Neurobiology of mother–infant interactions: experience and central nervous system plasticity across development and generations

A.S. Fleming\textsuperscript{a,}\textsuperscript{*}, D.H. O’Day\textsuperscript{b}, G.W. Kraemer\textsuperscript{c}

\textsuperscript{a}Department of Psychology, University of Toronto at Mississauga, Mississauga, Ontario, Canada L5L 1C6
\textsuperscript{b}Department of Zoology, University of Toronto at Mississauga, Mississauga, Ontario, Canada L5L 1C6
\textsuperscript{c}Department of Kinesiology, Harlow Primate Laboratory, University of Wisconsin, Madison, WI 53715, USA

Received 6 March 1998; received in revised form 19 November 1998; accepted 8 December 1998

Abstract

The optimal coordination between the new mammalian mother and her young involves a sequence of behaviors on the part of each that ensures that the young will be adequately cared for and show healthy physical, emotional, and social development. This coordination is accomplished by each member of the relationship having the appropriate sensitivities and responses to cues that characterize the other. Among many mammalian species, new mothers are attracted to their infants’ odors and some recognize them based on their odors; they also respond to their infants’ vocalizations, thermal properties, and touch qualities. Together these cues ensure that the mother will nurse and protect the offspring and provide them with the appropriate physical and stimulus environment in which to develop. The young, in turn, orient to the mother and show a suckling pattern that reflects a sensitivity to the mothers odor, touch, and temperature characteristics. This article explores the sensory, endocrine, and neural mechanisms that underlie this early mother–young relationship, from the perspective of, first, the mother and, then, the young, noting the parallels between them. It emphasizes the importance of learning and plasticity in the formation and maintenance of the mother–young relationship and mediation of these experience effects by the brain and its neurochemistry. Finally, it discusses ways in which the infants’ early experiences with their mothers (or the absence of these experiences) may come to influence how they respond to their own infants when they grow up, providing a psychobiological mechanism for the inter-generational transmission of parenting styles and responsiveness. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Maternal behavior; Brain plasticity; Development; Maternal experience; Olfaction; Somatosensation; Hormones; MPOA; Amygdala; c-fos; Signal transduction; PKC; CaMBPs; Maternal deprivation; Rat; Monkeys; Humans

1. Introduction

Non-human mammalian mothers typically display a stereotyped set of behavioral responses to their newborn. They exhibit species-characteristic ways of transporting, holding, feeding, and grooming the young, and of protecting them from the predators and other dangers [1]. For instance, the prospective mother rat constructs a nest before giving birth. She aids the birth by pulling individual pups from the vaginal canal, severs the umbilicus, eats the placenta, cleans the pups, and carries them one-by-one in her mouth to the nest. In the nest, she continues to lick the pups, especially their anogenital regions, and eventually adopts a nursing posture over them. In return, mammalian neonates exhibit behavior that is even more stereotyped and rigid than maternal behavior. This includes orchestrated orienting responses towards the mother, seeking and attachment to her teats, and emission of sound and odor signals that elicit maternal responses (crying, squealing, urination, and so forth). The reciprocal exhibition of maternal behaviors and newborn signaling promotes physiological and immunological resilience, physical maturation, and species-typical social and emotional development in the young (see [2–8]). Ultimately, reciprocal mother–infant behaviors increase the probability that the young will survive and, beyond survival, will mate and successfully rear their own offspring. In this article, we show how these behavior patterns, previously viewed as fixed and stereotyped, are in fact quite plastic, and depend on brain structure and function that was substantially influenced by experience at the time of birth and over the life-span.

As shown in Fig. 1, the development of the capacity to both express and modify maternal behavior patterns in adulthood may depend on mechanisms that were themselves activated and later tuned by early experiences. The interaction between the newborn and the mother alters basic
mechanisms of behavioral expression in both. How the mother responds determines, in part, how the neurobiological and behavioral changes in the infant proceeds. Changes in an infant may eventually play out as to how the individual will respond to the offspring as an adult, and so on.

2. Reciprocity in the mother–young relationship

2.1. Mothers learn about and from their infants: role of sensory, hormonal, and neural influences

Experiences acquired while mothers are with their infants influence their willingness to care for the young. In many primate species (including humans), prior experiences of holding and carrying the young either during adolescence (siblings) or after a previous birth can have profound effects on how competent or motivated females care for their offspring (humans, [9]; marmosets, [10], rhesus macaques, [11–13]; vervet monkeys, [14]). In some species, absence of pre-pubertal experience with younger siblings results in first-time mothers who neglect or even eat their infants [10]. Postpartum maternal experience can also affect mothers’ subsequent responsiveness to these same offspring at a time when the hormones of parturition are no longer behaviorally effective. In species that respond selectively to their own infants, to the exclusion of other infants (e.g., sheep mothers, ewes), mothers rapidly learn to identify their own infants based on their odor characteristics. In species that do not show selectivity (e.g., rats), the early postpartum experiences with the litter helps to maintain maternal responsiveness to young during subsequent lactation. Although processes of learning are likely to be involved in both types of experience, the mechanisms mediating mothers’ recognition of individual infants are somewhat different from those that mediate the effects of experience on maternal responsiveness in general.

2.1.1. Maternal experience affects individual recognition of offspring

Under the influence of parturitional hormones ewes who have just given birth may initially nurse any lamb, but they soon learn to recognize their own lamb by its odor [15]. Once an ewe has smelled her lamb’s odor (usually the mother’s own amniotic fluid), she Butts away alien-smelling lambs and permits to nurse only her own lamb. Her recognition requires only a few minutes of exposure to the lamb to form [15]. In humans also, new mothers come to recognize their own infants’ odors, cries and tactile characteristics [16–18]. They do so even with very brief exposure to the features of the infant during the first few postpartum days. Mothers who nurse their infants sooner after birth and/or who keep their faces in close proximity to their infants while holding them (hence acquiring more olfactory experience)
are both more attracted to their infants’ body odors and come to recognize them more easily [9].

We now have a substantial understanding of the endocrine mechanisms that mediate the enhanced responsiveness to offspring normally seen in the mother at parturition (see [1,19,20]). Endocrine and neurochemical mechanisms regulating the expression of maternal behavior intersect or overlap with those that activate or prime discriminate learning mechanisms. In most mammals that have been studied, the hormones that activate maternal responsiveness to young in general are those that change at the time of parturition. These include a period of elevated progesterone during pregnancy, followed by its pre-parturitional decline [20,21,106]; a late pregnancy rise in circulating estradiol and pituitary prolactin; and a rise with parturition in oxytocin [20,21]. In ewes, a variety of hormones and neuropeptides including estradiol, oxytocin, endogenous opioid peptides, and corticotrophin releasing hormone (CRH) are elevated at parturition and act in synergy with cervical stimulation (which occurs during the birth of the lamb and stimulates oxytocin release) to enhance the learning of the new lamb’s odors [15]. The catecholamines norepinephrine (NE) and dopamine (DA), along with glutamate and γ-aminobutyric acid (GABA) and nitric oxide are also released or synthesized within the olfactory bulbs at this time. In addition, levels of brain NE at parturition are higher in multiparous than in primiparous ewes [22]. Hence, the first maternal experience may prime (or sensitize) the neurochemical mechanisms regulating the formation of specific discrimination of subsequent offspring. At parturition, release of these neurochemicals facilitates changes in brain mechanisms underlying the recognition process [15,22–24].

Consolidation of the association between the mother’s birthing stimuli (cervical dilation) and attraction to the lamb’s odor appears to involve changes in the olfactory bulb cytoarchitecture and synaptic efficiency [22–24] and possibly, amygdala, and hypothalamic processes as well. The importance of these limbic and hypothalamic sites for the onset and maintenance of maternal behavior is most evident in the research on rodents (see the following).

2.1.2. Maternal experience affects maternal responsiveness

In contrast to the many species that require early prepubertal or subadult caretaking experience to show adequate mothering, female rats under laboratory conditions, and with no prior experience with rat pups, usually care adequately for their first litter. Female rats who have not given birth usually withdraw from or avoid pups, so changes surrounding the birthing process must alter this pre potent response. The inexperienced mother rat builds a nest, gives birth, and then gathers, licks, and nurses her young under the influence of changing levels of circulating steroidal and protein hormones (see [1,20]). The hormones associated with lactation may also contribute to the patterning of nursing after parturition [27]. However, the later persistence of a motivation to care for the young seems not to be hormonally regulated. Once the maternal behavior has been exhibited it persists for a number of weeks in the absence of parturitional hormones [28,29]. Hence, for the new mother, care of offspring appears to depend on hormonal activation of neural mechanisms that express maternal behavior. Once this has happened the hormones are no longer required.

Pup stimuli have intrinsic effects on the female nervous system. Virgin rats can be induced to become maternal through repeated exposure to pups over five to seven days [30]. Maternal behavior is exhibited most rapidly towards pups when the parturitional hormones are present, however. When interacting with the young, the hormonally influenced maternal rat associates how the pups smell, feel, and sound with motor responses involved in picking up and moving pups and adopting a crouch posture over them. Through concurrent hormone changes and exposure to pups, the mother becomes habituated to their odors and other novel aspects that would usually activate fear and withdrawal [31,32]. Unlike mother sheep who learn the individual odors of their lambs, rodent mothers do not develop individual pup recognition. They respond to their own and other litters of the same age in much the same way. Parturitional hormones enhance the attractiveness of pups and their odors [31] and facilitate maternal learning [33]. Pups become considerably more reinforcing to the dam once she has interacted with them and become experienced. In fact, mothers exhibit preferences for visual environments that have been associated with pups in only two trials [34]. Maternally experienced females show enhanced bar-pressing for delivery of pups by comparison to the inexperienced females [35].

As with other types of learning, the integrity and resiliency of maternal learning/memory varies with frequency and duration of exposure and the interval between exposure and test. If new mothers are separated from their young and not permitted to interact with them at all, their maternal responsiveness declines over the first postpartum week. By 10 days postpartum, the mother withdraws from the foster pups much as the naive females would [36]. However, if permitted as little as two hours of contact with the pups on day 1 postpartum, the mother rat shows very active maternal response to the foster pups presented 10 days later [36].

Initial maternal learning depends primarily on somatosensory and chemosensory modalities. If new mothers are rendered anosmic and cannot smell pups and are also unable to acquire somatosensory stimulation of the ventrum and mouth regions (due to application of anesthetic onto or into these regions), pups are not licked or retrieved [37,38]. Maternal olfactory and somatosensory processing is necessary for pups to acquire reinforcing value, and for the mother to retain responsiveness to pups over long periods of separation [37,39]. As an example, presenting mothers with pups scented with an artificial odor results in preferential attraction to that odor in an odor preference task and preferential maternal treatment of similarly scented (as...
opposed to ‘otherly’-scented) pups in tests 10 days later. In order to continue the caring of pups after the hormonal effects have subsided, the mother must continue to find them attractive. Hence, mechanisms of reinforcement, learning and memory are recruited. Hormones may facilitate the relationship, but learning factors maintain it. Facilitated postpartum learning also occurs in olfactory-social contexts which are not related to pups, indicating that the general learning processes are recruited [40].

The combined role of hormonal changes and sensory experience in promoting maternal behavior and learning is fairly well understood [9,29]. Until recently, however, there has been virtually no understanding of which neuroanatomical and neurochemical systems are responsible for the experiential modification of maternal behavior. One approach was to investigate the neurochemical systems that are known to be involved in the mediation of learning and memory in other functional contexts that involve affective changes. As with other types of learning, maternal learning requires protein synthesis for its consolidation. Injection of protein synthesis inhibitors (e.g. cycloheximide) into the ventricles of the brain after exposure to pups for three hours blocks the long-term retention of the behavior [41]. NE mechanisms are also involved as \( \beta \)-noradrenergic blockers administered after this exposure block the long-term effects whereas isoproterenol, an NE agonist, enhances the retention [42]. Finally, the development of maternal conditioned place preference using pups as reinforcing stimuli is blocked by \( \alpha \)-fluoxetine, a DA antagonist [34]. Our particular interest, though, is in the relation between learning systems and maternal systems [29,43].

As there is a considerable overlap of maternal learning with more general conditioning and learning reinforcement mechanisms and we know some of the neuroanatomical systems underlying aspects of general learning per se, a next step was to determine the role of these brain structures and those in the ‘maternal circuit’, in the acquisition and retention of maternal experience. For instance, work on the supraoptic nucleus shows that, with suckling experience in the lactating animal, there occur changes in the structural and functional properties of supraoptic neurons. These neurons release oxytocin in response to suckling stimulation and are necessary for the milk letdown reflex [44]. Modney and Hatton [44] found two kinds of change associated with the end of pregnancy and the initiation of nursing. One involves the formation of new (double) synapses on the cell body and dendrites of the supraoptic nucleus, while the other involves the increase in electrical coupling among these same oxytocinergic supraoptic neurons. These changes very likely contribute to the synchronized activity in these oxytocin cells prior to milk ejection. Of particular interest in this context are the additional findings that some of these modifications also appear in virgin animals induced to become maternal through long-term exposure to pups, but who did not receive suckling stimulation. Instead, there is evidence that olfactory and/or other chemosensory stimulation derived through licking and retrieving of pups may induce these changes in the virgin [44,45]. The time course of these effects in the nursing animal may be relevant; some synaptic changes are reversible, but apparently others are more permanent. Such long-term structural changes could provide a possible basis for the findings that, once dams have had some nursing experience, distal olfactory and other exteroceptive pup cues come to elicit the conditioned release of oxytocin in the absence of suckling [46].
Potential signal transduction pathways leading to maternal c-fos expression. Maternal hormones, neurotransmitters and pup stimulation (e.g. olfactory) can activate many receptor complexes. This leads to the elevation of neuronal calcium levels and the stimulation of protein kinase C (PKC). Calcium activates calmodulin (CaM), which in turn stimulates a wide range of calcium binding proteins (CaMBPs) such as CaM-dependent kinases. These kinases and PKC each phosphorylate specific upstream elements that ultimately lead to the expression of c-fos. As part of transcriptional complexes, such as AP-1, c-fos could then activate gene expression that underlies maternal behaviour.

Using quite a different approach we used the c-fos immunocytochemistry to assess which brain areas are activated during the acquisition and retention of a maternal experience.

3. Correlates of maternal behavior at the intra-cellular level

3.1. Fos as a neuroanatomical marker of maternal experience

Fos is a protein produced by a class of immediate early genes known as c-fos oncogenes that are present in brain neurons and activated by a variety of stimulus situations and behavioral states [47]. Acting with another proto-oncogene protein, Jun, as part of the AP-1 transcription factor, Fos can operate directly as part of the transcriptional apparatus to direct gene transcription or it can act by binding to enhancer elements to affect the gene regulation [48]. Therefore, c-fos immunocytochemistry can be used as a tool to determine which brain sites are activated when an animal first responds maternally, acquires an experience, and then retrieves the memory [43,49–52]. Moreover, the physiological relevance of Fos for maternal behavior is suggested by the recent observation that c-fos-knockout mice fail to show adequate maternal behavior under circumstances in which it would normally be seen in the wild-type mouse [53].

If an animal is maternally active for the first time, enhanced c-fos expression is found in a number of brain regions including the medial pre-optic area (MPOA), the bed nucleus of the stria terminalis, the medial, cortical and basolateral nuclei of the amygdala, the nucleus accumbens, the olfactory and somatosensory cortices, and the prefrontal cortex [51,52]. Fig. 2 shows the functional neuroanatomy mediating the maternal and related behaviors. Some of these sites are clearly part of the final common path for the expression of maternal behavior (e.g. MPOA, [29,43,55]). Others mediate stimulus salience and effect (medial and cortical amygdala, see [56,57]), and processes of learning, memory and reinforcement (pre-frontal cortex, basolateral amygdala, nucleus accumbens, see [51,58]). Others participate in sensory processing (cortical and medial amygdala, parietal and olfactory cortices [56,59]).

Only a few of these sites are activated at retention testing. When re-exposed either to pups themselves or to pup-associated conditioned cues (an environment or stimulus paired with pups), the only sites that are more active in the experienced than the inexperienced animal are the MPOA, the basolateral amygdala and the parietal cortex [50]. Experimental effects of performing maternal behavior and receiving pup stimulation in the postpartum mother are the basis for maintaining maternal behavior when hormonal effects have waned. MPOA lesions produce severe deficits in both the hormonal and experiential components of maternal behavior [43]. The transition from hormonal to non-hormonal regulation of maternal behavior, therefore, is probably dependent on MPOA mechanisms.

4. Effects of experience on signal transduction components

Although c-fos expression is clearly enhanced with the expression of maternal behavior and experience, it is not known whether this protein is necessary for the behaviors to be expressed and, if so, what role they play. As our interest lies in understanding the regulatory events that initiate maternal behavior and experience, we have started to determine how c-fos expression is regulated by upstream regulators of maternal behavior, and to determine what function the expressed proteins serve. In mammalian cells, there are numerous signaling pathways that can lead to c-fos expression [60]. One approach to dissect the major signaling pathways in specific regions of the rat brain is to immunolocalize selected proteins from those pathways, and then to determine if they are present during and are linked to the maternal behavior. Two major components of calcium-mediated signaling pathways that lie upstream to c-fos expression were examined: protein kinase C (PKC) and calmodulin binding proteins (CaMBPs; Fig. 3). At least two of the protein hormones involved in the expression of maternal behavior, oxytocin and prolactin, can produce intracellular neuronal increases in calcium levels, leading to the activation of PKC and CaMBPs [61]. PKC can be activated by diverse signaling pathways, including via G protein-linked phospholipases, receptor tyrosine kinases.
and non-receptor tyrosine kinases [62,63]. While numerous PKC forms of the protein exist (isozymes), the brain-specific PKC isozyme (PKC gamma) is a typical C kinase that is activated by calcium ions and diacylglycerol and undergoes developmental increases in the rat brain [63]. PKC is implicated in long-term potentiation (a neuronal model of memory) as well as in learning, memory, and plasticity processes [64,65]. PKC can also act as an upstream regulator of AP1 (c-fos/c-Jun) expression [48,66].

Immunocytochemical assay of a number of different PKC isozymes indicates that there is a considerable overlap in the regional and temporal pattern of expression of PKC and Fos protein in mother rats exposed to offspring [67]. There are also some incongruities in their patterns of expression that may be informative. For example, enhanced staining of both PKC and Fos protein is observed in the MPOA and the parietal cortex after maternal experience with pups [32]. If the pups are removed, enhanced PKC will still be observed in the mother four days later but Fos staining would have diminished by then. Active stimulation by pups or pup-associated conditioned cues is necessary to reinstate enhanced c-fos expression, and this occurs rapidly but is also relatively short-lived. The relation between the PKC and Fos results suggest that maternal experience initially stimulates enhanced PKC synthesis and an activation of the c-fos gene in the maternal system (e.g. MPOA). In the absence of pup stimuli, maternal PKC remains elevated for a considerable period, but c-fos gene activation declines. As PKC sits upstream in the biochemical cascade leading to c-fos activation, enhanced PKC resulting from past experience with pups would permit rapid activation of the c-fos gene in relation to new pup stimuli in the experienced female.

Another primary route for calcium function is via calmodulin (CaM) and the CaMBPs to which it binds and modulates. Upon activation by Ca$^{2+}$, CaM was shown to regulate c-fos expression but the specific CaMBPs that mediate this expression have not been identified [68]. However, the CaMBP, CaM-kinase II has been implicated in models of neuronal plasticity [69]. In addition, certain kinases and calcineurin (CaM-dependent protein phosphatase 2B), a major brain protein, regulate transcription factor phosphorylation upstream of Fos expression [70]. Cells also contain dozens of CaMBPs many of which mediate neurotransmitter release [71]. Previous studies have identified only a handful of the many CaMBPs in brain and other tissues of the rat. Rather than focusing upon one or two known CaMBPs, analysis of the pattern of changes in the total population of these proteins during maternal behavior has been a fruitful approach in elucidating the role of these important cellular regulators. A gel overlay technique with recombinant calmodulin (35S-VU1-CaM) reveals over two dozen CaMBPs, a number in keeping with the known population extent in mammalian and other eukaryotic cells [72]. Analysis of the quantitative changes in the CaMBP profiles reveals that there is a decrease in several CaMBPs associated with the onset of maternal behavior. Western blotting has further revealed the absence of calcineurin from the MPOA but not other regions of the maternal brain (O’Day et al., unpublished results). These changes and differences are localized only to the MPOA suggesting that there may be calcium-regulated signaling pathways that are specifically associated with maternal behavior and plasticity. The goal now is to characterize these CaMBPs to gain further insight into their possible functions.

5. A functional neuroanatomy of maternal experience

These studies not only reveal some of the basic molecular mechanisms underlying maternal processes, but also help to elucidate the neuroanatomy that underlies the acquisition and retention of maternal experience (see Fig. 2). A role for the MPOA, the limbic system, the olfactory and somatosensory systems in the initiation and retention of maternal behavior is consistent with more general learning, memory, and emotional functions of these structures.

Beyond this it is known that the MPOA contains receptors for the hormones that activate both the motoric and motivational aspects of maternal behavior [28,55]. Lesions of the MPOA eliminate maternal retrieving and nest-building as well as instrumental responding for pup-delivery in an operant apparatus [35,43]. Electrical stimulation of this area has opposite effects [55]. Of all the brain structures studied from a molecular perspective, the MPOA undergoes the most robust and substantial change with maternal experience. MPOA function is substantially altered by experience, and such alterations may play a role in the facilitated maternal behavior seen in the experienced animals. The hormonal responsiveness of the MPOA increases with increasing parity [21]. Moreover, electrical stimulation of this brain site is more effective in promoting maternal behavior in experienced as opposed to inexperienced animals [55]. In short, it appears that the MPOA is involved not only in the initial expression of maternal behavior, but also in retaining and mediating the effects of maternal experience and parity on the subsequent expression of the behavior.

Other central nervous system structures clearly mediate the sensory aspects of maternal behavior (e.g. parietal cortex and olfactory bulbs), being activated when the animals sniffs, licks, mouths and crouches over the pups [38]. The parietal cortex also appears to be changed by maternal experience, an effect that is consistent with evidence that this sensory receiving area is plastic and re-organizes in relation to experience in adult rodents. For example, in comparison to the non-lactating postpartum females, lactating (and hence more experienced) females have an expanded region of the cortex activated by stimulation of the ventral teat region [73]. What this probably means is that cortical mechanisms change in relation to experience; and subsequent experiences are almost certainly processed differently than were the initial experiences.

A role for amygdaloid nuclei in the expression and
retention of maternal behavior has also been demonstrated. Areas in the medial and cortical amygdala receive olfactory input and are believed to mediate avoidance responses to odors or have anxiogenic actions more generally. Indeed, these amygdalar mechanisms inhibit the expression of maternal behavior in virgin animals. Lesions of these nuclei or of pathways that project from the amygdala to the MPOA in the virgin animal permit rapid maternal responding to pups and reduce fear responses to odors in other contexts (see [9,32,43,55]).

The enhanced activation of the basolateral amygdala with maternal experience is consistent with the observation that this structure receives extensive primary or secondary input from all the relevant sensory modalities, thereby serving as a point of convergence where the formation of associations may occur [52,56,59,74]. Walsh et al. [52] demonstrated that the combined chemosensory and somatosensory desensitization in maternally-behaving animals produces an additive reduction in basolateral amygdaloid activity (reflected in c-fos expression). Moreover, lesions of this region eliminate the development of a conditioned place preference for pups and disrupt the postpartum expression of maternal behavior [35]. Not surprisingly, given its role in reinforcement [58,75], DA depletions or lesions of the nucleus accumbens also disrupt the consolidation of maternal memories [28]. Hence, the combined activation of basolateral and nucleus accumbens in response to pup stimuli, and the effects of lesions in reducing the maternal responsiveness, suggest that the basolateral amygdala and nucleus accumbens form an interconnecting neural loop that mediates the formation of associations between biologically relevant events (pup stimuli and maternal behavior, in this instance) [56].

The effects of maternal experience on the basolateral amygdala and on the parietal cortex reflects the general properties of these two structures (systems) that are recruited by many types of learning. Experience-related activation of MPOA seems to be specific to maternal behavior, however. Perhaps it makes sense that in mammals, as in birds [4,6], the long-term effects of memory should be most clearly seen in the very system that normally underlies the expression of the behavior.

6. Intergenerational effects: Does how one was mothered influence subsequent mothering?

6.1. The infant becomes experienced through the mother

Among mammals, the maternal and nest contexts provide a rich learning environment for the developing young. Mothers not only learn about their offspring; but the offspring also gain experiences during the pre-weaning period that affects their adjustment to the mother and later on to their own offspring.

6.1.1. Short-term experience effects

For instance, rat pups develop an attraction to the chemosensory characteristics of mother’s ventrum and first attaches to the nipples based on prior intrauterine experience with the amniotic fluid [76]. Attraction is often followed by the development of nipple-preferences. In fact, kittens develop a preference for a particular nipple or nipple location on the mother’s ventrum. Seeking the ideal nipple position is based on experiences with the tactile and thermal characteristics of the mother’s ventral surface [77]. In rats, the expression of food preferences is based on experiences acquired during the infant’s exposure first to the mother’s milk, then her odors (which are partially dependent on her diet), then to food particles remaining in the vicinity of the mother’s mouth and on her fur, and finally to following the mother to a food site [78–81]. More subtle discrimination by weaned animals of nutritious versus nutritionally deficient foods is also based on learning [82].

The behavioral effects of early experiences occurring in the maternal nest are mediated by neurochemical and neuroanatomical mechanisms that have been substantially changed by early experiences [2–3,83–85]. As an example, the recognition of the rat mother’s specific odor by pups occurs in conjunction with licking of the pups by the mother [86]. Formation of the association between licking and maternal odor depends on licking induced activation of the midbrain nucleus, the locus coeruleus (LC), whose axons terminate in the olfactory bulbs and release the neurotransmitter, NE [86]. Recognition of maternal odor involves both the neurochemical and cellular cytoarchitectural changes in the olfactory bulb [86,87]. Development of an attraction and preference for maternal odors (over other odors in the environment), depends on central processing of olfactory information by the limbic structure, the amygdala. More generally, processing of the olfactory bulb inputs by amygdalar mechanisms determines the salience of olfactory stimuli and the nature of affective responses to them [86]. The neuropeptides (oxytocin and opioids) may also play a role in the infant rat’s early affiliative behaviors in the nest and in the infant’s attraction to maternal odors [25–26,85,88]. The proclivity of rat pups to approach and attach to the mother is heavily dependent on the experiential effects on olfactory and limbic mechanisms that mediate attraction to and recognition of the mother and her environment.

6.1.2. Long-term experience effects

Postpartum experiences with the mother and nest influence the development of the infant prior to weaning. Concurrent early olfactory experiences (mothers’ odors) and somatosensory experiences (being nursed, licked, etc.) also appear to have long-term effects on the infants as they grow. For instance, infant rats who received more touch and licking stimulation from the mother in the nest show a higher level of pup-licking as juveniles and as adults.
when presented with new-born pups, by comparison to less stimulated infants; moreover, recent studies indicate that the quality of the infants’ nest experience may well affect their later behavior with their own offspring (Natterer, Lovic, Shah, and Fleming, in preparation). Similar early maternal stimulation in the nest also produces a dampening of the offspring’s emotional reactivity to novelty and stress when they become adults [89]. Reductions in stress reactivity are attributable in part to the increased density of hippocampal glucocorticoid receptors. These receptors normally mediate negative feedback effects of circulating adrenal glucocorticoids following hypothalamic-pituitary-adrenal (HPA) activation. Stimulation-induced changes in thyroid function and brain serotonin system activity early in the postpartum period are also involved in these long-term hippocampal effects [90]. Hence, long-term changes in brain mechanisms that modulate the stress reactivity in offspring are produced by natural variations in mothering behavior. To the degree that many interactions with offspring are stressful, this may canalize some aspects of the way individuals respond to their own offspring later on. In species in which mothers develop individual recognition of their offspring, as in sheep, the same or similar mechanisms used to promote attachment of the young female to her mother, are re-activated when she gives birth and exhibits recognition and attachment to her own offspring. This transfer of biological effects of early rearing experience to later maternal responsiveness and behavior may be especially evident when considering species in which the parent is intimately involved with disciplining or socialization of offspring, as in non-human primates.

In rhesus monkeys, measures of HPA axis activity in mothers and offspring are positively correlated [91]. In vervet monkeys, there is substantial evidence that the style of mothering exhibited by adult daughters is similar to the style of mothering shown by their mothers [14]. Vervet monkey mothers who engage in a high level of mother–infant ventral contact have daughters who also show high mother–infant contact. Abusive patterns of maternal care span generations as well, and the incidence of abuse varies across matrilines in pigtail macaques [14]. One cannot, of course, identify the mechanism underlying the intergenerational similarity based on these correlations. Similarity could be due to consistent (genetically pre-programmed) personality styles or due to the effects of observing the mother’s interactions with younger siblings. Using multivariate analyses in which these alternate influences were assessed, however, Fairbanks [14] demonstrated that the manner in which the infants were mothered did indeed exert an effect on their adult mothering behavior. Among humans, it is commonly assumed that there are often intergenerational similarities in maternal behavior. We have not yet found a longitudinal study that conclusively documents substantial and significant commonalities in specific practices of mother–daughter maternal behavior. However, rather, the long-term longitudinal story has to be pieced together based on findings of multiple short-term studies and there are missing pieces to the puzzle.

What has been investigated is the relationship between maternal and infant attachment style, and later personality of the infant-as-young-adult and attachment style of their infants. The results of short term longitudinal studies indicate that (1) the emotional quality of mothers’ responsiveness to infants is related to the infants’ attachment style, (2) infants’ attachment style in turn is related to social and affiliative aspects of adult personality, and (3) these adult personality styles are related to responsiveness to infants [92–94].

Scientific interest in intergenerational effects has also been driven by efforts to understand the mechanisms underlying the abnormal by comparison to normal psychosocial development. In social primates, the importance of early mothering in determining how the daughters will mother is clearly demonstrated under the conditions in which female offspring are partially or completely deprived of early mothering. For instance, rhesus monkeys can be reared with same aged peers rather than mothers (peer-reared monkeys) [79,95–98]. When peer-reared monkeys become mothers as adults, they are more likely to reject or abuse their infants than monkeys reared by their biological mothers (mother-reared monkeys). The mechanisms that mediate this effect are not understood. The idea that peer-reared monkeys are generally poor mothers because they are deprived of ‘learning how to mother’ from their own mother cannot entirely explain their deficits in maternal behavior. Some peer-reared monkeys are perfectly adequate mothers, but the proportion of who are not considerably exceeds that observed in mother-reared monkeys. As no peer-reared monkey has experience with maternal care, the range of variation in peer-reared maternal behavior cannot be explained by early variation in learning how to mother.

In general, how the individual copes with environmental change and stress may vary with how they cope with challenges presented by offspring. By comparison to mother-reared monkeys, peer-reared monkeys are behaviorally over-reactive to stressors such as competitive social interactions or forced separation from their social group [79,95–98]. The peer-reared monkey is both more likely to be inordinately aggressive in social altercations, and more inactive and withdrawn when isolated apart from its accustomed social group. They exhibit chronically lower levels of brain catecholamine (CA) system activity, but then have exaggerated increases in brain CA activity when stressed [79,95–98]. Their HPA axis activity is also chronically reduced, somewhat paradoxically, in relation to what seems to be CA system hypersensitivity, their HPA axis response to stressors is blunted [95]. In addition, there are lawful relations between neurochemical and neuroendocrine levels and behavior in mother-reared monkeys, and these relations are less prominent or simply absent in juvenile peer-reared monkeys [97]. Hence, in rhesus monkeys, one persisting effect of maternal deprivation is a...
neurobiological disorganization which is accompanied by a relative inability to cope behaviorally or physiologically common social stressors later in life [99]. Among such stressors would be caring for offspring, and as noted before, peer-reared mothers are substantially more likely to reject or abuse their infants.

Although the neurobiological effects of complete maternal deprivation have not been studied in humans, it is known that children reared in orphanages in Romania exhibit disrupted physiological, sensory-motor, emotional, and cognitive development reminiscent of that observed in socially isolated rhesus monkeys [98,103]. There is also substantial evidence that infants who received abusive or neglectful parenting may face difficulty in parenting their own offspring. Approximately 30% of children who were abused or neglected during their early lives come to abuse and/or neglect their own children many years later (versus a base rate of 5% for non-abused children, see [104,105]). The intergenerational effect may be that children who have been abused develop personalities as adults, lacking in self-knowledge and empathy for their own children’s pain and misfortune, and also fail to cope with the many challenges presented by the child. These effects are probably reduced or prevented if the abused child subsequently, or concurrently, has affiliative social experiences with a caring individual. This is likely to be the reason why 70% of abused children do not go on to be abusive themselves as parents [100,104, 105].

Based on our understanding of experience effects on brain in other animals, it is also possible that children who have been severely neglected or abused have experienced neurologic changes which result in altered affective, perceptual and cognitive function during development. Such changes are more than likely to affect how they perceive and respond maternally to their own offspring, how they approach maternal care responsibilities initially, and how they are able to learn or modify maternal care practices. Such conclusions may not be controversial, or not as controversial as they would have been decades ago when maternal behavior was generally accepted as a hard-wired aspect of female brain function. The major theoretical issue then is understanding why this aspect of brain function which is critical for species survival is so malleable.

7. A functional analysis: plasticity and development of species-typical behavior

Plasticity in behavioral mechanisms is not unique to mammalian mother–young interactions, but is exhibited across species and in a number of developmental contexts (e.g. song-learning, food caching, food preference development, imprinting, mate selection [4,5,7,8,82,101,102]. What might be the adaptive, and hence selective value of plasticity and dependence on learning, rather than ‘hard-wiring’ of innate behavioral control mechanisms for mother–infant recognition, attachment, and caregiving? Plasticity permits a certain latitude or flexibility in the relevant features that enable the offspring to identify the mother, and for the mother to identify her offspring. On the one hand, olfactory cues and other characteristics of the rodent mother may vary depending on her sources of food and dietary regimen. These resources vary geographically, and over days, weeks, and seasons, and consequently are not necessarily the same for all of her litters or even pups within a litter. Hence, the pup’s expression of attachment behaviors cannot be locked on a pre-determined and invariant set of salient maternal characteristics. On the other hand, variation in maternal diet and environmental effects on maternal preparturitional physiology, may affect infant odors, body size and conformation, and neonatal behavior. Successive offspring will differ in genotype as well as phenotype. If expression of maternal behaviors were narrowly locked to invariant neonatal characteristics, then the diversity of offspring nurtured and thus surviving would also be narrow. Hence, plasticity in mammalian mother–infant behavior: (a) allows for offspring to be nurtured in widely varying environments and circumstances, and (b) provides for preservation of genetic/behavioral diversity in those offspring. Also, by using conditioning mechanisms, a complex multimodal stimulus (say, of an infant, who has a characteristic odor, cry, and visual appearance) comes to be easily located and identified based on any one of these cues. This is important when not all the cues are present (as when the infant is concealed within a nest or strays away from the nest or mother).

Finally, plasticity in the maternal brain increases the reproductive fitness by allowing experience with one infant to modify the care of subsequent offspring in the changing environment in which the mother lives. Among many primate species, mothers of first infants are considerably less competent and motivated than are mothers of subsequent offspring. The experiences of the multiparous female are not limited to interactions with individual offspring. They include somatic and physiological experiences associated with pregnancy and parturition, as well as exposure to infants, peers, and the larger environment and society, more generically. This effect of parity and the associated experiences usually insures that the young of an experienced mother have an advantage in comparison to the first-born, the young of less experienced mothers. They are more likely to be cared for during adversity and receive more abundant nutrition, attention, and social stimulation provided by an older, more mature, less timid, and better socialized mother. The mother and young usually constitute for one another the earliest and most pervasive stimulus set present in the post-partum environment. To the degree that the nervous system of the infant is dependent for its development on an extended series of interactions with a mother, deprivation of these interactions might have adverse effects in the proportion. Plastic brain mechanisms take time to adapt, and their development can be adversely affected if they
are not exposed to the expected or common set of species-specific experiences.

8. Summary and future directions

In this article, we have described the importance of learning and plasticity mechanisms in the regulation of the mother–young relationship. In mammals, the attraction between mother and young, and their mutual recognition depends on olfactory and somatosensory experiences. Some effects of early experience are remarkably specific, leading to recognition of, and attachment to, the mother and siblings, and development of spatial location and food preferences. There is a striking similarity between mechanisms mediating the rat pup’s recognition of maternal odors on one hand, and the ewe’s recognition of her lamb’s odors on the other. Recognition of the mother by infant and the infant by mother involves the formation of an olfactory recognition in association with somatic stimulation (cervical stimulation–ewe, or being licked, nuzzled–pup). Both these involve somatosensory activation of the centrifugal Locus Coeruleus NE system. This activation promotes the formation of cytoarchitectural and synaptic changes leading to both an increased discrimination of odors, and an association of odor information with somatosensory stimulation provided either by birthing (in the case of the mother), or by maternal grooming or cleaning (in the case of the offspring). These processes occur within the olfactory bulb.

In mothers and offspring, NE system activation increases the signal-to-noise ratio for odors that are present, and promotes consolidation of neuronal changes at the cellular and synaptic level in the olfactory bulb. Further, the initial discrimination and its response seems to prime or sensitize olfactory-affective systems for more rapid or efficient subsequent discriminations and associations. Finally, in both the mother and the offspring, neuropeptides (oxytocin and endogenous opioids) were shown to enhance affiliative behaviors that are dependent on olfactory and somatosensory input. Collectively, these findings suggest that complementary mechanisms mediate mother-infant affiliation in mammals. The association of maternal odors with behavioral affiliation responses in infants may well prepare the developing nervous system for rapid expression of maternal behavior in response to infant odors in adulthood. Stated another way, the development of the rat pup’s ability to discriminate maternal odor means that the neural machinery from olfactory receptor mechanisms to more central processing was altered. This is likely to determine to some extent how pup odors are processed and discriminated when the pup becomes a mother.

Mothers also depend on postpartum experiences with their young to sustain their responsiveness during lactation, i.e. well past the period of hormonal priming. Experiences with offspring earlier in life or after a previous birth also enhance, refine or tune maternal responsiveness towards subsequent offspring. Other effects of some of the same early experiences (e.g. receiving adequate somatosensory stimulation) are more general, leading to different patterns of response to stressors and social stimuli. These behavioral effects of experience are mediated by changes in brain neurochemistry, structure, and function in both the mother and the young.

It is important to learn which biochemical pathways are operational in the appropriate brain regions and are temporally linked to the onset and consolidation of maternal behavioral. Any complex behavioral process, such as maternal behavior is unlikely to be mediated by a single molecular entity such as a specific PKC isozyme. Only by knowing the functional pathways that are operational during the process will it be possible to understand the potential interconnections and cross-talk between pathways that current research is revealing as standard operating procedure for mammalian cells. A complete understanding of these functional pathways is also essential for interpreting the results of genetic alterations of specific components of the signaling routes.

At a different analytic level, learning and plasticity within the mother–young context play a critical role in promoting adaptive fitness in mammalian species per se, and this role may be extended to non-human and human primates. In primates, early experience and associated brain changes clearly affect how the infants interact with the world in general, and with their own offspring as adults. Establishing exactly how the neurobiological changes produced by early experiences might persistently alter the neurobiological mechanisms providing for later maternal learning and plasticity constitutes the next challenge.

Acknowledgements

Many thanks to Bernie Schiff, David Sherry, Sarah Shettleworth, and Jeff Alberts and his students for their very helpful comments on earlier versions of this manuscript. Research and manuscript preparation supported by M.R.C., N.S.E.R.C. and S.S.H.R.C., to A.S. Fleming, The John D. and Catherine T. MacArthur Foundation, NIMH (MH 40748), NICHHD (HD 23042), NIAAA (AA 10079) to G.W. Kraemer and, N.S.E.R.C. to D.H. O’Day.

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