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Review

Flexibility and adaptation of the neural substrate that supports maternal behavior in mammals

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ABSTRACT

Maternal behavior is species-specific and expressed under different physiological conditions, and contexts. It is the result of neural processes that support different forms (e.g. postpartum, cycling sensitized and spontaneous maternal behavior) and modalities of mother–offspring interaction (e.g. maternal interaction with altricial/precocious young; selective/non-selective bond). To understand how the brain adapts to and regulates maternal behavior in different species, and physiological and social conditions we propose new neural models to explain different forms of maternal expression (e.g. sensitized and spontaneous maternal behavior) and the behavioral changes that occur across the postpartum period. We emphasize the changing role of the medial preoptic area in the neural circuitry that supports maternal behavior and the cortical regulation and adjustment of ongoing behavioral performance. Finally, we discuss how our accumulated knowledge about the psychobiology of mothering in animal models supports the validity of animal studies to guide our understanding of human mothering and to improve human welfare and health.

Contents

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1. Introduction

Parental behavior is very diverse and expressed in different forms and modalities. It generally consists of a series of behaviors that contributes to the survival of the young by providing food, warmth, shelter, protection from predators and conspecifics, and appropriate stimulation. Lactating females are commonly responsible for providing all these benefits but, depending on the reproductive strategy of each species, males and other family members can also contribute (Numan et al., 2006). Maternal behavior is displayed by females in different hormonal states and physiological conditions, and under different social contexts. Mothers also need to adapt to the growth of their offspring, which requires different attention and care depending on the sensory, nutritional, and motor competence of the young. This flexible caregiving strategy displayed by mothers requires a highly motivated and flexible brain. This review discusses how the brain adapts to and regulates maternal behavior in different species, and under different physiological and social conditions. In the present manuscript we review the neural basis that supports the different forms and modalities of maternal behavior, putting emphasis on the flexibility and adaptation of the system. In the first two sections we introduce the topics discussed in the review and summarize the diversity of forms (parturient, cycling sensitized, and spontaneously maternal females) and modalities (precocial vs. altricial young; prolonged vs. short/infrequent interactions, selective vs. non-selective bond) of maternal behavior in the different species. The third section makes a comparative analysis of the hormonal and sensory factors that mediate the onset, maintenance and decline of maternal behavior in the different species and physiological conditions. Section 4 revises our current neural models, analyzes their advantages and limitations, adapts those models to explain the quick pup-induced onset of maternal behavior, and adds a temporal dimension to explain the decline in maternal responsiveness across postpartum. Finally in Section 5, we discuss the contribution of animal studies to the understanding of human mother–infant interactions with potential applications to human welfare and health. In the last section we summarize the main new concepts that have come out of this review and raise some of the future challenges for the maternal behavior field.

2. Diversity and complexity of parental behavior

Parental behavior is very diverse among mammals. Mothers are most commonly responsible for taking care of the offspring but, in some species like prairie voles, California mice, or marmosets, the father or other members of the family group assist the female in the care of the young (Numan and Insel, 2003). The majority of lactating mammals share many behavioral features; they clean off the neonates and consume fetal membranes and amniotic fluids, are very interested and attracted to young, and respond maternally protecting and nurturing them. However, the specific behaviors exhibited and the pattern of mother–young interactions varies across species, the developmental status of the neonate, and other factors.

2.1. Maternal behavior in parturient and naïve cycling animals

Parental motivation is very high at the time of parturition, when females (and in some cases males) show immediate interest in the newborn. In most rodents and primates, the parents build a nest or find a refuge, transport or retrieve the newborns to the nest or refuge, clean and lick them and adopt nursing postures (González-Mariscal and Poindron, 2002; Numan and Insel, 2003). In other species (e.g. capybaras and ungulates) mothers do not retrieve, transport or crouch over the offspring, and maternal behavior is mostly expressed through nursing, licking, guarding, and call vocalizations. These different maternal strategies have been associated to the degree of physical development of the offspring, as will be discussed later.

Maternal behavior can also emerge under other physiological and social contexts. For instance, cycling female rats become maternal after relatively long term period of continuous exposure to foster newborn (ranging from 2 to 10 days, depending on the strain, age, experience, and sex, among other factors, Cosnier, 1963; Rosenblatt, 1967). This process, which leads to a pattern of behavior very similar to that of the lactating mother, is often referred to as the pup-induction or *sensitization* of maternal behavior (Numan et al., 2006). During that sensitization period, the animal generally overcomes an initial aversion to pups, then tolerates them, and finally becomes attracted to them, leading to the display of all components of maternal behavior. However, some non-parturient rodents and primates readily interact with newborns, displaying immediate maternal or paternal behavior without requiring long-term exposure to infants. For example, most female and male prairie voles when first exposed to newborns, retrieve and lick them, adopt nursing postures and build a nest (Olazábal and Young, 2005). Mice have also been reported to display maternal behavior rapidly (30 min–2 days), although not all the components of maternal behavior are

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always observed immediately (Kuroda et al., 2011; Lucas et al., 1998).

Studies in eusocial rodents (naked mole rats) also show that subordinate males and females with suppressed reproductive activity contribute with the care of the offspring (Kalamatianos et al., 2010). Cooperative breeding, or the presence of non-breeding helpers within social groups, occurs in 30% of rodent families, in many Canidae and in primates (e.g. marmosets, cappuchins). These helpers assist in rearing offspring through activities such as feeding, carrying, babysitting, and infant thermoregulation. In these cooperative breeding/rearing systems, helpers do not need a long sensitization period and they quickly get involved in the care of the young. In humans, maternal behavior can also be expressed in non-reproductive contexts, as shown by baby-sitters and other care providers (i.e. grandmothers), or mother substitutes when parents are not available (Hrdy, 2008).

2.2. Parental behavior in species with altricial, precocial or intermediate young

Altricial young are very immature at birth; hairless, with closed eyes, limited locomotor ability, and unable to regulate body temperature. After the mother has selected a site to build a nest, she usually gives birth to numerous young (González-Mariscal and Poindron, 2002; Numan et al., 2006). The site of the nest can be underground, as in many rodents and in rabbits, or at ground level, as among carnivores, or in trees, as in squirrels and prosimians (Denenberg et al., 1969; González-Mariscal and Rosenblatt, 1996; Kapeller, 1998). Mothers nurse their young in the nest and stimulate them to urinate or defecate by licking their ano-genital area. In many species, they also retrieve them back to the nest. Marsupials are an extreme case in this group as their young are very altricial and initially carried by their mothers at all times. The embryonic young crawl at birth into the mother's pouch until they emerge as fully-developed, mobile animals (Kimble, 1997).

In contrast, precocial newborns have completely functional hearing and vision at birth, rapid locomotive development, and good thermoregulation. The young stand up and start suckling within minutes of being born. Mothers can eventually lead their offspring, or be followed by them, as the mother moves with her conspecifics in a herd ("leading-following" pattern of behavior displayed by sheep and horses). Follower species are usually herd animals (Lévy and Keller, 2008). In other species, the pattern of behavioral interaction is adapted to protect the young from predators while mothers are foraging. That is the case of "hider" species, in which the newborn stays hidden for several days, before starting to follow its mother or grazing with her (e.g. goat, deer). During this hidden stage the mother returns periodically to feed her offspring (Ralls et al., 1986).

In other species (suids and many primates including humans), young at birth are semiprecocial or semialtricial. In those cases, hearing and vision are functional, but neonates have poor locomotor and thermoregulatory autonomy. The number of neonates varies from small (primates) to large (suids) litter. In primates, the newborns are generally carried by their mother, father, or other members of the family group. Human mothers and other primates carry their infants in their arms, or transport them on their backs, side or chest (Nakamichi and Yanada, 2009). In suids, the mother does not transport them and remains in a nest for the first two weeks (Algers and Uvnäs-Moberg, 2007).

2.3. Selective vs. non-selective maternal behavior

In many species with altricial young (rodents in particular), mothers can recognize their own offspring but will take care of alien newborns, not establishing a selective attachment (Beach and Jaynes, 1956; Pereira, 2006). However, care of the offspring is sometimes associated with a substantial cost to the mother because postnatal investment in developing young through lactation up to weaning can reduce her opportunity to produce additional offspring. Therefore, in some species natural selection has favored the evolution of mechanisms to ensure that the offspring of a caregiver are the only beneficiaries of such parental investment. This is common in species in which the young can be mixed, as occurs in a variety of gregarious mammals with precocial young (Poindron et al., 2007). Mothers of some of these species develop selective maternal care, favoring their own young and rejecting any other young that are not theirs (e.g. sheep and goats). In these cases the young also often recognize their mother (Nowak et al., 2011). However, in other group-living species (e.g. bats, capybaras, water buffalo), mothers do not develop strong selectivity and will take care of, or nurse, young belonging to other mothers. Therefore, communal breeding systems can be an alternative to maternal selectivity for resolving this investment conflict in certain group-living species (Kerth, 2008; Macdonald et al., 2007). Extreme cases of non-selectivity, and interspecific adoption in group-living species have been observed in a population of capuchin monkeys that adopted a marmoset young (Izar et al., 2006).

3. Onset, maintenance, and offset of maternal behavior

3.1. Onset

How does a cycling female become a mother? Are the hormones of pregnancy necessarily involved in this transition? Experimental approaches to these fundamental questions have revealed that some common mechanisms exist across mammals to promote the expression of maternal behavior. However, the diversity and complexity of forms of maternal behavior also show significant differences and species-specific mechanisms.

Some of the behavioral components typically displayed by mothers begin at the end of pregnancy, like the preference for pup odors in rats (Bauer, 1983; Fleming et al., 1989; Kinsley and Bridges, 1990), rabbits (González-Mariscal and Chirino, 2011), and sheep (Lévy et al., 1983). The odors of newborn rats placed in bed soil are strongly attractive for pregnant or cesarean delivered primiparous rats (Kinsley and Bridges, 1990), even without any interaction with the young. In addition, the olfactory information in the amniotic fluid that covers the lamb is highly attractive for the ewes at parturition, before the delivery or interaction with the lamb (Lévy et al., 1983). Human mothers are also attracted to infant odors and vocalizations (Fleming et al., 1993, 1997a,b; Stallings et al., 2001), including mothers who had undergone delivery by cesarean section, and had reduced or no experience with their babies prior to testing (Porter et al., 1983). Therefore, the parturient animal does not need to learn or interact with the newborns to find them attractive. Once the mother approaches and interacts with the young, other stimuli (e.g. tactile) strengthen maternal behavior. After that, maternal behavior is maintained throughout lactation in the absence of the hormonal profile typical of the end of pregnancy.

Estradiol (E2) and progesterone (P4) hormonal profiles stimulate maternal behavior at the end of pregnancy in many species (González-Mariscal et al., 1996; Numan et al., 2006). An increased ratio of E2/P4 is associated with the onset of maternal behavior in many species, including rats, rabbits, sheep, and some primates (González-Mariscal and Poindron, 2002; Numan et al., 2006). However, there are some exceptions, as in hamsters that show a rise in both E2 and P4 levels during pregnancy followed by a decline after parturition without a change in E/P4 ratio (Numan et al., 2006). Yet, knocking out the gene for the E2 receptor-alpha (ERKO) increases infanticide (pup killing) and reduces retrieval in naïve

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cycling mice (Ogawa et al., 1998). In contrast, male P4 receptor knock out mice (P4RKO) are less infanticidal (Schneider et al., 2003). In addition, antagonists of the P4 receptor facilitate parental responses in naïve cycling mice while agonists increase infanticidal behavior (Schneider et al., 2003). Thus, ERKO and P4RKO studies in mice support the idea that an increase in the E2:P4 ratio and a functional E2 receptor alpha are essential for the onset of maternal behavior while a role of the P4 receptor seems to differ between male and female mice.

Prolactin (PRL) and oxytocin (OXT) also facilitate the onset of maternal behavior in several species (Bridges, 1996). In early studies, Bridges et al. (1985) showed that PRL administration in hormonally primed rats facilitated the induction of maternal behavior. Later it was shown that central PRL or placental lactogen infusions also facilitated maternal behavior in rats, and rabbits (Bridges and Freemark, 1995; González-Mariscal et al., 2004b). When the receptors for PRL were knocked out (PRLRKO), Lucas et al. (1998) found that, compared to wild type virgin mice, the homozygous PRLRKO naïve females had longer latencies to start showing all components of maternal behavior (6 vs. 2 days). Central OXT infusions also facilitated maternal behavior in rats and sheep, while OXT receptor (OXTR) antagonists delayed the onset of maternal behavior in rats (Da Costa et al., 1996; Kendrick et al., 1987; Lévy et al., 1992; Pedersen and Prange, 1979; Pedersen et al., 1985; van Leengoed et al., 1987, see also Section 6). Knock out models of the OXT system (including OXTR), however, have found no or minor deficits both in postpartum and in naïve pup-induced maternal behavior (Macbeth et al., 2010; Nishimori et al., 1996; Pedersen et al., 2006; Takayanagi et al., 2005). OXTKO or OXTRKO females, although unable to nurse their young, show only minor deficits in retrieval or licking behavior that recovered on subsequent testing days or pregnancies. Perhaps, this minor effect is the result of the low inhibition of maternal behavior that is typically present in virgin cycling female mice. However, Ragnauth et al. (2005) found higher infanticidal responses in OXTKO females when tested in a semi-natural environment. Globally, transgenic models have shown that these systems (E2, P4, PRL, and OXT) are more important during the initial onset of maternal behavior, but not during the subsequent postpartum maintenance of the behavior, especially in multiparous females.

The mechanisms by which a female modifies her perception of pup odors, from unattractive (or aversive) when she is a virgin to attractive at parturition are still unknown. Daily exposure to neonates provokes a gradual onset of maternal behavior in virgin rats (Rosenblatt, 1967), but this manipulation is not effective in rabbits (Chirino et al., 2007; González-Mariscal et al., 2004a). Yet, in both species lesions to the main, or the accessory olfactory systems promote maternal behavior in virgins, especially under the action of estradiol (Chirino et al., 2007; Fleming and Rosenblatt, 1974a,b,c; González-Mariscal et al., 2004a). Anosmia can also induce maternal behavior in non-pregnant sheep when combined with vaginocervical stimulation (Poindron et al., 1988). Together these findings show that the maternal responsiveness of non-pregnant animals of many species is under a tonic inhibition from the olfactory system that must be removed across pregnancy to resolve, at parturition, the approach-withdrawal conflict of a cycling virgin female towards the young.

However, in some other species (i.e. prairie voles and mice) this initial conflict is almost absent or resolved rapidly by naïve cycling females. For instance, most naïve cycling female prairie voles display retrieval behavior, licking, and crouching postures over newborn (even toward newborn mice, D.E.Olazábal personal observation) after only 15–90 s with them (Olazábal and Young, 2005, 2006a). Juvenile rats (19–21 days of age) also show less conflict when first exposed to newborns, displaying high levels of contact and attractiveness toward pups from the beginning of the interaction (Bridges et al., 1974a; Mayer, 1983; Mayer and Rosenblatt, 1979). This suggests that there is an intrinsic maternal responsiveness that is inhibited in some species or at some ages or stages of the reproductive cycle of the individual. At parturition, this intrinsic maternal responsiveness is optimally stimulated by hormonal changes to satisfy newborn needs. In the case of human parental behavior, maternal responsiveness (reflected in attitudes to the developing fetus) grows during pregnancy, peaks towards the end of pregnancy and further develops across the early postpartum period with experience (Fleming et al., 1997a).

3.2. Maintenance

The hormonal combinations present during pregnancy change drastically around delivery and throughout lactation (for reviews see: González-Mariscal and Poindron, 2002; Numan et al., 2006). However, while hormonal changes related to parturition are implicated in the onset of maternal behavior, the maintenance of maternal responses does not depend on the endocrine background of lactation. There is extensive evidence (Rosenblatt and Siegel, 1981) that around parturition, during which there is a heightened sensitivity to the neonate's signals, a transition from a hormonal control to a somatosensory regulation of maternal behavior occurs. The disruption of the mother–young contact at parturition (or the immediate postpartum period) invariably provokes long-lasting alterations in maternal behavior in rats, rabbits, and sheep, especially in primiparous females (for reviews see: González-Mariscal and Poindron, 2002; Numan et al., 2006). Thus, the expression of maternal behavior is mostly maintained by the continuous stimulation coming from the young. Distal stimuli (visual, auditory, and olfactory) play an important role in the activation and orientation of mothers to the young, while proximal stimuli (taste, temperature and skin texture) which are perceived in the physical interaction, are essential for the motor performance of active components such as retrieving and licking in rats (Stern and Kolunie, 1989). Besides, in this species, a threshold amount of suckling stimulation by the pups is crucial for the adoption of the arched-back (kyphosis) nursing posture (Stern and Johnson, 1990). In sheep, recognition of the mother's own lamb to allow suckling relies mostly on the learning and subsequent perception of the lamb's individual olfactory signature, although visual and acoustic signals also play a role (Lévy and Keller, 2009; Nowak et al., 2011; Poindron and Le Neindre, 1980). In rats a threshold amount of suckling stimulation is crucial for the adoption of the arched-back (kyphosis) nursing posture (Stern and Johnson, 1990). In rabbits, the temporal dimension of maternal behavior is totally dependent on the characteristics of suckling stimulation: various manipulations that reduce its amount alter both the frequency of nursing (does enter the nest box more times than the usual one per day; González-Mariscal et al., 2011) and its duration (nursing bouts last longer than the usual three min; González-Mariscal, 2007; González-Mariscal et al., 2012). The quality and quantity of the sensory stimulation received by the mother, changes as the newborn get older and independent, and this change might induce a reduction in maternal interest or motivation.

3.3. Offset

Maternal behavior gradually declines across late lactation. As weaning approaches, some mothers avoid the suckling attempts of the young, which also increase their time exploring and foraging out of the nest and eating solid food (Cramer et al., 1990). These behavioral changes of the mother and the offspring eventually lead to the cessation of nursing (Cramer et al., 1990; Reisbick et al., 1975). The pattern and frequency of vocalizations of the mother and offspring, and other components of maternal behavior such as licking and grooming, are also reduced across the postpartum

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period in many species (Numan et al., 2006; Pereira and Morrell, 2009). In rodents, there is evidence that the main reasons why mothers reduce maternal behavior across lactation are the changes in the stimuli coming from the growing litter: by continuously replacing older pups with younger ones maternal behavior is prolonged while doing the opposite procedure provokes a premature decline in nursing behavior (Bruce, 1961; Grosvenor and Mena, 1974; Reisbick et al., 1975). However, other factors also appear to be important. For example, the single, brief, daily nursing bout characteristic of rabbits remains unchanged across lactation, despite the fact that milk output decreases from around day 20 onwards (González-Mariscal et al., 1994). The growing young play a minor contribution to the termination of this component of maternal behavior because doe rabbits continue to enter the nest box even when milk production is minimal and the kits are already ingesting solid food. However, if mated at post-partum estrus, rabbits become concurrently pregnant and lactating; under these conditions, they stop nursing the "first" litter earlier than they do when they are lactating only (Martínez-Gómez et al., 2004). On the other hand, pregnant lactating rats only reduce the time spent nursing the newborn near the second parturition (Rowland, 1981; Uriarte et al., 2008), but once the new litter is delivered the older juveniles are still nursed and cared for (Uriarte et al., 2008). Juvenile pups receive even more maternal stimulation when a second litter of newborn pups is present (Uriarte et al., 2008, 2009). Therefore, these findings suggest that pregnancy-associated factors (hormonal and extra-hormonal) operate at the end of lactation in postpartum estrous-mated females to induce weaning in rabbits and to alter maternal behavior in rats. French et al. (2008) also found changes in maternal behavior (less carrying behavior) associated to changes in the levels of androgens in marmoset pregnant mothers.

Although cessation of nursing is commonly associated with the end of maternal behavior in non-human animals, the maintenance of a bond and association beyond nutritional weaning has not been investigated in detail. Suckling and mother–infant associations are maintained for a longer period of time than necessary from a nutritional point of view in many species (Buckley, 2001; Cramer et al., 1990; Hrdy, 2008; L'Heureux et al., 1995).

4. Neural basis of maternal behavior: a comparative analysis of its flexibility and adaptability

Considering the diversity of biological and physiological contexts under which parental behavior can be expressed, it is necessary to discuss the similarities and differences in the neural mechanisms underlying the onset, maintenance, and decline of maternal responsiveness in different species and physiological contexts. Today, there is a disparity between our knowledge of the neural basis of postpartum maternal behavior, compared to our understanding of paternal, sensitized or spontaneous parental behavior. Studies in rats and sheep have contributed most to what we know about the neural basis of postpartum and hormonally-induced maternal behavior (Lévy & Keller, 2008; Numan et al., 2006). Research in other species (González-Mariscal et al., 2009; de Jong et al., 2009, 2010; Katz et al., 1999) and MRI studies both in rodents and humans (Barrett et al., 2012; Nephew et al., 2009; Febo, 2011; Kim et al., 2011; Swain and Lorberbaum, 2008), support previous evidence collected in rat and sheep, but also add complexity to our understanding of the neurobiology of the parental brain.

4.1. Comparative analysis of the neural basis of postpartum maternal behavior

The classic view of the onset of maternal behavior in mammals proposes that increases in E2/P4 ratio (see Section 2), and rises in PRL and OXT at the end of pregnancy act on the brain to stimulate maternal responsiveness. Although other neurotransmitters and peptides also participate in the regulation of the onset of maternal behavior (Bridges, 1996), in this review we have limited our discussion to a few systems. These hormones would act on their receptors located in the medial preoptic area (mPOA), ventral portion of the bed nucleus of the stria terminalis (vBST) and other areas of the brain, promoting the activation of brain pathways that stimulate maternal responses, while suppressing pathways that inhibit them (Bridges, 1996; González-Mariscal et al., 2005; Numan, 2006).

4.1.1. Inhibitory and stimulatory pathways

The classic neural models of maternal motivation and control of maternal behavior are based on a significant amount of studies that identified brain regions that, when monitored (in vivo microdialysis and voltammetry analysis, immediate early genes activation, electrophysiological recordings, receptor up- or down-regulation, etc.) or manipulated in different ways (lesions, chemical infusions, electrical stimulation, temporary inactivation), were associated with rather specific stimulation or inhibition of maternal behavior. However, a challenge is to demonstrate that a subset of neurons, within the monitored or manipulated brain regions, have a similar function or form an ensemble, or neural network, specific to the motivation or control of the behavior of interest. Subsets of neurons within those brain regions might share, or not share, electrophysiological/chemical properties and connectivity and could play a role in neural processes related to more than one behavior or motivation (see also Olazábal et al., submitted for publication-a,b). The neural models proposed in the present review do not resolve this issue, but follow a previous strategy in the field that consists of focusing on identification of subregions of the brain associated with stimulatory or inhibitory functions of maternal behavior; with the implicit view that these brain regions might be specifically engaged in maternal motivation and behavioral control. In order to identify a subset of neurons within a brain region that might specifically participate in the mediation of maternal behavior we need, at least, to use research tools that have good spatial resolution. For this purpose, this review will pay particular attention to the evidence obtained by using immediate early gene expression, associated with different parental behaviors and conditions. Unfortunately, few electrophysiological studies have been done in the analysis of maternal behavior. Fos genes, commonly referred to as immediate early genes, are activated in response to a variety of extracellular stimuli (e.g., hormones, neurotransmitters, neuromodulators). This activation produces several protein products (c-Fos, Fos B, Fra-1, Fra-2) that serve as transcription factors that will alter target genes and their protein products, modifying the function of neurons (Sheng and Greenberg, 1990). Generally, Fos expression has been used as a neuronal marker of transcriptional activity, neuronal activity or engagement in response to certain stimuli (González-Mariscal et al., 2009; Kalinichev et al., 2000b; Numan et al., 2006).

The classic neural model of maternal motivation and control proposes that the primary olfactory and the vomeronasal systems would be involved in the initial ofactory inhibitory process observed in many species, in particular in rats and rabbits (see also Section 3). This olfactory information is sent to the main (MOB) and the accessory olfactory bulbs (AOB), then to the medial (MA) and cortical amygdala (CA) and, from there, to the mPOA (to stimulate maternal behavior), or the Anterior and Ventromedial Nucleus of the Hypothalamus (AH/VMN) to inhibit maternal behavior in rats (Bridges et al., 1999; Fleming et al., 1980; Numan, 2006; Numan et al., 2006) and rabbits (Chirino et al., 2007; González-Mariscal et al., 2004a; see also Fig. 1). Under the influence of hormones at the end of pregnancy, newborn-related stimuli would facilitate the activation of the pathway to the mPOA/vBST, and inhibit that to

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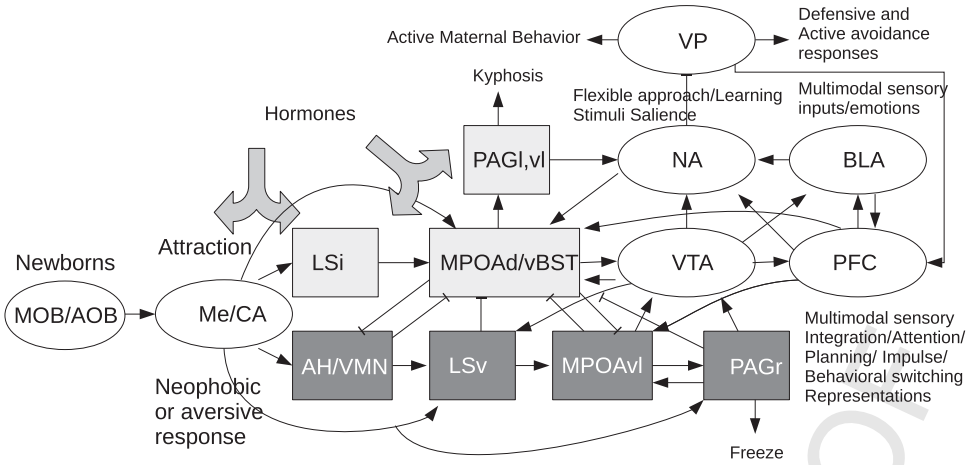

Fig. 1. The figure shows a hypothetical model for explaining the stimulation and inhibition of maternal behavior and its modulation by cortical areas and the mesolimbic system. Olfactory inputs can either stimulate or inhibit maternal behavior depending on the physiological stage of the animal. The action of hormones at the end of pregnancy stimulates different subregions of the medial and cortical Amygdala connecting to stimulatory (LSi-mPOAd/VBST-PAGl,vl; represented as light gray squares) or inhibitory (AH/VMN-LSv-mPOAvl-PAGr; represented as dark gray squares) pathways. Areas of the brain represented as white ovals (MOB/AOB, MA/CA, VTA, NA, PFC, BLA, VP) participate in the processing of stimuli that have a positive or a negative impact on maternal behavior. These brain regions might also have different subregions (still not identified) specifically associated with attraction or aversion towards pups. All brain regions that appear in this figure have been shown to express oxytocin receptors in at least one species. PVN likely projects to most of them. Note that the model is highly redundant (not all projections are shown) and that olfactory, visual, auditory and tactile information that stimulates or inhibits maternal behavior is processed by different brain regions, likely modifying its weight in the model, depending on the sensory channel mostly used by the different species. Lines ending in arrows signify excitatory projections, and those ending in a vertical bar are inhibitory.

the AH/VMN. In contrast, in non-maternal animals, the olfactory stimuli from pups would activate the AH/VMN, and subsequent areas associated to defensive and aversive responses (midbrain periaqueductal gray, mPAG) such that escape, behavioral avoidance, or attacks would occur. Note that the ventro lateral portion of the PAG (vlPAG) has also been implicated in the regulation of the kyphosis (high-arched nursing) posture (Lonstein and Stern, 1998). Therefore, the PAG is a complex neural region and while some of its efferents may oppose maternal responsiveness, other PAG circuits contribute to nursing behavior.

A more complex model of interaction among these brain regions is proposed here and will be discussed in this section (see Fig. 1). The current anatomical, lesion, and immediate early gene activation studies have shown that different subregions of the mPOA (i.e. dorsal and ventrolateral), MA, and other areas of the brain could either stimulate or inhibit maternal behavior (Sheehan et al., 2000). Evidence indicates that knowledge of a more detailed neuroanatomy and neurochemistry underlying the functional connectivity of the different brain subregions can enhance our understanding of the neural basis of maternal behavior (also see Sections 4.2 and 4.3). For example, different subregions of the lateral septum (LS) appear to promote either the inhibition or the activation of maternal behavior. There is strong activation of the immediate early gene *fos* in the ventral region of the LS (vLS) in non-maternal rats exposed to newborns. Thus, this area may be associated with the inhibition of maternal behavior in rats. However, c-Fos is also expressed in the LS during parental behavior in voles (Kirkpatrick et al., 1994), and rabbits (González-Mariscal et al., 2009), and in the intermediate portion of LS (LSi) in maternal rats (Sheehan et al., 2000, 2002). Also, lesions in the LS disrupt nursing and nest building in mice, rats and rabbits (Cruz and Beyer, 1972; Fleischer and Slotnick, 1978; Slotnick and Nigrosh, 1975), and increase infanticidal responses in mice and rats (Fleischer and Slotnick, 1978; Slotnick and Nigrosh, 1975). This evidence suggests that different subregions of the LS (vLS and LSi) might be engaged in the processing of pup related stimuli under different motivational states. The LS also receives DA and OXT innervation in many species (including mice, rats, voles, and rabbits), two systems well known for their mediation of maternal behavior (see also Olazábal et al., submitted for publication-a,b and Sections 3.1 and 4.1.4). However, the specific neurochemical modulation of this brain region and its subregions by DA and OXT has not been studied in detail. The possibility that OXT and DA release in the LS during parturition or nursing contributes to removal of the inhibition of maternal behavior and defensive responses by depressing vLS, while facilitating nursing via an action on LSi is intriguing and deserves more investigation.

Pup related stimuli processed by the hormonally primed brain can activate the mPOA and influence the NA (and other limbic and cortical regions) directly or indirectly through mPOA output to the VTA, thereby modifying the incentive salience of pup related stimuli and promoting maternal responses (Numan et al., 2006; Numan and Stolzenberg, 2009; see also Olazábal et al., submitted for publication-a,b). Lesions or inactivation of the mPOA disrupt retrieval, and in some cases also licking, nursing, and nest building in rats, and sheep (Numan et al., 1988; Pereira and Morrell, 2009; Perrin et al., 2007), and also in male and female California mice (a biparental species, Lee and Brown, 2002, 2007). Lesions or inactivation of the NA fail to affect the active components of maternal behavior in rats and mice (i.e. retrieval, Lee et al., 1999; Lee and Brown, 2007; Numan et al., 2005b). However, bilateral inactivation of the ventral pallidum (VP) disrupts maternal behavior in rats, as does the unilateral inactivation of VP paired with a contralateral depression of MPOA activity (Numan et al., 2005b). Therefore, Numan's model of the neural basis of the active components of maternal behavior (Numan and Stolzenberg, 2009) proposes that mPOA stimulation of VTA DA input to NA acts to *suppress* NA GABAergic inhibitory input to VP, allowing VP efferents to promote active maternal responses. Besides, the NA and the VP can also adjust the ongoing behavioral performance projecting back to the mPOA via NA-mPOA or VP-medial thalamus-mPFC-NA projections (Fig. 1).

The basolateral (BLA) and the central amygdala (CA) have also been implicated in the facilitation of maternal behavior processing of emotionally relevant information related to pups (Champagne et al., 2001; Lee et al., 1999). Lesions or inactivation of the BLA, implicated in associative learning, mainly of emotional stimuli, disrupt maternal behavior in rats (Lee et al., 1999; Numan et al., 2010) and mice (Lee and Brown, 2007), suggesting that this area is critical for the processing of pup related stimuli that facilitate the expression of parental behavior and remembering previous

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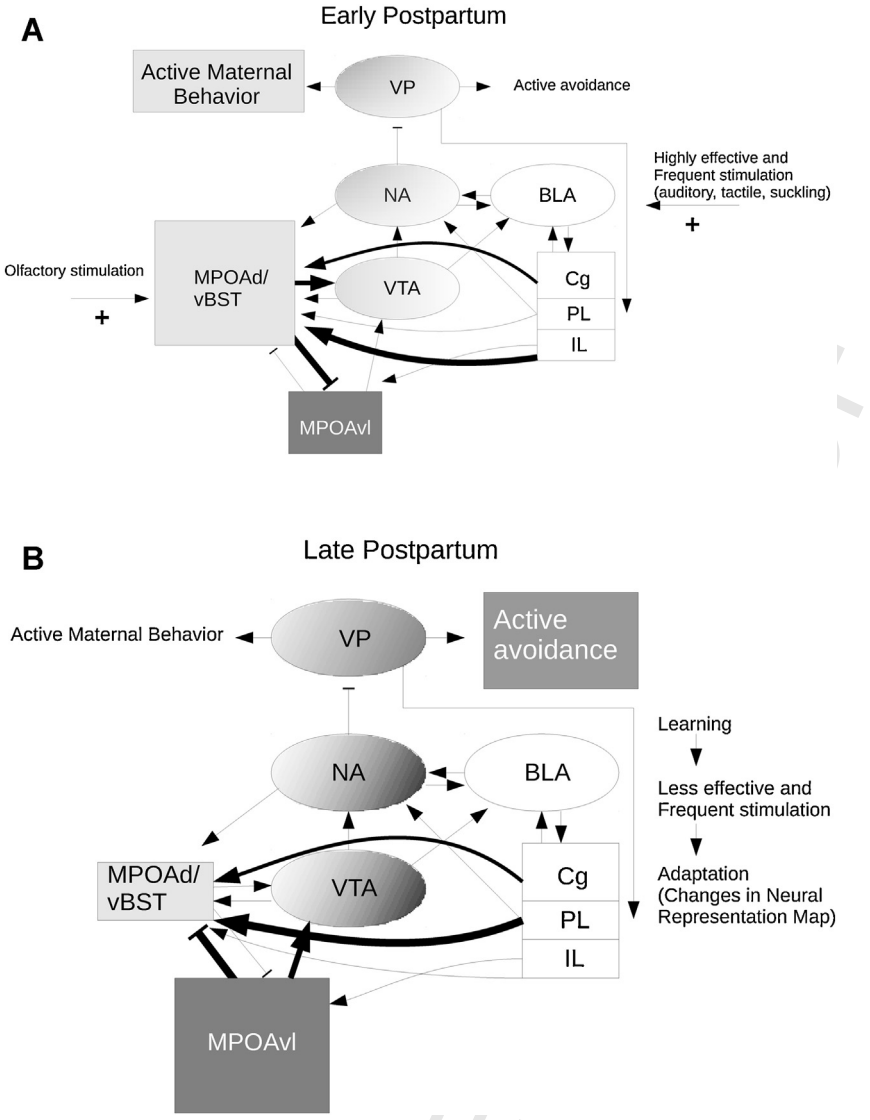

Fig. 2. Hypothetical model of the changes in path weight and neural representations at early and late postpartum. Subpart A proposes an increased activity or engagement of a subpopulation of neurons (mPOAd/vBST, big light gray square) that stimulate maternal behavior during early postpartum. This might be the consequence of the strong influence of hormones of the end of pregnancy and the highly effective and frequent stimulation by the newborns. IL and Cg inputs are critical to maintain full maternal behavior at this stage. Subpart B proposes increased activity or engagement of a subpopulation of neurons (mPOAvl, big dark gray square) that inhibit maternal behavior during late postpartum. Changes in the function of the PL, and IL might be consequence of and adaptation due to the experience and learning of motherhood and the characteristics of the near-weaning offspring. Lesions in these brain regions or in the mPOA would produce different effects at early or late postpartum (see also text in Section 4.2). Abbreviations as in Fig. 1.

maternal experiences. The hormones of the end of pregnancy or the stimuli emitted by the young can then influence the BLA and the mPFC facilitating maternal behavior. This pathway might acquire significant importance after maternal learning and experience have occurred, as in the late postpartum period (see Fig. 2 and Section 4.2). These brain regions also project to the mPOA and NA, modulating mPOA-VTA-NA-VP information processing. However, the BLA and CA can also be critical in fear and defensive responses toward newborns (Bosch and Neumann, 2012; Wartella et al., 2003), and therefore distinct population of neurons in these brain regions may play different roles (stimulation or inhibition) in maternal behavior.

4.1.2. Cortical modulation of maternal behavior

The role of the cortex, in particular the PFC and orbitofrontal cortex (OFC), in maternal behavior was mostly minimized or ignored for a long time, with a few exceptions (Broad et al., 2002; Da Costa et al., 1997; Slotnick, 1967). Interestingly, Febo et al. (2008) found that suckling and nursing provide a multisensorial experience that activates many cortical areas representing different sensory channels. Just recently, several authors have begun to pay attention again to the PFC and OFC in rats, and proposed that, via their projections to the mPOA and NA, these areas might be involved in the temporal organization of many of the maternal behavior components, and the regulation of attentional/motivational processes related to maternal behavior (Afonso et al., 2007; Febo et al., 2008; Pereira and Morrell, 2011).

Early studies of Slotnick (1967) found that females with PFC/cingulate lesions showed disorganized and persistent retrieval behavior. More recently, Afonso et al. (2007) also found that lesions in this region altered the frequency, duration, and execution of many maternal behavior sequences that require the coordination of sensory and motor information in a spatial context (including retrieval behavior and licking). Maternal behavior can be adjusted and organized by hippocampal, PFC, and amygdalar inputs to the NA, modulated by DA projections from the VTA. Pereira and Morrell (2011, 2012) extended earlier findings (Afonso et al., 2007; Febo Q7

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et al., 2010), by demonstrating a specific necessary role for the infralimbic (IL) subregion of mPFC in early postpartum maternal behavior. Pereira and Morrell (2011, 2012) also found that, with the progression of the postpartum period, the facilitatory role of the IL subregion wanes, whereas additional mPFC subregions, such as the prelimbic (PrL), are recruited and contribute to the expression of late postpartum maternal behavior (Pereira and Morrell, 2011; see also Section 4.2). The importance of the mPFC in mothers planning, and cognitive flexibility has also been studied, and is still more obvious in humans, and will be reviewed in more detail in Section 5.

4.1.3. OXT modulation of maternal behavior

OXT function in maternal behavior has been extensively studied and its interaction with the DA system might be informative about the neural processes that support maternal motivation and behavior. The most likely role of DA in the regulation of maternal behavior is discussed in Olazábal et al. (submitted for publication-a,b). In this section we will discuss the role of OXT across species and OXT/DA interaction.

OXT, released by the paraventricular nucleus of the hypothalamus (PVN) at parturition, lactation, or during pup-interaction, acts on the mPOA, VTA, PVN, and in some species on the NA (see Section 4.3), facilitating the quick onset of maternal behavior (Da Costa et al., 1996; Fahrbach et al., 1984, 1986; Kendrick et al., 1987; Olazábal and Young, 2006a,b; Pedersen et al., 1994; Pedersen and Prange, 1979; van Leengoed et al., 1987) and maternal memory (D'cunha et al., 2011). In rats, the olfactory bulb is also a site where OXT acts to facilitate the onset of maternal behavior (Yu et al., 1996). In sheep, OXT modulates noradrenaline and acetylcholine release within the olfactory bulb, and infusions of OXT into this area reduce aggressive behavior towards newborn lambs in hormonally-primed ewes (Kendrick, 2000; Lévy et al., 1995). Neurons in the PVN are engaged (show *c-fos* activation), both during the first exposure to newborns and during early postpartum in rats (Stack and Numan, 2000), rabbits (González-Mariscal et al., 2009), and sheep (Keller et al., 2004a) and lesions in this brain region disrupt the onset of maternal behavior in rats, but not its maintenance (Insel and Harbaugh, 1989; Numan and Corodimas, 1985). There is important intra- and inter-specific variability in OXT receptors (OXTR) that have been associated with natural variation in maternal behavior (Champagne et al., 2001; Olazábal and Young, 2006a,b). Interestingly, Champagne et al. (2001) found higher OXTR in the ventrolateral portion of the mPOA, an area previously suspected to inhibit maternal behavior (Sheehan et al., 2000). OXT appears to reach its target receptors via PVN projections, but also by diffusion (Landgraf and Neumann, 2004). It is intriguing, and still unknown, how OXT and DA systems interact in the VTA, NA, or other brain regions. Shahrokh et al. (2010) found that OXT infusions into the VTA increased DA release in the NA, which, the authors propose, would promote active behavior such as retrieval or licking (see also Olazábal et al., submitted for publication-a,b). In contrast, other authors (Kovacs et al., 1990; Qi et al., 2008) suggest that OXT acts to reduce the use of DA in the NA. In particular, OXT has been shown to attenuate hyperactivity and stereotyped behaviors induced by psychostimulant drugs (Kovacs et al., 1990; Qi et al., 2008; Sarnyai et al., 1991), and psychological dependence on such drugs (Qi et al., 2009; Yang et al., 2010). If OXT is released at high levels during suckling and contact interaction with newborns, it should result in the mother's quietness and relaxation (typical of nursing) instead of invigorating the animal and activating motor components of the behavior (as expected with high DA in the NA). Our lack of information on the effects of OXT on the dopaminergic system in the different brain regions (NA, septum, mPFC, etc.) and how the different projecting pathways (from parvocellular vs. magnocellular neurons) to these different regions regulate these target regions and the behavioral processes that they control warrants future investigations. Some evidence suggests that OXT may attenuate the behavioral effects of psychostimulant drugs by interfering with mPFC glutamatergic projections to the NA (Qi et al., 2009).

4.1.4. Neural basis of individual recognition of the young

Finally, a major species difference lies in the development of selective care in mothers of some precocial species, which relies on a specific neural network different from the one involved in maternal motivation. Mothers of some precocial species (sheep, goat) acquire the ability to recognize their own young soon after birth, and refuse to nurse alien offspring (i.e. maternal selectivity). In sheep and goats, such discrimination is established within 2–4 h after parturition and relies on olfaction. The neural substrate controlling olfactory memory processes has been extensively studied in sheep and is thought to interact with brain regions regulating maternal motivation to stimulate or inhibit it (Lévy and Keller, 2008). Recognition of the young is mediated by the MOB in which coding of the familiar lamb odor is established. Noradrenergic inputs from the locus coeruleus to the olfactory bulb are in part responsible for the formation of this memory. Increases in noradrenaline release at parturition, with the help of OXT, cause the activation of cells in the olfactory bulb permitting potentiation of the glutamate system by the retrograde messenger, nitric oxide. This results in an enhanced cellular activity in response to own-lamb odors. In this way, the output is decoded by subsequent olfactory processing regions. Among them, the CA and MA play a pre-eminent role (Keller et al., 2004b). Inactivation of either of these nuclei prevents mothers from learning to discriminate their own from an alien lamb. The basal forebrain cholinergic system is also activated at parturition and its lesion impairs the formation of olfactory lamb recognition (Ferreira et al., 2001). How this neural network is functionally interconnected with the one regulating maternal motivation is currently unknown but a possible link between MA and the mPOA could be involved.

4.1.5. Limitations of current neural models of maternal behavior

Current models of maternal motivation propose that the brain must be able to inhibit incompatible motivations in order to adapt to complex and challenging situations (Numan, 2006, 2007). However, our models and paradigms of maternal motivation do not currently include mechanisms to coordinate several compatible motivations and behaviors or switch among incompatible motivations to quickly adapt to a particular context (see also Olazábal et al., submitted for publication-a,b). Besides, until recently (Pereira and Morrell, 2011), our current models did not include a temporal dimension that explains the dynamic of maternal responses along lactation, and mostly focused on the onset and early maintenance of the maternal state (see Section 4.2). The quality of mother–offspring interactions, and frequency and type of contacts vary in different species. The maternal brain should also be affected in different ways by precocial or altricial young, accounting for differences in mother–offspring interactions. However, little is known about the neural basis of mother–offspring interaction in hider species, in particular the neural mechanisms that regulate their encounters, as in rabbits. Besides, the neural basis and the dynamics of regulation or control of mother–offspring interaction can be expected to differ significantly in precocial vs. most altricial and semi altricial species that are in contact with the offspring most of the time until weaning.

Another unexplored aspect of maternal behavior related to the regulation of mother–offspring encounters is, for example, the vocalizations of the mother. These vocalizations play a critical role in the initiation of encounters in many species including deer, sheep, and primates (Biben et al., 1989; Sèbe et al., 2008; Torriani et al., 2006). However, the neural correlates of these vocalizations,

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their motivational basis, and their changes across lactation have not been studied. What makes these mothers 'call' the young just once a day, or every 1 or two hours? Only newborn vocalizations (also critical for the orientation of the mother in her search) and their processing and recognition by the maternal brain, have been studied in rats, mice, ungulates, and humans (Blumberg and Alberts, 1991; Cromwell, 2011; Harmon et al., 2008; Numan et al., 2006). Less attention has been paid to the neural regulation and function of mothers' vocalizations when the offspring are at a distance. An exception is the study by Perrin et al. (2007), which showed in sheep a reduction in call vocalizations after inactivation of the mPOA. This finding is particularly interesting in the context of the discussion of brain regions and neurochemical systems implicated in active and passive maternal motivation. Call vocalizations are part of a 'seeking' system and they can include or not an important locomotor component. In the Perrin et al. study, mPOA inactivation appeared to reduce motorically active seeking (also called appetitive) and rather passive (vocalization calls) behavioral components that do not require locomotor activity (see also Olazábal et al., submitted for publication-a,b). The frequency and function of the vocalization of the mother and the infant are also known to change as lactation proceeds in many species, including rodents and ungulates (Farrell and Alberts, 2002; Grimsley et al., 2011; Hiryu and Riquimaroux, 2011; Motomura et al., 2002; Olazábal et al., unpublished; Sebe et al., 2008). Both mother and offspring frequency of vocalizations change in some ungulate species as the newborn get older and the dyad comes to recognize each other more easily through visual stimuli (Nowak et al., 2011; Olazábal et al., unpublished). The neural basis of these behavioral changes is still unknown. Species or periods at which the relevance of olfactory, visual, auditory, or tactile stimuli changes, can inform us on how the brain adapts to maintain maternal behavior by relying on different sources of information (see also Febo et al., 2008 for multimodal sensory representations).

4.2. Functional reorganization of the neural circuitry of maternal motivation across the postpartum period

Maternal experience modifies the brain in such a way that the behavior is sustained during lactation and adjusted with little or no influence of gonadal hormones (see Section 3). As previously described (see Section 4.1), the mPOA is critical for the maintenance of maternal responsiveness in mice, rabbits, rats, sheep. However, recent studies revealed that the role of the mPOA changes across lactation according to maternal experience (Pereira and Morrell, 2011; Perrin et al., 2007). Even though postpartum females remain highly responsive to their young througout postpartum, their maternal responsiveness undergoes considerable plasticity from birth to weaning, resulting in marked variations in maternal care attuned to the changing needs of the rapidly developing young (Pereira and Morrell, 2009, 2011).

In a series of studies, Pereira and Morrell (2011) employed a transient site-specific neural inactivation method (infusion of bupivacaine) to map the neural circuitry that subserves rat maternal motivation across the postpartum period. Collectively, their findings provided strong evidence that the ability of postpartum females to successfully care for their young is subserved by a distributed neural network that carries out efficient and dynamic processing of complex, constantly changing incoming environmental and pup-related stimuli, ultimately promoting the progression of appropriate care-giving behavior across the postpartum period. Specifically, these authors and others (Afonso et al., 2007; Slotnick and Nigrosh, 1975) found evidence that strongly suggests that during the early postpartum period the integrated functional contribution of the mPOA, VTA, the infralimbic (IL) region of the mPFC, and other cortical subregions, is essential for the extensive maternal commitment of behavior, time and resources required for the care and protection of the altricial newborn pups. This series of studies provided important support for the role of cortical regions of higher-order cognition and polymodal sensory inputs in the expression of maternal behavior in rats. They found that the mPFC, and in particular the IL subregion, is critical for maternal behavior in conflicting contexts, at which the animal must chose between a newborn and another salient stimulus (i.e. cocaine).

As the postpartum period progresses and the pups grow older, these authors found that the mPOA and the mPFC IL activity changed, and additional network components, including the mPFC PL subregion, were recruited with maternal experience, and contributed to the expression of late postpartum maternal behavior in rats (Pereira and Morrell, 2011). Specifically, they found that transient inactivation of the PL subregion of the PFC inhibited late (but not early) postpartum maternal behavior. On the other hand, transient inactivation of the mPOA, and IL blocked early (but not late) postpartum maternal behavior. Transient inactivation of the mPOA at late postpartum facilitated some components of maternal behavior. In multiparous ewes, mPOA inactivation at parturition induced less deficit in maternal behavior than in primiparous mothers (Perrin et al., 2007). As discussed in Section 4.1 (also see Numan et al., 2006), the mPOA appears to be a complex brain region with several subregions playing different (maybe opposite) functional and behavioral roles. Indeed, several studies have found evidence suggesting that neurons in the mPOA can be stimulatory and inhibitory on maternal behavior (Olazábal and Morrell, 2005; Sheehan et al., 2000, 2002). Sheehan et al. (2000, 2002) found that the dorsal part of the mPOA (mPOAd) showed higher *c-fos* activation in maternal, and the ventrolateral part (mPOAvl) in non-maternal animals. Besides, a different temporal pattern of Fos expression in the mPOA has been found in maternal animals of different species, contexts or physiological conditions that also suggest adaptive processes in this brain region (see Section 4.3). Finally, neurotoxic lesions in this area have also revealed atypical effects in juvenile and cycling maternal rats (Kalinichev et al., 2000a; Olazábal et al., 2002). It is likely that hormonally- or experience-mediated changes in the cortex and other brain regions not only supplement but also change the mediation of maternal behavior by the mPOA (Febo et al., 2011; Pereira and Morrell, 2011). In addition, maternal experience and hormones of the end of pregnancy induce important plastic changes (e.g. increased brain-derived neurotrophic factor levels, neuron somal size, astocytic remodeling, changes in dendritic arborizations) in the different components of the neural circuitry that supports maternal behavior, including the mPOA, septum and PFC (Featherstone et al., 2000; Kinsley and Lambert, 2008; Kinsley et al., 2008; Salmaso et al., 2009; Shams et al., 2012).

The fact that the mPOA is a key region implicated in the regulation of active components of maternal behavior in most species, contexts and physiological conditions, warrants future studies to understand its anatomical, neurochemical, and functional complexity, and how this brain region stops promoting maternal behavior at weaning. The model shown in Fig. 2 needs more experimental support but reflects how interaction among brain regions might change as the newborn grow older. This model is based on a hypothesized change in the neural representation or neuroanatomical map in the mPOA and the different subregions of the mPFC across the postpartum period. Similar changes can also be hypothesized for other brain regions or pathways of the maternal neural substrate. PFC-mPOA-VTA circuit may flexibly remap affective-generating functions as external situations change as proposed by Reynolds and Berridge (2008) for NA. Note that the hypothesized inhibitory role of the mPOAvl in maternal behavior must be taken with caution given that there is no study showing facilitation of maternal behavior after lesions specifically located into this

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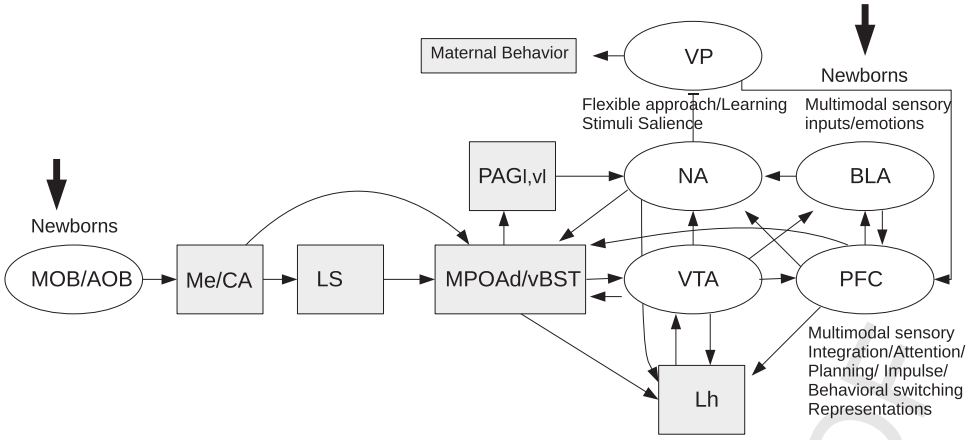

Fig. 3. Hypothetical model to explain rapid or spontaneous parental responses. The abscence of an initial aversion or inhibition would promote a rapid engagement (or *read out*) of the maternal pathway either by olfactory, auditory, visual, tactile or multimodal sensory inputs. Note that this model includes the lateral habenula (Lh) through which most pup related stimuli can reach the VTA and NA. Because there is no inhibition to overcome, the mPOA might suffer less adaptational changes to stimulate maternal behavior in these conditions.

subregion. However, inactivation in the whole mPOA might then have different impact due to the weighed outputs to the VTA at early or late postpartum. At early postpartum, inactivation of the mPOA inhibits maternal behavior blocking the strengthened projections from the dorsal part of the mPOA to the VTA that stimulate maternal behavior. At late postpartum, inactivation of the mPOA may have facilitatory effects on maternal behavior by blocking the strengthened projections from the MPOAvl to the VTA that stimulate the avoidance of the pups (Fig. 2).

4.3. Neural basis of sensitized and alloparental behavior

Some primates (including humans), canids, and rodents species (including gerbils, mice, rats, voles) can eventually display parental responses without being pregnant, undergoing the hormonal changes of the end of pregnancy, or receiving the sensory experience typical of parturition and lactation. Studying sensitized maternal behavior and spontaneously parental species has the advantage of testing the neural substrate that regulates maternal behavior without the interventions of major hormonal changes, something that also occurs in humans. In this section we will review the neural basis of maternal behavior when this behavior occurs outside the postpartum reproductive period. A model of spontaneous or rapid pup induction of maternal responsiveness that assumes no or almost absent inhibition on maternal behavior is shown in Fig. 3.

Young male and female rats (20 days of age) can be induced to display parental behavior very quickly (1 or 2 days, Bridges et al., 1974b; Olazábal and Morrell, 2005), and voles do it in a few seconds or minutes (Olazábal and Young, 2006a,b; Roberts et al., 1998). It is important to note that these young individuals display all the behavioral components that are present in lactating animals (retrieval, crouching, licking, nest building), except for nursing (Bridges et al., 1974a; Olazábal and Young, 2005). The presence of parental behavior in young weanling rodents, however, is not universal. For example, weanling mice (20–22 days of age) rarely show parental responses after several days of exposure (Noirot, 1972).

The neural basis of these maternal responses of young animals has been little studied. The mPOA, due to its critical role in adult postpartum maternal behavior, has been one of the most studied brain regions. However, the role of the mPOA in the regulation of weanling parental responses is still unclear (Kalinichev et al., 2000a,b; Olazábal et al., 2002). Although electrolytic lesions in the mPOA can disrupt maternal behavior in 20–21 day-old juveniles (Oxley and Fleming, 2000), the effect of neurotoxic lesions and the activation of *c-fos* in weanling females differed from the responses found in adults. Larger neurotoxic lesions of the mPOA are needed to disrupt juvenile (20–25 days of age) maternal behavior (Kalinichev et al., 2000a; Olazábal et al., 2002). Besides, in adult sensitized or postpartum female rats, high expression of c-Fos is maintained in the mPOA after multiple exposures to pups, and at least during 47 h of exposure (Stack and Numan, 2000). However, when juveniles are exposed to pups, mPOA Fos immunoreactivity increases only during the first exposure, but not after subsequent exposures when the animal is already maternal (Kalinichev et al., 2000b; Olazábal and Morrell, 2005). Fos expression in the mPOA in maternal juveniles is adult-like at around 25–29 days of age (Gonzalez and Fleming, 2002), interestingly associated with the beginning of an inhibitory behavioral response (neophobia) toward newborns (Mayer, 1983). Although Fos expression to first pup exposure has generally been associated with brain regions that inhibit maternal behavior (Olazábal and Morrell, 2005; Sheehan et al., 2000), that is not the only possible explanation. Transient Fos expression in the mPOA of spontaneously or rapidly-induced maternal females can still represent an egagement of this brain region in the onset of maternal behavior. However, young juveniles or spontaneously parental animals with less or no initial inhibition may not longer need the neural adaptation that represents the continuous mPOA *fos* activation found in maternal sensitized or lactating adult rats. Transient expression of Fos in some area of the brain (e.g. mPOA) might represent rapid adaptation of this region in the processes that lead to the expression of maternal behavior but, once the behavior is expressed, other brain regions (perhaps the lateral habenula) might also be recruited and *fos* activation (an the neural adaptation that it represents) not longer be needed in the mPOA. It is unlikely that the initial *c-fos* activation found in the mPOA in juvenile rats represents a subset of cells that inhibit maternal behavior because weanling rats are attracted to pups from the beginning. In addition, evidence in other species (prairie voles and california mice) also supports a different function for the mPOA in the regulation of maternal behavior. Maternal and paternal prairie voles show c-Fos expression in the mPOA (Kirkpatrick et al., 1994; Katz et al., 1999). However, this mPOA c-Fos expression occurs during the first 8 h of the interaction. After 24 h, the authors did not detect increased Fos immunoreactivity in the mPOA. The pattern of Fos expression during the first exposure to newborns (that in voles results in parental behavior), agrees with the pattern of expression of Fos in juvenile rats exposed to pups for the first time, or in parental mice (increases in the mPOA, BNST, LS, PVN, among other brain regions). Paternal mice also show increased Fos in the mPOA

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(de Jong et al., 2009), but not in all experiments (de Jong et al., 2010). When expressed, this mPOA Fos response declined from the first to the third day of pup exposure, as also seen in juvenile rats and adult voles. Lack of continuous activation of the mPOA in juvenile sensitized maternal females or spontaneously parental mice or voles cannot be interpreted as the mPOA having no role in the maintenance of parental behavior in these species or conditions. However, it shows that the function of the mPOA can change among different species, social or physiological conditions. A decline in mPOA Fos expression was also found in postpartum ewes after a few hours of interaction with the lamb (Keller et al., 2004a, 2005). Another example of species-specific function for maternal brain regions is shown by lesions of the MA in voles and rats. While rats are neophobic and lesions in the MA facilitate maternal behavior, voles are not (they even spontaneously take care of mice) and these lesions disrupt maternal behavior (Kirkpatrick et al., 1994).

Juvenile and spontaneously or rapidly induced maternal behaviors have in common a low or absent initial inhibitory behavioral response. A brain region that is consistently activated during spontaneous parental behavior in voles, and in California mice, or in the rapid induction of parental behavior in weanling animals (also in postpartum rats) is the lateral habenula (LHb). Lesions in the LHb disrupt maternal behavior in rats (Corodimas et al., 1993; Felton et al., 1998). The LHb, which has neural connections with the mPOA, and the mesolimbic DA system (Bianco and Wilson, 2009; Hikosaka et al., 2008), is positioned in an optimal place to regulate rapid maternal behavioral responses (de Jong et al., 2010). Future studies should investigate its role in the induction of maternal behavior in other species and conditions, and particularly its role in rapid pup-induced parental responses.

Finally, there is also strong correlational evidence (Kalamatianos et al., 2010; Olazábal and Young, 2006a,b; Schorscher-Petcu et al., 2009), and a few pharmacological and genetic manipulations that support the role of OXT in the NA in the quick stimulation of parental responses in weanlings (also in rats) and adult voles (Keebaugh and Young, 2011; Olazábal and Young, 2006a,b; Peterson et al., 1991). Therefore, considering the proposed model of the neural basis of maternal behavior in the previous section (see Fig. 1), the areas of the brain that support maternal behavior could change their function or relevance to the maternal circuitry in different species or under different physiological contexts, where their connections can be strengthened or weakened. Investigation of the neural basis of spontaneous parental or infanticidal behavior can contribute to distinguishing inhibitory vs. stimulatory pathways or brain regions associated with rapid pup-induced maternal behavior. How brain regions control the output of rapid or spontaneous behavioral responses is a topic of research that needs to be further developed (Fig. 3).

5. Animal studies and their implications for human health

In this section we will address the validity of our experimental models and experimental strategies to understand human maternal motivation and behavior. Most experimental models used in the laboratory carefully consider the biology and the natural needs of the studied species, and all the maternal contexts and physiological conditions discussed in this review have also been found in the wild. However, generalization of our findings in the lab to the life of the species in the wild is something that we cannot always do because of the lack of information on the behavior of our experimental animals in the wild. The social and parental interactions in the wild are clearly more complex, and the environment more unstable than in the lab. That difference suggests that animals that change their behavior and adapt to their environmental needs would survive in better conditions. This seems to be also valid in humans, as shown below. Many of our interpretations and studies that dealt with the complexity of the neural basis of maternal motivation need to adopt a similar philosophy. Maternal motivation needs to be adjusted to the real life and the challenges and changes that all species, including humans confront. The capacity of humans to be flexible, break old habits and build new ones to enhance their adaptation to the needs and demands of infants is critical for a good parenting (Barrett and Fleming, 2011). Therefore, it is intriguing to compare the neural bases of animal and human parental motivation and behavior: their flexibility, the role of learning, and patterns of behavioral switching. These features are interesting considering MRI studies supporting a critical role for the animal and human cortex in maternal responsiveness and adaptation (Febo et al., 2001; Swain and Lorberbaum, 2008; Barrett and Fleming, 2011). Studying the same behavioral processes in different species will help us establish both the universality of some maternal processes as well as the important differences. This is particularly relevant in species in which neural circuit differences can be hypothesized or predicted based on different ecological needs and adaptations.

5.1. Similarities and differences found in rodents and human studies

Much of what we know about the mechanisms regulating maternal behavior in mammals is derived from work on nonhuman mammals, especially rats, mice, voles, rabbits, sheep, and monkeys (Numan et al., 2006). Here we will briefly compare nonhuman mammals (primarily rats) and humans in terms of the role of hormones, sensory stimulation, the brain, and genetics in mothering and in other behavioral systems relevant to mothering.

Many cognitive functions are enhanced in the new mother as compared to the nonmother or pregnant animal; new mothers are more attracted to young (Mattson et al., 2001), less fearful in general (Hansen and Ferreira, 1986), and less avoidant of pups, specifically (Fleming and Luebke, 1981), more attentive (Lovic and Fleming, 2004), less impulsive (Lovic and Fleming, 2004), more susceptible to effects of experience (Fleming and Korsmit, 1996), and more able to learn about certain aspects of their environment, although they may in fact learn less about other domains (Love et al., 2005). New mother rats are also less easily stressed by general stressors (Tu et al., 2005; Neumann et al., 1998). These behavioral changes and adaptations postpartum contribute to a well orchestrated, highly motivated pattern of maternal responding even after the first parturition (see Barrett and Fleming, 2011). Associated with these changes there also occur changes in the animals' endocrine state (see Section 3), neurotransmitter function (see Section 3 and Olazábal et al., submitted for publication-a,b), patterns of brain activation and plasticity (Stack and Numan, 2002; Kinsley et al., 2008), and epigenesis of some of the relevant receptor systems (Cameron et al., 2008).

Using the animal model as a guide, Fleming and colleagues have explored maternal sensitivity and mothering in human mothers of newborns, on day 2 post-partum, and at 3 and 6 months postpartum. They have concentrated on the early postpartum period when mothers in most cultures are still nursing their infants, and when the mother and infant are most exclusively in contact with one another. These studies focused on some of the cross-cultural similarities across mothering, while at the same time recognizing the huge differences that occur cross-culturally in styles of mothering and societally-dictated socialization patterns.

5.1.1. Pregnancy changes in attachment

Assessments of maternal feelings of nurturance across pregnancy in women, determined through factor analyses of responses on maternal questionnaire items, show that these feelings develop across pregnancy showing two periods of elevation from the

non-pregnant state or early pregnancy. The first period would be at the time of quickening, at the end of the first trimester and likely result from the internal movements of the infant and the recognition by the mother of the reality of the developing fetus (Fleming et al., 1997a). The second period occurs close to parturition and peaks immediately postpartum (Fleming et al., 1997a). These changes are similar to the 'pregnancy effect' reported for pregnant rats by Siegel and Rosenblatt (1975) but unlike the rat situation, in humans, these changes seem to have a psychologic basis and are not related to the hormonal changes of pregnancy.

5.1.2. Hormonal associations with mothering

An association has been found between mother's feelings of nurturance on the first postpartum day and their earlier pregnancy hormonal profile (Fleming et al., 1997a). In addition to the steroids (see Section 3), E2 and P4, other hormones have also been studied in human mothers. In a series of studies in new mothers, Fleming et al. (1997b) found that the adrenal hormone cortisol was positively associated with higher levels of affectionate contact and attraction to infant odors. Later in the postpartum period, this relationship was reversed, where high cortisol was associated with more dysphoria, which in turn was associated with less interaction with the infant (Fleming et al., 1997b). Rat work by Rees et al. (2004) indicates a similar role for corticosterone in rat dams. Finally, there is a growing literature in humans showing that in the early postpartum period, there are also associations between OXT and measures of maternal behavior, which has been widely reported in the animal work (Feldman et al., 2011; Nissen et al., 1998; Skrundz et al., 2011, also see Sections 3, 4 and 5.2).

5.1.3. Salience of Infant cues

There are other interesting features of new mothers' responses to their infants that we have encountered in the animal literature. New mothers find infant body odors to be more attractive than do nonmothers. Presentation of other non-baby odors (spice, cheeses, etc.), do not produce the same differential response. Mothers were tested 'blindly' and they were all unaware of the source of the odorants. Hence, infant odors are particularly salient to the new mother; but as in rats that attraction is increased by experience. Mothers with more experience interacting with their infants on the first days of life give more positive ratings (Fleming et al., 1993). They also are better able to recognize their own infant based on their odors, when presented with two containers, one containing own infant t-shirt; the other a same aged and gendered other-infant t-shirt. Again, this early recognition and learning about the odors of their own infants involves quite rapid learning, similar to what has been described in sheep, albeit less exclusively so (Lévy and Keller, 2008; Nowak et al., 2011). Interestingly, again the hormone cortisol seems to be the hormone most associated with these hedonic responses (Fleming et al., 1997b). New mothers are also particularly sympathetic to the sounds of infant cries, showing heart rate accelerations and cortisol responses that are not seen in nonmothers (Fleming et al., 1997b; Stallings et al., 2001). In this case, the salience of the cry stimuli elicits not only mothers expressed sympathy but is also associated with a pattern of cortisol response that seems to be associated with alertness and arousal in the new mother.

5.1.4. Affect and post partum depression

It is well known that new mothers are also quite moody, with 50–70% experiencing postpartum blues during the first postpartum weeks and 15–20% experiencing more severe depression that extends into months (Letourneau et al., 2012). In general, blues is characterized by lability and one of its primary features is where mothers feel both elated and tearful alternately and even simultaneously (Buttner et al., 2012). Anxiety, as well, figures prominently in the blues. Depression usually does not include elation but does include anxiety, and negative mood or flat affect, fatigue and cognitive distortions (Letourneau et al., 2012). Although these early post-partum phenomena are clearly associated with some of the largest hormonal shifts in a woman's life at the time of parturition, surprisingly few studies have demonstrated a consistent and robust hormonal mechanism. Candidate hormones have included parturitional changes in P4, E2, cortisol, PRL, thyroid hormones, and serotonin (Barrett and Fleming, 2011). Although the nature of the parturitional affective change cannot be compared between rat and human, some change in affect occurs in both, and in both the mood change is related to responsiveness to infants. Mothers who are depressed are less responsive to their infants; they are characterized as less sensitive, more easily irritated, and less contingent (Barrett and Fleming, 2011). These behavioral characteristics clearly impact on the infant who, as a consequence, also becomes less responsive and interactive (Letourneau et al., 2012).

5.1.5. Cognition and executive function

Humans are also cognitive creatures and learn a lot from experience. Nowhere is this more apparent than with motherhood. There are very considerable differences between first time mothers and multiparous mothers indicating that maturity and experience together give the multiparous mothers additional knowledge and self-confidence. In fact, if one compares the first time mother with the multiparous mother in responses to the recorded cries of infants, the experienced mother responds predominantly to the pain cry of the infant whereas the new primiparous mother responds equally to the pain and hunger cries, indicating that they are not yet familiar with the meaning of the cry and so become alerted to both (Stallings et al., 2001).

Recent studies that explored executive function in new mothers support the evidence found in the rat by Lovic and Fleming (2004). These authors found a negative relationship between errors in attention set-shifting, and elevated impulsivity, and amount of maternal licking in rats. Maternal rats that were less attentive in attention tasks were also less attentive to their offspring. In a recent series of studies González-Mariscal et al. (2012), and Deater-Deckard et al. (2012) reported very similar findings in human mothers. Postpartum mothers and mothers of 3–7 years old children who had problems with executive function tasks, whether attention set-shifting, or spatial working memory, were less sensitive mothers (González-Mariscal et al., 2012), or less capable of minimizing the effects of harsh parenting (Deater-Deckard et al., 2012). This is particularly true of teenage mothers who, as a group, have the most problem with the planning, organization, attention, and flexibility, and also are well known to have more problems interacting sensitively with their babies (Giardino et al., 2008). Despite these clear associations between executive function and mothering, we still do not have a good handle on whether new mothers differ from non-mothers in their executive function. However, it seems clear that appropriate flexibility to adapt to the new situation and the changing baby is advantageous for mothers. We do know, however, that in fMRI studies of maternal responses to infant cues, the areas of the brain most activated in response to pictures of own infants are regions and circuits important for animal maternal behavior, including the amygdala, the striatum, and the PFC, regions well-known to be implicated in the regulation of emotion, reward, attention, and executive function (Barrett and Fleming, 2011). The similarities found in animal and human studies show that to understand mothering it is important to understand the psychological components that make up mothering, including mothers' perception, affect and cognition, and their physiological correlates.

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5.2. Human genetic studies derived from animal research

An interesting approach that is also extensively used today, consists in investigating the interaction between gene variants and the environment and family context of parents. A genetic polymorphism consists of a difference in DNA sequence among individuals. Single Nucleotide Polymorphisms (SNP) are the most common type of genetic variation in the human genome, and occur when single nucleotides in the genome differ among individuals, groups or populations. SNPs can be present in non-coding or coding regions and are commonly associated with different phenotypes (including diseases). For example, several gene polymorphisms have been associated with many healthy and pathologic behaviors in humans (Chen et al., 2011; Costa et al., 2009; Walum et al., 2012). A recent series of studies that investigated several genetic polymorphisms in the oxytocinergic and dopaminergic systems in human mothers conforms with the data from animal studies (see Section 3 and Olazábal et al., submitted for publication-a,b). Associations between OXT and different aspects of maternal behavior and social interaction with infants has been found in humans (Bakermans-Kranenburg et al., 2012; Bick and Dozier, 2010; Skrundz et al., 2011; Strathearn et al., 2009). Strathearn et al. (2009) found higher serum OXT response to infant contact at 7 months in secure compared to insecure mothers. Human mothers who presented increased levels of affectionate contact demonstrated an OXT increase subsequent to the mother–infant interaction (Feldman et al., 2007, 2011). However, results by Bick and Dozier (2010) suggest the nurturance-OXT relation may not be so clear-cut; these authors found that urine OXT was in fact higher when mothers were interacting with unfamiliar compared to their own children. Finally, low plasma OXT levels during mid-pregnancy predicted symptons of postpartum depression 2 weeks following birth (Skrundz et al., 2011). Skrundz et al. (2011) propose that OXT is implicated in stimulating mother's well-being and reducing anxiety during mother–offspring interaction. Bakermans et al. (2008) looked to a variant of the OXTR gene and found a polymorphism (rs53576) related to lower levels of sensitive parenting. More recently, Feldman et al. (2012) found that OXTR polymorphic variants (rs2254298 and rs1042778) were associated with lower plasma OXT and less parental touch. Finally, in a recently completed study Mileva-Seitz et al. (unpublished) explored the associations of early experience and mothering and the moderating effects of OXT genotypes on that relation. The study examined associations between polymorphisms in OXT and OXTR in a sample of 187 Caucasian mothers at six months postpartum and found that two separate OXT SNPs (rs2740210 and rs4813627) significantly associated with maternal-infant directed vocalizing regardless of early maternal environment. They also found a significant genotype-environment interaction between these two SNPs and maternal early life experiences, on maternal instrumental grooming, and on maternal postpartum depression. Although it is currently not known how these OXTR and OXT polymorphisms relate to OXTR density and OXT levels (in the brain or other organs), respectively, these are promising studies when included within a family, experience, and contextual background.

Despite the substantial evidence implicating the dopaminergic system in maternal motivation (Olazábal et al., submitted for publication-a,b), few studies have focused on DA facilitation of maternal behavior using knockout mice. The only exception is a study that found a deficit in retrieval behavior in postpartum knockout female mice for DA transporter (DAT), but only in some genetic backgrounds (Morice et al., 2004; Spielewoy et al., 2000). There is no information on changes in infanticidal or rapid pup-induced parental responses in knockout mice for DAT or for other DA system genes (i.e. D1, D2, D4 receptors). However, in humans, polymorphisms for the dopaminergic system have been extensively investigated and variants that are less efficient in this system (dopamine D4 receptor, catechol-Omethyltransferase, dopamine transporter) have been associated with different forms of parenting and parental responses to infant's behavior (Kaitz et al., 2010; and Lee et al., 2010; van Ijzendoorn et al., 2008). The main finding of van Ijzendoorn et al. (2008) was differential susceptibility to hassles depending on the gene variants of the dopaminergic system found in parents. When parents had a DRD4-7R (7-repeat DRD4 allele) as well as a COMT val allele, they displayed less sensitive behavior to the attachment needs of their children when they had to deal with more daily hassles. However, they were more sensitive when they experienced few daily hassles, suggesting that the combination of SNPs implied increased susceptibility to daily stresses in parents. Later, Kaitz et al. (2010) found that mothers with the DRD47R allele responded more sensitively to infants that were fussier and less sensitively to infants who were less fussy, suggesting DRD47R was associated with increased susceptibility to context (Kaitz et al., 2010). These authors propose that the presence of a DRD4 7-repeat allele predicts better performance in more arousing or challenging contexts and poorer outcome in less arousing or challenging contexts. Lee et al. (2010) also found an association between a variant in the gene of the dopamine transporter (DAT1 genotype) of the mother and negative parenting. This association was significantly stronger in mothers whose children were very disruptive during the mother–child interaction task, suggestive of a gene–environment interaction. In a more recent study, Mileva-Seitz et al. (2012) asked how individual haplotypes (a set of SNPs that tend to be inherited together, possibly because the SNPs are located within a single chromosome) of the DRD1 and DRD2 genes related to different measures of mothering. Consistent with predictions from the animal work, they showed that genetic variation in both DRD1 and DRD2 genes in human mothers predicted variation in specific maternal behaviors during a 30-min mother–infant interaction at 6 months postpartum. DRD1 SNPs and haplotypes were significantly associated with maternal orienting away from the infant, while DRD2 haplotypes were significantly associated with maternal vocalizing/speech to the infant. Taken together these gene polymorphism studies suggest that different gene groups may be associated with different maternal phenotypes and that the environment can moderate genotype-behavior associations to different extents for these different maternal phenotypes. They also highlight the importance of analyzing different components of mothering and pay attention to its multidimensionality. Alltogether these studies support a role for OXT and DA systems genes in human maternal motivation. One of the main conclusions from these genetic studies is the importance of the context and of the dynamics of mother–child interactions in studies on human parental behavior. Polymorphisms for other hormonal receptors systems such as ERalpha, and P4 receptors, or PRLR have not been investigated in relation to variations in human or animal parental behavior.

6. Conclusions and perspective

The rich exchange of ideas among the participants of the present review has led to a revised neural model of parental behavior and has also revealed unexplored aspects related to the neural basis of maternal behavior.

First, although the literature on parental behavior covers a good range of species and strategies, our understanding of the neural basis of maternal behavior in these species is very uneven. Increasing the diversity of species and the physiological conditions at which maternal behavior is studied will strengthen our understanding of how a certain brain substrate or circuitry has been adapted to respond maternally under different conditions and with different modalities of mother–offspring interaction. For

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example, the comparisons of the neural basis of altricial vs. precocial species, or of species requiring extensive vs. brief daily periods of mother–offspring interaction can provide information on different mechanisms that would be needed to maintain maternal motivation with or without the continuous stimulation by the offspring. This comparative analysis or approach is informative given that existing adaptive mechanisms may remain mostly hidden or minimized in some species or contexts, but be activated or obvious in others.

Second, focusing our studies on multiple species can also provide information on the changes in neural substrate that support the different components of this complex behavior across lactation. Altricial and precocial offspring develop differently and require different kinds and degrees of attention from their mothers. Different species use different sensory modalities for mother–offspring interaction and the importance of different modalities changes across lactation and with the development of the young. We have advanced significantly in understanding the neural substrate that mediates some components of maternal behavior most commonly present in rodents (retrieval, licking, nursing). However, the role of mother's vocalization, not investigated in rodents, is critical in many species, including most ungulates and primates. The neural basis of this aspect of maternal behavior and motivation has not been explored in detail, and is one of the components of maternal behavior recruited during the search for displaced offspring in many species. This is particularly interesting considering that this highly motivated *active* seeking behavior eventually requires minor or no displacement or movement of the mother. Furthermore, the switching of maternal activities and the offset of maternal behavior should be regulated differently in species with precocial young than in those with altricial young, considering the quick development of motor and nutritional independence in precocial species. The neural basis of these differences is likely the result of an adaptation to satisfy the needs of the offspring, including the strengthening of sensory channels that are relevant to maintain maternal motivation at each specific developmental period.

Third, the present discussion on the neural basis of maternal behavior in different physiological and social contexts, and their regulation and adaptation across lactation, resulted in the formulation of several integrated neural models that could explain how the brain might adapt to these different situations. Here, we put particular emphasis on the critical, but changing, function of the mPOA in the control of maternal behavior expressed under different physiological and social contexts. We incorporate into these neural models the role of cortical regions in the organization of, and switching between, different behaviors or motivations. We also propose hypothetical changes in neural representation of different subregions of the circuitry that supports maternal behavior, with possible relevance in the proceess of short or long term maternal adaptation and memory. We also discuss a neural model to explain the reduction or absence of inhibition of maternal behavior in many species and how the brain might adapt to express maternal behavior in those cases.

Finally, we review the enormous contribution that animals studies have made to our understanding of human maternal behavior and motivation. We highlight the remarkable similarity in many fundamental biological processes (including neural processes) found in animals and humans. However, we also highlight that the neural basis of maternal motivation must be adapted to the particularities of the human condition and behavior. Therefore, we have put particular emphasis in this review on the role of the cortex in the control of maternal behavior, in particular its role in executive functions related to maternal behavior. As part of these investigations, we consider that new MRI studies provide an opportunity to reveal the neural basis of human parenting. We also suggest that studies on genetic aspects of maternal behavior should follow the current trend that includes, in its analysis, aspects related to the social and family context, as well as the style and dynamics of parenting. These studies will necessarily require a multidisciplinary approach designed to assess which features of parenting are uniquely human and which vary across cultures and species. The identifcation of the physiological and experiential causes of both normative and maladaptive or inappropriate parenting in human populations is essential if we are to develop effective interventions and strategies to enhance sensitive and appropriate parenting skills and practices.

Uncited references

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Sheehan and Numan (2002) and Bakermans-Kranenburg and van Ijzendoorn (2008).

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