenous OT alters activation of some brain sites when non-mothers are exposed to infant cries (Riem et al., 2011), further suggesting that even if the mPOA and hypothalamus do not themselves show increased BOLD in response to infant cues, magnocellular activity originating from that region probably influences human maternal brain activation (see Rocchetti et al., 2014).

Stimulus salience and reward: Mesolimbic system—Also consistent with the literature on laboratory rodents, the mesolimbic DA system of postpartum women is highly responsive to infant cues. Studies using infant cries (e.g., Kim et al., 2011; Swain et al., 2008) or pictures (e.g., Atzil, Hendler, & Feldman, 2011; Strathearn, Li, Fonagy, & Montague, 2008) have often found heightened fMRI activity when women are exposed to cues from their own infant compared to unknown infants. Interestingly, the greatest mesolimbic activation is in response to happy infant faces (compared to neutral or sad faces; Strathearn et al., 2008), suggesting greater salience and rewarding qualities of positive infant emotional states. It is the mothers that are not depressed (Laurent, Stevens, & Ablow, 2011) and who have the highest capacity for secure attachment with their infants who show the greatest activity in the ventral striatum when exposed to their infant's cues (Strathearn et al., 2009). This may indicate that the cues are not inherently rewarding and that mothers must be socioemotionally prepared to respond positively to them. In further support of this hypothesis, Moses-Kolko et al. (2011) found that mothers with postpartum depression show a faster attenuation of the typical ventral striatal reward response during a monetary reward task. Another brain region with a known role in the processing of hedonic stimuli, specifically reward-based decision-making and inhibitory control, is the orbitofrontal cortex (OFC). Of interest for mothering, Nitschke et al., (2004) found that positive mood ratings

correlate with increased activation in the OFC when women viewed pictures of their own infant and Silverman (2007) found reduced activity in OFC to negative stimuli in mothers with higher postpartum depressive symptomology.

Sensory arousal systems—Amygdala Human maternal amygdala responses to infant cues have been suggested to be especially related to the fundamental arousing properties of those cues rather than the processing of their emotional content (Swain et al., 2014), and mixed results have emerged for its response to those cues. Some studies find that it responds the most to stimuli from one's own infant (Barrett et al., 2012; Lenzi et al., 2009; Strathearn & Kim, 2013; Wan et al., 2014; Wonch, DeMedeiros, Barrett, Dudin, Cunningham, Hall, Steiner, & Fleming, in press), particularly cues indicating their infant's happiness vs. sadness (Kim, Fonagy, Allen, & Strathearn, 2014), and in mothers that are the most sensitive (Kim et al., 2011; Musser, Kaiser-Laurent, & Ablow, 2012). Level of response in the amygdala is also positively associated with other maternal factors including positive mood, lack of distress, high feeling of attachment (Barrett et al., 2012), reduced anxiety (Barrett et al., 2012), no history of trauma (Kim et al., 2014), vaginal delivery (Swain et al., 2008), breastfeeding (Kim et al., 2011) and plasma OT (Atzil et al., 2012). However, others have found higher amygdala activity in mothers of infants lacking secure attachment (Laurent & Ablow, 2012), a negative effect of exogenous OT on amygdala activity in response to infant cries (at least in non-mothers; Riem et al., 2011), and amygdala deactivation in psychologically healthy mothers (Bartels & Zeki, 2004).

As an example of a recent study focusing on amygdala response to infant cues in new mothers, Barrett et al. (2012) studied new mothers of mixed parity that were presented with pictures of their own infants and other infants whose expressed affective state was either positive or negative. Results revealed that a greater amygdala response to the mother's own infant positive face when compared to that of an unfamiliar infant was associated with: 1) lower maternal anxiety, lower parental distress, and fewer symptoms of depressed mood, and 2) more positive attachment-related feelings about her infant. Thus, the greater amygdala response to one's own, as opposed to another, infant's face likely reflects more positive and pro-social aspects of maternal responsiveness, feelings, and experience. Mothers experiencing higher levels of anxiety and lower mood demonstrated less amygdala response to their own infant and also reported more stressful and more negatively valenced parenting attitudes and experiences. In a follow-up study, Wonch et al., (in press) found that trait anxiety was negatively related to overall BOLD for both own and unfamiliar infants, but not to the difference score between the two, as reported by Barrett et al. (2012).

The findings for mothers who have or are currently experiencing postpartum mood disorders are less straightforward. Strikingly similar results to those described previously have been described in recent findings of Moses-Kolko and colleagues (2010) in a study using fMRI to examine response to emotional faces in mothers with postpartum depression. Although their results were limited to negative adult faces, rather than positive infant faces, the authors found a negative correlation between amygdala response to faces and postpartum depression severity, and a negative correlation between amygdala response to faces and infant-related hostility. On the contrary, another recent study (Laurent & Ablow, 2013) examined the brain response in mothers with late postpartum depression (15–18 months after parturition) to

positive pictures of their own infant versus positive pictures of an unfamiliar infant. They identified no group differences in the amygdala, or any other brain regions. These stark differences could be accounted for by differences in the type of analysis (e.g., region-of-interest versus whole-brain, respectively). Further clarification of the relationship between amygdala response and postpartum mood symptoms comes from recent work by Wonch et al. (in press). These authors used a region-of-interest approach to examine amygdala response to positive infant stimuli (own and other). While they identified no group differences between depressed and non-depression mothers in their amygdala responses to positive pictures of one's own infant versus positive pictures of an unfamiliar baby, they did observe overall increased amygdala response in mothers with depression to positive pictures of other infants, as well as to non-infant stimuli. It appears as though mothers with postpartum depression engage their amygdala in response to positive stimuli more so than mothers without depression.

While average BOLD response has been a primary measure for some time throughout the fMRI literature, we increasingly understand that altered connectivity patterns may underlie individual differences in variables measured outside of the scanner (e.g., affect, cognition and behavior). Wonch et al. (in press) examined whether differences in connectivity between the amygdala and other brain regions may be observed in mothers who are depressed, as compared to mothers who are not depressed, when they are viewing positive pictures of their own versus another infant. Indeed, they found that the amygdala is bilaterally more strongly connected to the right insular cortex in the non-depressed mothers. Furthermore, these connectivity differences were related to depressive symptomology and trait anxiety. The insular cortex has a proposed role in interoception and subjective emotional experience (Craig, 2002; 2009) and is a prime example of a brain structure whose function is difficult to study using non-human animal models.

Some of the cross-study differences may derive from the fact that increased BOLD could also reflect activation of cells mediating inhibitory signaling rather than downstream excitation (Arthurs & Boniface, 2002). It may also derive from what part of the amygdala constitutes each study's relevant region of interest. As indicated above while discussing non-humans, the amygdala is a functionally heterogeneous region, with major subregions often parceled into the central nucleus and the basolateral complex (lateral, basal, and accessory basal nuclei; Amunts et al., 2005). The former is more strongly linked to arousal, vigilance, and attention, and the latter is more strongly linked to value representation including that related to appetitive function and reward (reviewed in Bzdok et al., 2013). Further complicating the investigation of the maternal amygdala is that there is functional heterogeneity of neural responses even within the same subregion, including that individual amygdala cells in rodents and primates can become prone to encode either positively or negatively valenced stimuli with training or experience (Belova et al., 2008; Schoenbaum et al., 1999). Interestingly, a recent study by Gamer, Zurowski, and chel (2010) found that the administration of OT enhanced the response of the lateral amygdala to happy adult facial expressions. Not surprisingly, the region of the amygdala more responsive to own positive infant faces in the Barrett et al. (2012) mothers was restricted to the basolateral region. Recent work by Wonch, Steiner, Hall, & Fleming (in preparation) suggests that, indeed, there may be differences in how various subregions of the amygdala respond in new mothers

to pictures of infants, and how this may relate to measures of maternal behavior captured outside of the fMIR scanner regardless of womens' postpartum mood or anxiety. Using connectivity analyses, Wonch et al., (in preparation) found that non-postpartum depressed mothers showed increased connectivity between the basolateral amygdala and ventral striatum compared to postpartum depressed mothers when viewing their own versus another baby, whereas seeds in the central and superficial amygdala did not show this pattern. Finally, in terms of the relation of brain activation to maternal behavior and sensitivity, it seems that the right basolateral connectivity with the right insula is positively correlated with maternal sensitivity, a pattern not found for analyses of seeds in other amygdala sites.

Higher-order function: Cortex—The cortex many have only recently received renewed interest for research on laboratory rodent mothering but, of course, has always been a primary focus of the human fMRI studies. A functional systems view of cortical organization is increasingly being adopted in human neuroimaging work. Because most fMRI studies find multiple cortical sites activated when infant stimuli are presented, it can be difficult to disentangle what systems are being activated in relation to the particular features of mothering. Barrett and Fleming (2011) recently discussed the extant literature and suggest three primary cortical regions of interest as an organizational framework for understanding the cortical bases of the psychology of mothering - the anterior cingulate region of the mPFC (for affect response and regulation valance, stimulus salience, executive function, social cognition), the orbitofrontal cortex (for stimulus salience, affective valence, and reward), and the dorsolateral PFC (for affect regulation and working memory).

To summarize briefly, a wide range of cortical sites are activated by a variety of infant stimuli including cries, positive or negative photographs, and video clips. The sites activated include those involved in diverse psychological constructs such as emotional, cognitive, reward or basic sensory processing and include brain regions including the insular (Leibenluft, Gobbini, Harrison, & Haxby, 2004; Noriuchi, Kikuchi, & Senoo, 2008; Strathearn et al., 2008), orbitofrontal (Nitschke et al., 2004; Noriuchi et al., 2008), medial frontal/anterior cingulate (Barrett et al., 2012; Seifritz et al., 2003), temporoparietal (Leibenluft et al., 2004; Swain et al., 2008), and fusiform cortices/visual processing regions (Kim et al., 2011; Leibenluft et al., 2004; Ranote et al., 2004). Structural changes have also been observed across the postpartum period in cortical sites in the frontal lobes (Kim, Leckman, Mayes, Feldman, et al., 2010a), parietal lobes, and insular cortex (Kim, Leckman, Mayes, Newman, et al., 2010b). In addition, maternal factors influence the degree to which some of these cortical sites are activated. For example, positive mood is correlated with higher BOLD in the orbitofrontal cortex, a brain region with a known role in reinforcement processing and reward-base decision making, in response to viewing one's own infant (Nitschke et al., 2004). Also, maternal sensitivity is positively correlated with BOLD in the frontal pole, inferior and superior frontal gyri when hearing one's own infant cry to their own infant's cry compared to that of an unfamiliar infant (Kim et al., 2011; Musser et al., 2012).

Brain metabolic deactivation when mothers are exposed to infant cues is rare, but the medial frontal gyrus has been repeatedly seen to have a negative BOLD response to own-infant stimuli compared to stimuli from unknown infants (Bartels & Zeki, 2004; Seifritz et al.,

2003; Swain, Leckman, Mayes, Feldman, & Schultz, 2006). The medial frontal gyrus is involved in regulating mood, decision making and processing of the sense of self (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014; Karch et al., 2009; Lemogne et al., 2010). Whether this deactivation reflects positive affect and selflessness vital for healthy maternal caregiving remains to be seen in future studies that attempt to relate fMRI measures to individual differences in mothering behavior or maternal attitudes measured outside of the scanner.

Similar to the work described above conducted by Wonch et al. (in press) examining the relationships between BOLD in the maternal amygdala and other brain structures, the vast movement by the greater neuroimaging community employing network approaches to understanding brain activity may reconcile some of the disparate or contradictory findings that exist in the current literature examining the neurobiology of human mothering. A recent study by Moses-Kolko et al. (2010) examined functional connectivity in mothers with and without postpartum depression while they viewed negative adult faces, and the researchers identified decreased top-down dorsomedial prefrontal cortex-amygdala connectivity in mothers with postpartum depression. Atzil et al. (2011) also used a functional connectivity approach in their examination of mothers who vary in maternal responsiveness and found that synchronous mothers demonstrate greater NAC and amygdala connectivity with emotion modulation, theory of mind and empathy networks, all of which involved higher-order cortical regions. These findings highlight the role of functional connectivity approaches in integrating what we know about the role of subcortical regions in mothering from animal work, with what we know about the role of higher-order cognitive processing important for human mothering that are governed by brain regions difficult to study in non-human animals.

IX. Conclusions - What do non-human mothers tell us about human mothers?

In this review we have attempted to illustrate the similarities among some of the best studied mammalian species, including humans, in a number of the regulatory mechanisms for mothering (Table 1). Such similarities may not be surprising considering that all mammals undergo many of the same physiological processes associated with pregnancy, parturition, and lactation. Included among these mammalian commonalities are the hormonal fluctuations during pregnancy (especially in progesterone, estrogen, lactogens), then during expulsion of the fetus at parturition (prostaglandins, OT), and during milk synthesis and letdown (lactogens, corticosterone/cortisol, OT). We believe these similarities in the peripheral functions of the maternal reproductive hormones generalize to the behavior that the mother must exhibit towards the offspring in order for these peripheral functions to succeed. Thus, the endocrine factors involved in pregnancy and parturition are the same ones acting on the hormone-sensitive neural substrates that simultaneously activate mothers' initial attraction to young and expression of their early caregiving behavior. Of course, differences exist among species in the details of their reproductive physiology and have been well documented, but those differences are also expressed by differences in the physiology of early mothering (Table 1). One such difference in the link between physiology and

behavior can be seen in the importance of prolonged progesterone exposure followed by its withdrawal at term for the onset of maternal behavior in the laboratory rat, which is not required in the hamster (Siegel & Greenwald, 1975). Also, while PRL strongly stimulates the onset of maternal behavior in laboratory rats, it seems not be involved in sheep (Lévy & Keller, 2008; Poindron, Orgeur, Le Neindre, Kann, & Raksanyi, 1980). Hormones of any type also play only a small role in maternal behavior of many strains of mice that are instead spontaneously parental (see Lonstein & De Vries, 2000b), although the hormones released during pregnancy, including PRL, can sometimes act upon this high baseline to even further strengthen maternal responding (e.g., Larsen and Grattan, 2010).

The sensory and neural mechanisms involved in maternal behavior show similar principles across species, making translational work a valuable enterprise. We have described many similarities in new mothers' response to the odors, visual cues and vocalizations of the young, both before and after gaining extended experience with the offspring and learning how to interact with them. Furthermore, all mammalian mothers require somatosensory inputs from the offspring to modulate their immediate, ongoing interactions with them and to maintain very high maternal responsiveness over the longer term. Hypothalamic activity - especially the mPOA and paraventricular/supraoptic nuclei - is essential for reproduction in most female mammals by regulating ovulation, early pregnancy, parturition, and milk letdown. Again, it is not surprising that these same brain regions figure so centrally in regulating the hormones essential for maternal behavior and are also found activated in human brain imaging studies.

Although we have demonstrated that many of these physiological and behavioral processes seem to be shared by non-human and human mothers, the extent that these mothers depend on them likely differs considerably. As an example, the shift across pregnancy in the ratio of progesterone to estrogen followed by a rise in PRL and OT occurs in rats, and each component of this profile has been shown to exert either essential or modulatory effects on the induction of maternal behavior. The correlation between the shift in estrogen:progesterone ratio (but not absolute levels of pregnancy hormones) and postpartum nurturant feelings in humans is striking, and would not have even been assessed in humans without the prior non-human animal work. A similar conclusion can be made for the associations between OT and PRL and human mothering and other aspects of our social affiliation.

This is not to say that the direct causality between hormones and maternal behavior demonstrated in rats and sheep has also been demonstrated in humans. It has not. The nature of most correlational studies in humans and the complexity of human environments have precluded strong conclusions about hormone-behavior causality. Given that, the processes reflecting hormone-behavior relationships across species may not be so different as they may seem on the surface; in none of the species studied do we believe that hormones are deterministic - i.e., activating maternal behavior under all conditions independent of environmental and experiential constraints. Instead, we think of hormones as creating a positive bias towards young and altering the probability that maternal behavior will be expressed in their presence. These effects are more clearly demonstrated in laboratory rodents and sheep than in humans, whose environments are rarely as controlled, but we

believe the same principle of hormone action applies to both humans and non-humans. Moreover, it is more likely in humans compared to other species that hormonal influences interact with a host of experiential factors, including mothers' age, stress levels, early and recent life experiences, etc. Clearly, hormones are not necessary for humans to express mothering, as evidenced by 'alloparents' - siblings, aunts, uncles, grandparents, friends, or individuals adopting children - who, as far as we know, do not experience hormonal changes similar to pregnancy and parturition but nevertheless take on parental roles and become strongly attached to infants. Likewise in rats, most non-hormonally primed nulliparous females will show maternal behavior that in many ways is indistinguishable from the behavior of postpartum mothers (Bridges, Zarrow, Gandelman, & Denenberg, 1972; Fleming & Rosenblatt, 1974a; Lonstein, Wagner, & De Vries, 1999) if given sufficient experience with foster pups. It must be the case, then, that experiential and sensory routes other than hormones can activate mothering, even possibly acting on many of the same neurochemical systems that are influenced by hormones. Whether human alloparents and postpartum parents undergo similar neurochemical changes in, for example, striatal dopaminergic activity (which occurs in both postpartum and maternally sensitized nulliparous rats) is unknown but positron emission tomography scanning in combination with fMRI would make this a testable hypothesis.

Numerous other features are shared between non-human and human mothers. In order to parent effectively, all mothers must develop an attraction to the young and be motivated to expend considerable resources and withstand substantial challenge to care for and protect them. This motivation is first promoted by hormone-enhanced attraction, and then more enduringly by the rewarding properties of the young that develops with physical contact and experience. Part of this process is based on maternal emotional regulation, particularly reduced anxiety or fear, which helps promote approach to young and inhibits withdrawal from them. As far as we know, postpartum depression is probably unique to human mothers, but nonetheless, features of human depression (e.g., anhedonia and low perseveration) can be modeled in laboratory rodents and affects mothering in both species. In terms of how learning impacts mothering across species, both human and non-human mothers do learn about their offspring. They learn to recognize them and they learn the 'art' of mothering. Parity effects are seen in both non-human and human mothers, and in both likely involve an experience-based reduction in anxiety and increase in motor competence. In humans, an enhancement of competence is also associated with a possibly uniquely human characteristic, self-esteem.

The development of fMRI technology has only recently made it possible to begin examining similarities and differences in how non-human and human brains respond to offspring cues. We believe the similarities are more notable than the differences. While human mothering is very reasonably thought to be relatively more cortically than subcortically driven when compared to non-primate mothers (Curley & Keverne, 2005), activation of the hypothalamus and surrounding region is still commonly reported in postpartum mothers exposed to infant cues, and numerous endocrine products of hypothalamic origin are correlated with this fMRI activity. Such findings nicely complement data from non-imaging studies showing correlations between hormones and mothers' attitudes about their infants and the caregiving behaviors they express. The mesolimbic system is also very often found

to show increased fMRI activity in stimulated human mothers, again indicating the importance of subcortical activity for the human maternal state. Conversely, the traditional idea that maternal behavior in non-primates is reflexive, fixed, and subcortically driven has been recently upended by numerous interesting studies on the role of the prefrontal cortex in mothering by postpartum rats, despite the apparently still-lingering question about whether rodents have a prefrontal cortex or not (Uylings, Groenewegen, & Kolb, 2003). We are not suggesting that non-humans and human mothers do not differ in the relative contributions of cortical and subcortical systems for their mothering, but the literature appears to be bringing "us" and "them" neurobiologically closer together.

Although we have not examined this topic directly, it also seems that human maternal behavior is more variable across cultures, and between mothers within cultures, than what we see within individual non-human mammalian species. In humans there are many ways, for instance, to transport young (slings, strollers, back-boards, etc.) that keep the young in close proximity to a caregiver, warm and protected; or to soothe the young through singing, cooing, motherese, use of lullaby audiotapes, or providing a pacifier. Moreover, individual human mothers exhibit a variety of caregiving behaviors that vary by context and the individual needs of the mother who may nurse at home but bottle feed elsewhere. As we discussed earlier, there are some commonalities across cultures in some features of mothering, especially around nursing, but there are many more cultural differences in the behaviors utilized to accomplish the same caregiving goals or functions. Finally, although we now know in non-human mammals that the cortex plays a larger role in mothering than originally believed, human mothering nevertheless depends on extensive cortical function because human mothers exhibit complex theory of mind in relation to their infants, ascribe meaning and causes to their behaviors, organize their lives, plan for the future, benefit from experience, model other mothers, receive advice, read about caregiving and infants, and exchange information.

This review emphasizes the commonalities between non-human and human mothers in the factors regulating maternal behavior. It does not delve into obvious differences that are species-typical or species-specific. We have not discussed roles of uniquely human characteristics afforded to human mothers, which include language, the transmission among women of stories about and models for how to mother, cultural expectations about mothering, and the existence of future thinking by mothers implicit in the 'understanding' that there is a relationship between mothering style and the culture's goals for how a child should develop. These human features have the effect of increasing variability across and within cultures in mothers' maternal interest and motivation, the quality and form of the behavior mothers' exhibit, and mothers' goals for how their children should develop.

For many animal researchers, the study of motivated social behaviors such as parenting has become more and more "translational" in its perspective. As well, many clinicians and others working with humans have shown increased interest in understanding biological mechanisms underlying psychosocial factors influencing mothering. This impetus for increased communication among researchers of non-human and human mothers will certainly increase integration between the fields and lead to greater insights that benefit our

understanding of the normal and pathological expression of this fascinating and complex social behavior.

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Highlights

* We review many biopsychological influences on maternal behaviors in rats, sheep, humans

* Examine how conceptual framework established in animals hold for human mothering

* Are many similarities between animals and humans in factors influencing mothering

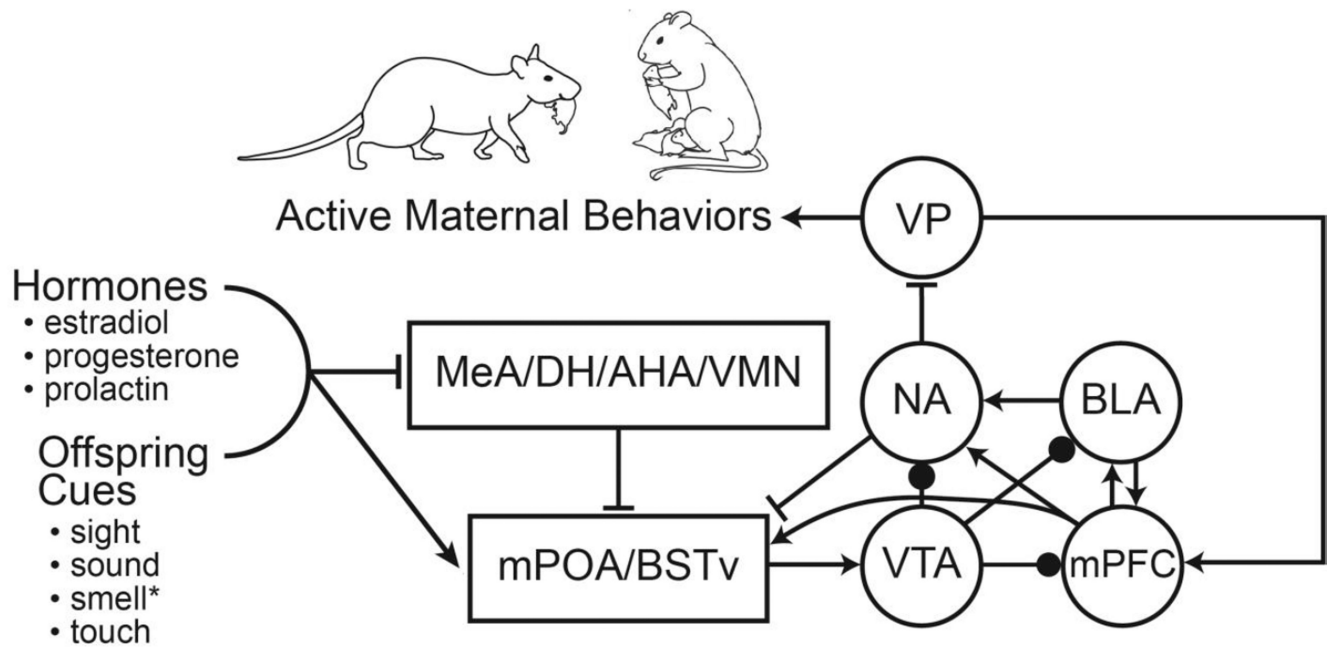* Notable differences are also discussed

Figure 1.
Proposed neural model for the performance of active maternal behaviors such as offspring carrying and licking, based mostly on studies of laboratory rats. Pregnancy hormones and sensory cues of offspring suppress inhibitory input from the MeA/DH/AHA/VMN to the mPOA/BSTv. At the same time, they simultaneously stimulate mPOA/BSTv projections to the VTA. Consequent dopamine (DA) release occurs in the NA, PFC and BLA. DA release in the NA inhibits VP output, which promotes active components of mothering. The NA, VP, PFC and BLA modulate this pathway by connections to the MPOA/vBST or NA. AHA - anterior hypothalamic area, BLA - basolateral amygdala, BSTv - ventral bed nucleus of the stria terminalis, DH - dorsal hypothalamus, DA - dopamine, MeA - medial amygdala, mPOA - medial preoptic area, NA - nucleus accumbens, PFC - prefrontal cortex, VP - ventral pallidum, VTA - ventral tegmental area. Lines ending in arrows = excitatory input; lines ending in vertical bars = inhibitory input; lines ending in circles = DAergic neurotransmission. Modified with permission from Olazabal et al. (2013b). *Role of olfaction especially differs among species, even within laboratory rodents, see text for details.

Table 1

Comparisons between animals and humans in the role of behaviors, hormones, sensory systems and brain regions in new mothers.

	Maternal responsiveness/sensitivity		Maternal recognition/selectivity		Reward system/Stimulus salience		Emotions		Postpartum learning /Executive functions	
	Animals	**Human**	**Animals**	**Human**	**Animals**	**Human**	**Animals**	**Human**	**Animals**	**Human**
Behavior										
Reward system	+ (rodents)	+	+	?			?	?	?	?
Emotions	+ (rodents)	+	?	?			?	?	?	?
Learning/executive function	+ (rodents, sheep)/+ (rodents)	+/+	+/	+/						
Hormonal Factors										
Ovarian steroids	+ (rodents, sheep)	+Positive correlation	?	?	?	?	0 (rodents more than a few hours after parturition)	?	?	+ (impaired memory)
Prolactin	+ (rodents), 0 (sheep)	?	?	?	?	?	?	?	?	+ (impaired memory)
Cortisol	+ (rodents)	+Positive correlation	?	+	?	?	?	?	?	+ (impaired memory)
Oxytocin	+ (rodents, sheep)	+Positive correlation	+ (sheep)	+	?	?	?	+	+ maternal experience (rodents)	?
Sensory Systems										

	Maternal responsiveness/sensitivity		Maternal recognition/selectivity		Reward system/Stimulus salience		Emotions		Postpartum learning /Executive functions	
	Animals	Human	Animals	Human	Animals	Human	Animals	Human	Animals	Human
Olfaction	+ (rodents, sheep)	+	+ (sheep, rodents)	+	+ (rodents, ungulates,)	+	+ anxiety (virgin rodents) -- neophobia (parturient rodents)	?	0 (rodents)	+
Somatosensory	+ (rodents), 0 (sheep)	+	+ (sheep, goats)	+	+ (rodents, ungulates)	+	-- anxiety (postpartum rodents)	-- anxiety	+ (rodents)	+
Vision	+ (primates), 0 (rodents, sheep)	+	+ (sheep)	+	?	+	?	?	?/0(rodents) +(sheep)	?
Audition	0 (rodents, sheep)		+ (sheep)	+	?	+	?	?	?	+
Brain Regions										
mPOA/BST	+ (rodents, sheep)	+hypothalamus	+ (sheep)	?	?	?	+ anxiety (BST in postpartum rodents)	?	?	?
Olfactory Bulb	+ (rodents, sheep)	?	+ (sheep)	?	?	?	?	?	?	?
DH/AHA/VMN	-- (virgin rodents)	?	?	?	?	?	+anxiety (postpartum rodents)	?	?	?
Locus coeruleus	?	?	+ (sheep)	?	?	?	?	?	?	?
PAG	+ retrieval, nursing	?	?	?	?	?	+anxiety (postpartum rodents)	?	?	?
Amygdala	(See subregions)	+	+ (sheep)	+ (own vs other)	?	+	+anxiety (virgin rodents)	+activated by one's own infant and by cues indicating their infant's happiness	?	?

	Maternal responsiveness/sensitivity		Maternal recognition/selectivity		Reward system/Stimulus salience		Emotions		Postpartum learning/Executive functions	
	Animals	Human	Animals	Human	Animals	Human	Animals	Human	Animals	Human
MeA	-- (rodents)	+ (own vs other)	+ (sheep)	?	?	?	+anxiety (virgin rodents)	?	?	?
BLA	+(rodents)	+ (own vs other)	?	+	?	+	?	+	?	?
Mesolimbic system	+ retrieval, nest building, licking -- quiescent nursing	+	?	+ cries and visual cues of own vs other infant	+(rodents)	+activated by infant cries and visual cues from their own infant	?	+ correlated with positive mood ratings	+ maternal experience (rodents)	?
Prefrontal cortex - mPFC, OFC	Activated by infant cues (rodents, sheep) + retrieval	?	?	+ (own vs other)	?	+	?	+	+ attention, impulsivity (rodents)	+activated by infant cries, positive or negative infant photographs and video clips

+ = activator; 0 = not involved; -- = inhibitor; ? = not yet studied in mothers or evidence is inconclusive. Table not intended to be exhaustive. See text for abbreviations. Note: the + in the human columns indicates a correlation