The Biopsychology of Maternal Behavior in Nonhuman Mammals

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Abstract

The term "maternal behavior," when applied to nonhuman mammals, includes the behaviors exhibited in preparation for the arrival of newborn, in the care and protection of the newly arrived young, and in the weaning of those young, and represents a complex predictable pattern that is often regarded as a single, comprehensive, species-specific phenomenon. Although the delivering first-time mammalian mother is immediately and appropriately maternal, a "virgin" with no prior exposure to young does not show immediate and appropriate behavior toward foster young. Nevertheless, the virgin female, and indeed the male, possess the neural circuitry that underlies the pattern referred to as maternal behavior, despite not exhibiting the pattern under normal circumstances. At parturition, or after extensive exposure to young, what emerges appears to be a single stereotyped maternal behavior pattern. However, it is actually a smoothly coordinated constellation of simpler actions with proximate causes that, when sequenced properly, have the appearance of a motivated, purposive, adaptive pattern of caretaking. Over the past 50 years, much research has focused on finding the principal external and internal factors that convert the nonmaternal behavior patterns of the nonpregnant nullipara, the virgin, to the almost immediate and intense maternal behavior characteristic of the puerpera, the mother. This review is an attempt to summarize the many comprehensive, even encyclopedic, reviews of these factors, with an emphasis on brain mechanisms, and to highlight the gaps that remain in understanding the processes involved in the almost immediate onset of maternal caretaking behaviors observed in mammals at delivery. Where possible, the reader is directed to some of those excellent reviews.

Key Words: birth; delivery; hormones; labor; mammal; maternal behavior; neural circuitry; parturition

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Introduction

What most people generally regard as maternal behavior in nonhuman mammals comprises a fairly stereotyped constellation of behaviors on the part of the mother that function to prepare her for the arrival of the newborn, take care of it (or them), and, eventually, promote the independence of the offspring. It is tempting to enlist the mother or prospective mother in efforts to understand the eventual purpose or advantage of these individual behaviors by assuming that she understands the consequences of her actions, but that would be to commit the error of anthropomorphism. Regardless of the wishes or intuitions of the human observer, the pregnant female mammal does not anticipate the arrival of young and the need to prepare a safe, nurturing environment; neither does she nurse the young because she perceives this action as vital to their survival. In general, individual animals act on very simple proximate causes and respond to immediate stimuli: they do things on the basis of what feels good, smells good, tastes good, or sounds good. The ultimate benefits or consequences of their actions are the province of nature (i.e., natural selection) and not attributable to the prescience of the individual animal.

The specific components of maternal behavior are different in species with different ecological demands. Carnivores and many omnivores give birth to altricial young—those that are helpless, blind, deaf, and usually hairless. Herbivores and many omnivores give birth to precocial young—those that can see, hear, locomote, and feed themselves to a certain extent. Altricial young require a much more extensive maternal commitment of behavior, time, and resources than do precocial young, which primarily need only some nursing, grooming, and protection. All mammals, by definition, nurse their young, but major differences exist in caretaking behaviors based on different demands within altricial and precocial divisions. These different demands depend on the ecology of the species: whether it is adapted to arboreal, terrestrial, or aquatic environments and, within those categories, whether the animals live in tropical, temperate, frigid, arid, or wet climates; whether they are adapted to diurnal, nocturnal, or crepuscular portions of the day-night cycle; and, finally, the extent to which the mother alone cares for the young (for review, see Gubernick and Klopfer 1981; Hafez 1969; Krasnegor and Bridges 1990; Lehrman 1961; Sluckin and Herbert 1986; Young and Insel 2002).

A Model: Maternal Behavior in the Laboratory Rat

Most experimental work on the biopsychological bases of maternal behavior in nonhuman mammals has focused on the laboratory rat, which serves nicely as a representative altricial mammalian species because of the elaborate, stereotyped, and comprehensive nature of its maternal behavior (Dollinger et al. 1980; Rosenblatt and Lehrman 1963; Wiesner and Sheard 1933). But other rodents, both altricial and precocial, have also been the subjects of a fair amount of experimental study (e.g., Champagne et al. 2007; Elwood 1983; Noirot 1972; Shoji and Kato 2006; Wynne-Edwards and Timonin 2007), as have some nonrodent herbivores and omnivores such as rabbits, sheep, and several primate species (e.g., for review, see González-Mariscal and Poindron 2002; Krasnegor and Bridges 1990; Sluckin and Herbert 1986), and carnivores such as ferrets and mink (e.g., Baum et al. 1996; Malmkvist et al. 2007).

The maternal behavior of rats and other altricial mammalian species has many demands, some beginning well before the birth of the young. Mothers of altricial species generally prepare nests during pregnancy or change the architecture of existing nests; for example, the high-walled, corner nest that is characteristic of late pregnancy is significantly different from the flat, centrally located sleeping pad of the nonpregnant female. The change is gradual; the quality and elaborateness of a rat's nest increase over the course of pregnancy if the pregnant female is forced to build a new nest every few days (Rosenblatt and Lehrman 1963). Thus it appears that the pregnant rat alters her nesting activity, as pregnancy proceeds, in anticipation of the arrival of young. But such an interpretation attributes the ability to anticipate the consequences of pregnancy to animals that almost certainly do not possess that level of cognitive ability and that may have neither experienced pregnancy nor witnessed parturition (although observing parturition in others seems to have little effect on virgin rats; Kristal and Nishita 1981). Instead of the rat anticipating the arrival of young, analysis reveals that the quality of the "brood" nest in pregnant rats is indistinguishable from the type of nest a nonpregnant rat would build if the ambient temperature decreased by a couple of degrees every few days or if she had undergone a thyroidectomy (which impairs the rat's ability to thermoregulate). Therefore, rather than anticipating an event, the pregnant rat is almost certainly responding to proximate stimuli: a hormonally or neurohormonally induced alteration in her perception of ambient temperature (e.g., Denenberg et al. 1969; Korda and Komorowska 1987; Satinoff 1964).

The pregnant rat also alters her self-grooming pattern: as the pregnancy proceeds, she spends more time each day grooming, and proportionally more grooming time on her nipple line and urogenital area (Rosenblatt and Lehrman 1963; Roth and Rosenblatt 1966). These changes in self-grooming during pregnancy as well as in nest building and repair during and after pregnancy, and ingestion of the afterbirth (placentophagia) at delivery, are not maternal behaviors in the sense of pup-directed caretaking behaviors. They are, however, characteristic of soon-to-be-maternal (nest building and self-grooming) or maternal (placentophagia) females, and therefore most researchers include them in the general category of maternal behavior.

At delivery, which usually occurs outside the nest, even the first-time mother rat engages in behaviors that aid in the expulsion of the fetus, such as adopting a "head between the heels" posture and biting and tearing the vaginal opening. Upon delivery she licks and protects the neonate. The mother devotes an inordinate amount of attention to the birth fluids and material as soon as they are expelled, both before (amniotic fluid) and after (placenta, umbilicus, and membranes) expulsion of the fetus. And as each pup emerges, the mother repeats the sequence of aiding in delivery, licking the neonate, and ingesting the expelled afterbirth. Almost all nonaquatic species typically consume the placenta, amniotic fluid, and associated membranes (for review, see Kristal 1980, 1991), and in experimental contexts in rats it is actually easier to remove the infant from the mother than to remove the placenta.

After delivery of all the pups, the mother licks the entire body of each, with an emphasis on the anogenital area. Because altricial neonates often cannot eliminate urine and feces on their own, this anogenital licking aids in such waste elimination. However, from the mother's perspective, she needs water and pup urine is apparently attractive; ingestion of the pup urine has been shown to aid in the mother's fluid balance (Friedman et al. 1981). Male pup urine odors seem to be more attractive to the mother than are female pup urine odors (Moore 1985), as mother rats have been observed to spend more time licking male neonates than they do female neonates (Moore 1984; and see Baum et al. 1996).

When the mother has concluded the pup licking, she carries each pup to the nest. Rat pups that are handled or mouthed too roughly, or are stepped on, emit an ultrasonic vocalization of 22-23 kHz, producing a signal that translates anthropomorphically as a "stop what you're doing" message (for review, see White et al. 1998). Once all are in the nest, the mother hovers over them and enters an immobile phase of maternal behavior by showing a dorsoflexion of the spine called kyphosis (Stern and Lonstein 2001) and allowing the pups to suckle. After an interval of nursing, she leaves the nest for a while, periodically returning and engaging in licking and nursing sequences. The timing and duration of the nursing bouts in rats was initially attributed to thermoregulation on the part of the mother—she would terminate nursing and leave when she became too warm (e.g., see Adels and Leon 1986)—but recent reports have reexamined and rejected this thermoregulation explanation (Stern and Azzara 2002; Stern and Keer 2002).

Pups that wander from the nest and emit ultrasonic vocalizations of 40-50 kHz (regarded anthropomorphically as the "I'm cold, come get me" call) are retrieved to the nest (Brunelli et al. 1994; White et al. 1998). Retrieval requires

the mother to employ certain mouth grips on the pup (cervical, cranial, or abdominal) and an inhibited or soft bite, while the pup aids in the process by adopting a passive, reflexive, hanging posture. Retrieval becomes more necessary as the young mature motorically and wander away more often. (Ruminant mothers, such as giraffes, demonstrate an analog of retrieval, guiding or moving their young from one location to another by using their body or knees to push or bump them along; Kristal and Noonan 1979.)

A little-noted characteristic of maternal females with nests and litters is the tendency to keep the nest area free of feces and urine. Virgin female rats in a test cage may show a slight tendency to avoid the sleeping pad or nest itself, but generally urinate and defecate everywhere. Maternal female rats with litters, on the other hand, for the most part deposit their feces and urine only in the half of the cage not containing the "brood" nest (Noonan and Kristal 1979). Although it appears that the mothers are attempting to keep the nest clean, perhaps the odor of their urine and feces becomes more aversive during lactation.

In the second week of age, the pups begin finding the mother when they are hungry rather than waiting for her to group them and hover over them when she wants or needs to be suckled; the pups then have the opportunity to initiate feeding bouts as well as does the mother. The pups locate the mother by an anally released odor, possibly a pheromone (generated in the mother's caecum and requiring the action of both bile and prolactin; Leon 1974; Moltz and Leidahl 1977). By 3 weeks of age, the pups begin to require more nourishment than the mother can supply, and their growing teeth become a source of irritation and pain to her. (Although the pain threshold of a nursing mother is elevated during the early phase of lactation, as pups age and begin to spend more time away from the dam, her pain threshold drops significantly; Cruz et al. 1996.) The mother begins to avoid the pups by burying herself, climbing out of reach, or pressing her ventral surface against the floor. The pups are forced to find sustenance elsewhere, and weaning is thus accomplished.

During the lactation period, mammalian mothers are characteristically defensive of their young and their nest, if there is one. This "maternal aggression" or "maternal defense" has spawned an entire literature of its own (for review, see Krasnegor and Bridges 1990; Lonstein and Gammie 2002). Again, though, it is worth interjecting a cautionary note about interpreting the mother's behavior as deliberately protective of her young. Lactating mothers of the vast majority of rodent species show a form of irritable aggression from high levels of hormones such as progesterone, prolactin, and oxytocin, and from the modification of certain neurotransmitters such as serotonin (in the wild, lactating female rodents are also almost certainly pregnant as a result of copulation during the postpartum estrus, and therefore are physiologically and hormonally slightly different from—and likely to be more irritable than—their nonpregnant counterparts used in maternal aggression experiments). High levels of steroids produce increased sensitivity of dermal receptors (e.g., Komisaruk et al. 1972) and are associated with increased levels of irritability. Irritability produces a need for increased personal space, partly to reduce contact with irritating stimuli. Theoretically, when confronted with an intruder, the nonlactating female, with a much smaller (normal) "personal-distance" comfort level, either tolerates the proximity of other individuals or moves to adjust her personal distance. The pregnant lactating mother, on the other hand, has an expanded personal space that now, presumably, includes the young and the nest, which are relatively immovable. Likewise, a male with high testosterone levels, resulting in irritability, shows a "personal space" that expands to the limits of his territory. He can no more leave the territory than the lactating pregnant mother can leave her nest and young. Each has no alternative but to drive away the intruder. The lactating female shows this heightened tendency even when the pups are temporarily absent. In contrast, maternal virgins (female rats that become maternal by prolonged exposure to foster young and do not have high levels of steroids or prolactin) do not readily exhibit "maternal defense" when they are caring for pups (Erskine et al. 1980). Therefore, invoking the concept of "protection" of the young, although intuitively appealing, is both teleological and unparsimonious.

Finally, subsequent to the first delivery, or after becoming maternal as a result of exposure to young, rats show a permanently enhanced rate of induction of maternal behavior to foster young. Mothering experience adds an additional redundant route, via memory, to the process of activating maternal neural circuitry (e.g., Kinsley and Lambert 2006).

Problems with the Concept and Model of Maternal Behavior

Research on maternal behavior over the past 50 years has focused primarily on the observation that late pregnant and parturient females (puerperae) perform behaviors associated with the impending arrival of young and the newly arrived young almost immediately, completely, and appropriately. In contrast, females that have never been pregnant ("virgins") do not perform maternal behaviors immediately in response to the appropriate stimuli, and in fact may kill or avoid the young. As mentioned above, there are four types of appropriate maternal behavior:

- preparation (nest building, changes in self-grooming),
- onset (the first expression of maternal behavior upon emergence of, or long-term exposure to, the young),
- maintenance (the continuation of maternal behavior through lactation despite changing stimuli and periodic absences from young), and
- noncaretaking (behaviors that are characteristic of maternal females; e.g., placentophagia, nest maintenance, aggression).

Research on maternal mammalian behavior has focused on the question, "What external and internal stimuli and

processes are responsible for and involved in converting the 'virgin' to the 'mother,' as defined in each case by the female's behavior?"

A Constellation of Behaviors

Before the current era of systematic research, scientists, and particularly ethologists, regarded maternal behavior as an "instinct" or, more precisely, a complex "fixed action pattern." However, as Lehrman (1970) pointed out, although such terms may describe the stereotyped nature of the behavioral processes, they do little to help elucidate the mechanisms that cause the behaviors. Behavioral analysis of maternal behavior over the years has gradually revealed that what appears to be a smoothly developing constellation of preparatory and caretaking behaviors is actually the result of numerous behaviors and tendencies:

- the resolution of conflicting tendencies (e.g., approach, avoidance, and inhibition of approach; active and passive behaviors; mobility and immobility),
- strings of mini-behaviors that have different causes and mediating factors (e.g., placentophagia; entering the nest to suckle pups, then leaving; licking of pups' anogenital areas; carrying of pups, nest material, and food),
- inputs and mediation from a variety of behavioral categories (e.g., emotion, motivation, motor systems, thermoregulation), and
- a host of inhibitions (e.g., of approach, of handling or mouthing pups too roughly, of ingestion of pups, of attack).

A challenging alternative to conventional thinking is that what appears to be "maternal behavior" in most vertebrates (or perhaps in most nonprimate vertebrates) may be an illusion produced by teleological and anthropomorphic thinking on the part of the human observer. In reality, this apparently complex, purposive behavior may just be a particular, smoothly transitioning (perhaps largely inescapable) sequence of mini-behaviors and subroutines. (This alternative view might also be fruitfully applied to other patterns of behavior, such as aggression, sex, and other aspects of social interaction.)

Responses and Competing Responses

Virgin females are not usually spontaneously maternal—in fact, they actively avoid pups (Rosenblatt and Mayer 1995). But continuous exposure to healthy pups causes this avoidance gradually to become indifference, which eventually gives way to approach. Depending on the strain of the virgin female rat, this transition from avoidance to indifference to approach can take from 4 to 10 days with the resupply every 11 or 12 hours of freshly nurtured foster pups, a technique called "concaveation." This method seems to induce a slowed version of the behavioral processes and nonhormonal mechanisms that characterize and underlie the onset of maternal behavior, and this slowed onset from minutes to days enables detailed study of the mechanisms involved.

The initial response of virgin rats to pups, avoidance, is likely attributable to the aversiveness of pup odors (of clean pups used for concaveation), as studies in which virgins were deprived of olfactory cues have shown an accelerated onset of maternal responsiveness (for review, see Fleming et al. 1979; González-Mariscal and Poindron 2002; Lévy et al. 2004; Stern 1989). Researchers have confirmed the aversiveness of foster-pup odors in studies showing that the rate of a virgin rat's transition from avoidance to indifference to approach increases with the application of attractive substances—such as placenta, amniotic fluid, or a cookie-milk slurry—to the pups' skin (Dunbar et al. 1981; Kristal et al. 1981; Lévy and Poindron 1984, 1987). Forcing contact between a virgin and pups (e.g., by confining them to a smaller cage; Terkel and Rosenblatt 1971) may also significantly advance the onset of fully developed maternal behavior.

A more fine-grained analysis of what appears to be the avoidance phase reveals that the virgin will actually kill some types of pups based on the characteristics of the pup stimuli, such as the age of the pup, its vocalizations and movements, and the extent to which its skin has been cleaned of birth materials and blood (Peters and Kristal 1983). During the avoidance phase, this tendency toward infanticide is in the process of being suppressed and perhaps almost counterbalanced by the tendency to approach and care for the pups. Only after the infanticidal tendency has been completely suppressed and the tendency to approach and care for pups has been fully developed do we see full-scale, intense maternal caretaking behavior in virgins. Experimentally, virgins exposed for several days to both cesarean-delivered uncleaned foster pups and to cleaned 3- to 5-day-old foster pups demonstrate their ability to mother older pups while still killing the younger ones. The inhibition of infanticide does not follow precisely the same time course as the emergence of caretaking behaviors; the complete suppression of infanticide slightly precedes the full development of approach and caretaking.

Infanticide and cannibalism, two separate behaviors, occur for a variety of reasons. The term "infanticide" denotes the killing of young. This may or may not be linked to the act of cannibalism. Mothers of carnivorous species and some (especially, altricial) omnivorous species may deliberately kill their young, usually because the young are moribund or because of the condition of the mother. The young have to be able to emit the stimuli necessary to keep the adult female from killing them, and the adult needs to be able to sense, perceive, and process those stimuli, the success of which may be partly a function of the completeness of hormonal and neural conditions associated with pregnancy, parturition, and lactation. If not, the mother may regard the young as prey or intruders, and attack them, or as edible, and merely extend grooming or mouthing behaviors to biting and eating. At delivery, parturient carnivores and omnivores show a tendency to ingest everything they deliver, and only a constellation of stimuli emanating from the viable newborn (e.g.,

squirming, warmth, and loud 22-23 kHz vocalizations) produces inhibition of ingestion by the mother. Moribund or weak newborn cannot produce this inhibition, and so they are eaten, almost casually (but not attacked) (Noirot 1972; Peters and Kristal 1983). An attack on a healthy newborn rat by its mother, or on the newborn of another omnivorous or carnivorous species, may well be the result of insufficient suppression of infanticidal tendencies in the mother, or of interference with maternal caretaking tendencies by stress or pain (e.g., see Chen et al. 2008). "Cannibalism" is distinct from "infanticide" and usually applies to the eating of dead or dying conspecifics, regardless of the cause of death. In the present context, mothers or virgins of carnivorous or omnivorous species may eat their own or other dead or dying pups regardless of whether the adult engaged in infanticide; the term cannibalism is not particularly informative.

The initial phase of contact between the adult and pup, then, not only requires the resolution of approach and avoidance tendencies but also involves the conflict between approach and inhibition of approach. If there is insufficient approach, the result is avoidance or neglect and ultimately the death of the young; if there is too much approach or insufficient inhibition of approach, the result is damage to the neonate (the mother may inadvertently break the skin with her teeth, or nip off a limb or the tail) accompanied by or resulting in ingestion of the young (in carnivores and altricial omnivores) or perhaps accidental smothering or crushing of the young by the mother (in precocial species). The efficient and effective mother must approach and interact with the young just enough and no further. The outcome of the proper balance of approach and inhibition of approach appears to be, and ultimately functions as, efficient, purposive, caretaking behavior. In this way, anosmic virgins (those deprived of the sense of smell) approach and take care of infants more readily than do intact virgins, as mentioned above, but also exhibit a very high level of infanticide of the casual ingestion variety (Fleming and Rosenblatt 1974a,b), although it was reported as "cannibalism." The high incidence of both rapid-onset maternal behavior and infanticide can be interpreted as the result of the right amount of both approach of pups and inhibition of approach in some anosmic virgins, or of either too much approach or too little inhibition of approach, or both, in other anosmic virgins.

As indicated above, the parturient mother's behavior is characterized by almost immediate and appropriate maternal caretaking behavior, whereas the initial behavior of the virgin exposed to pups is avoidance. What changes the female? Until the late 1960s the automatic response to this question was that pregnancy and the associated hormone changes produce the conversion, and that maternal behavior was caused by, rather than just facilitated by, the hormone dynamics of pregnancy. To be sure, rapid-onset maternal behavior occurs after an extended period of pregnancy and also after the abrupt termination of that pregnancy; the two factors, each with its characteristic pattern of hormone changes, can be teased apart experimentally (Rosenblatt et al. 1979). Researchers were also aware that virgins would eventually become maternal if exposed to foster pups (replaced every 11.5 hours, or sometimes 23.5 hours, with the same number of freshly nourished pups of the same age, eliminating the effect of pup development on the induction of maternal behavior).

However, Rosenblatt demonstrated in 1967 that the concaveation-induced onset of maternal responsiveness was independent of the presence in the adult of ovarian steroids, pituitary gonadotropins, or even the female genotype, in a study showing that ovariectomized females, hypophysectomized-ovariectomized females, and males could all be induced to behave maternally if exposed to pups long enough (Rosenblatt 1967). The latter finding was most surprising because mother rats do not permit males to come near the pups (Mennella and Moltz 1988). The term "maternal behavior" was applied to the behavior of these concaveated male rats precisely because they do not normally participate in the care of young.[1]

The Mechanisms

Maternal responsiveness results from the activation of neural circuitry—a "maternal neural substrate" (Moltz et al. 1966, 1970)—by stimuli that emanate from neonates. Furthermore, this substrate exists in males as well as females, as evidenced by (1) the finding that male rats, which are kept away from young by the mother, exhibit maternal behavior after extensive concaveation and (2) the fact that many mammalian species are biparental. Apparently it is more advantageous, simpler, and more efficient for all members of the species to have the circuitry even if in some species it is activated in only one sex. In that sense, the presence of maternal-behavior circuitry in both sexes is analogous to the presence of nipples in both sexes in mammals (although frequently vestigial in males) and the potential capacity for animals to exhibit the sexual behavior patterns of both sexes.

Maternal behavior depends on the coordination and orchestration of systems involved in (1) sensation, perception, and cognition regarding input arriving through different modalities at different times; (2) motivation and reward; (3) learning and memory; (4) emotion and stress; and (5) motor output. Many of these processes are involved in delivery itself: some of the mechanisms that present the neonates to the mother (delivery) are also involved in producing appropriate behavior toward those neonates. The processes are all coordinated by various hormones, neurotransmitters, sensory receptors, and neural circuits. In fact, there are relatively few brain structures, reproductive hormones, neurohormones, or neurotransmitters that, when manipulated, do not directly or indirectly affect some aspect of maternal behavior.

[1]If the behavior of both parents toward the young is essentially the same, as in some rodent species (Lonstein and De Vries 2000; Wynne-Edwards and Timonin 2007), their behavior is referred to as "parental." If the male participates in care of the young but his behavior differs from that of the female (i.e., there's a division of labor), his behavior is referred to as "paternal."

Hormonal Milieu

The central neural substrate involved, as well as the peripheral sensory apparatus of the adult female, is primed or "sensitized" by the hormonal milieu associated with pregnancy and parturition to the extent that at delivery, only minutes of neonate stimuli are necessary and sufficient to activate the circuits and therefore the behavior. The rapid onset of caretaking behavior at parturition is so vital to the survival of species that it is assured by a number of partially interacting but primarily parallel and redundant systems. Nevertheless, research into the physiological causes of maternal behavior over the past 50 years has often focused on attempts to find "the trigger." In reality, the process has numerous trigger mechanisms and a number of background conditions, so that, although eliminating one trigger mechanism may disrupt the onset of maternal behavior, no single trigger is both necessary and sufficient to elicit fully developed immediate maternal behavior in the absence of all other triggers and background conditions.

That said, the rise in estradiol that accompanies and follows a rapid decline of progesterone (from its high pregnancy levels) seems to be one of the key precipitating hormonal factors in the induction of rapid-onset maternal behavior during the periparturitional period (Figure 1). Ovariectomized virgin rats treated systemically with various regimens of progesterone, then estradiol, so that the estradiol rises as the progesterone declines (Bridges 1984, 1990; Moltz et al. 1970; Siegel 1986), and in some regimens treated with prolactin (Mann and Bridges 2001, for review), show a significantly faster induction of maternal behavior (during concaveation) than do vehicle- or single-hormone-treated test virgins, but the delay is still on the order of days. Although there is some disagreement in the field, most researchers lean toward the estradiol increase, and its concomitant effect on central nervous system areas (e.g., the ventromedial hypothalamus, habenula, medial preoptic area), as the most significant hormonal variable (for review, see González-Mariscal and Poindron 2002). In general, these studies suggest that closely mimicking the hormone dynamics of pregnancy and pregnancy termination facilitates the onset of maternal behavior (Bridges 1984; Rosenblatt and Mayer 1988).

Pseudopregnancy (especially one in which a deciduoma has been induced) mimics the pattern if not the magnitude of the maternal hormone changes of pregnancy and the termination of pregnancy, but eliminates the confound of the presence and secretions of the fetoplacental unit. Researchers have found that pseudopregnancy termination in virgins presented with foster pups produces a significantly faster, but not immediate, onset of maternal behavior than was seen in unmanipulated virgins (Steuer et al. 1987; Terkel 1974). Therefore, the long-term dynamics of gonadal steroids influence the onset of maternal responsiveness but, because there is still a significant delay in the onset of maternal behavior in virgins experiencing those manipulations, do not solely account for the rapid onset of maternal behavior at parturition.

Terkel and Rosenblatt (1972) demonstrated that blood transfused from periparturient rats produces a rapid onset of maternal responsiveness in virgin recipients, showing conclusively the importance of blood-borne factors in speeding up the process. In the same series of studies, the authors showed that blood transfused from maternal virgins does not speed up the rate of onset of maternal responsiveness in

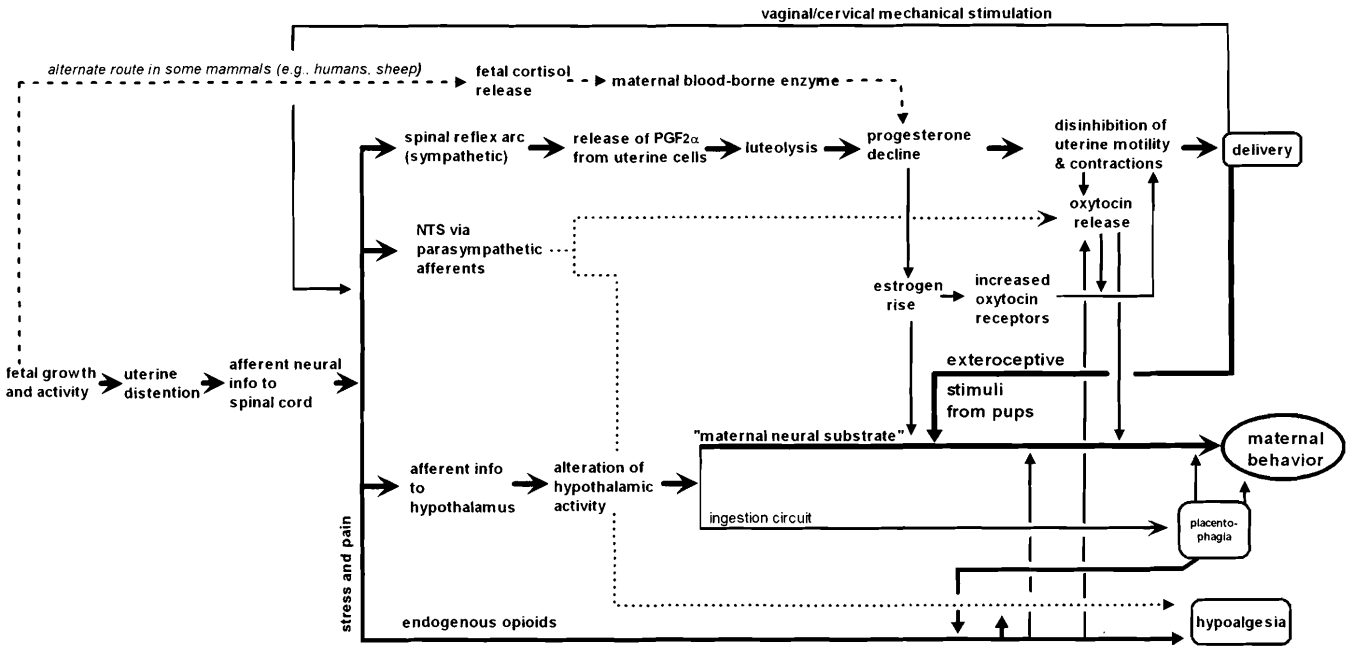

Figure 1 Flow chart of some of the physiological events leading up to the emergence of rapid-onset maternal behavior in a primiparous rat during the periparturitional period, as well as other characteristic events at delivery: placentophagia, hypoalgesia, and expulsion of the fetus. Heavier lines suggest more important effects; dotted line represents a parasympathetic subsystem. NTS, nucleus tractus solitarius.

virgin recipients during concaveation, thereby demonstrating that maternal responsiveness induced solely by exposure to pups is not mediated by, and does not induce, hormonal changes in the maternal virgin. Terkel and Rosenblatt's blood-transfusion experiment indicated that 45 minutes of exposure to blood from a female rat at or within 12 hours of delivery is sufficient to induce maternal behavior in virgins even more rapidly than does systemic hormone treatment (10-15 hours as opposed to 2-3 days). Either a prolonged series of hormone injections, administered to mimic the dynamic changes in hormones over many days, is not really necessary, or Terkel and Rosenblatt's effect was attributable to something in the blood that is present only within 12 hours of delivery. The results suggest the latter, supporting the idea that multiple redundant hormonal systems facilitate the onset of maternal responsiveness. One system is suggested by the effectiveness of the dynamic changes of various hormones during pregnancy, and the other by the effectiveness of an acute blood-borne factor present only within 12 hours of delivery and requiring less than a 45-minute exposure to have an effect. The combination (as yet untested) of systemic hormone treatments (or pseudopregnancy) and blood transfusion from a parturient female might reveal the extent to which Terkel and Rosenblatt's effect interacts with a background of dynamic hormone changes.

Neurohormones

Oxytocin may be one of the acute factors that affected the virgin recipients that received blood from parturient donors in Terkel and Rosenblatt's experiment, and may represent one of the parallel but partially interactive mechanisms that elicit rapid-onset maternal behavior during the periparturitional period. Studies have demonstrated that oxytocin and vasopressin are involved in different aspects of social bonding in mammals (e.g., Lim and Young 2006), and mother-infant interactions arguably fall into the category of bonding. An increase in estradiol before labor produces a proliferation of oxytocin receptors in the uterus and mammaries, and thereby renders those areas of the female more sensitive to the effects of the oxytocin released. But the effect of oxytocin on the induction of maternal behavior (Figure 1) seems to be the result of action both at the olfactory bulb (Yu et al. 1996) and more centrally. Although peripheral oxytocin does not facilitate the onset of maternal behavior (except perhaps in wild mice; McCarthy et al. 1986), oxytocin injected or manipulated centrally (Russell and Brunton 2006) in rats (Lin et al. 2003; Pedersen and Prange 1985; Pedersen et al. 1994), sheep (Kendrick et al. 1987; Keverne and Kendrick 1991), and voles (Olazábal and Young 2006) is effective in stimulating the onset of maternal behavior, but not essential in all species (e.g., laboratory mice; for review, see Insel et al. 2001; Kendrick 2000; Nishimori et al. 1996). The central response to oxytocin, or perhaps vasopressin, at parturition seems to depend on the action of both estradiol, which increases oxytocin levels (McCarthy 1995; Shughrue et al. 2002), and endogenous μ-opioids, which have an inhibitory effect on oxytocin release but are downregulated in many parts of the brain at that time (Bicknell 1985; Doi et al. 2001; Douglas and Russell 2001; Douglas et al. 1995; Kutlu et al. 2004; Wigger and Neumann 2002).

Opioids also contribute to the onset and maintenance of maternal behavior, not only because of the interaction with oxytocin but also almost certainly because of the importance of opioids to motivation and reward (Nelson and Panksepp 1998; Panksepp et al. 1994) and to pain and hypoalgesia. Endogenous opioid levels in rats rise at the end of pregnancy, peak at about the time of delivery, and return to normal levels 12 to 18 hours afterward (Catheline et al. 2006; Dondi et al. 1991; Facchinetti et al. 1982; Hoffman et al. 1984; Joshi et al. 1993; Petraglia et al. 1985; Wardlaw and Frantz 1983; Weiland and Wise 1990). There is a concomitant rise and decline in pain threshold ("pregnancy-induced analgesia"; Dawson-Basoa and Gintzler 1996, 1997; Gintzler 1980). Afterbirth material contains a substance, placental opioid-enhancing factor (POEF[2]), that, when ingested, potentiates the antihyperalgesic properties of endogenous (or exogenous) opioids (for review, see Kristal 1991, 1998), although by itself it does not produce analgesia. Thus the amniotic fluid that becomes available for ingestion by the dam minutes to hours before delivery enhances opioid-mediated pain relief during delivery. Ingested POEF apparently does not act directly in the central nervous system but rather activates gut vagal receptors that, in turn, enhance central δ- and κ-opioid-receptor activity while attenuating central μ-opioid-receptor activity (DiPirro and Kristal 2004).

There is evidence that the direct injection of morphine and more specific μ-opioid-receptor agonists into the medial preoptic area (MPOA[2]) interferes with the expression of maternal behavior in maternal rats (Rubin and Bridges 1984). Increased opioids in the MPOA also produce a disruptive effect on copulatory behavior (e.g., van Firth et al. 1995). At parturition, however, hypothalamic μ receptors are downregulated, perhaps to protect against the disruptive effects of opioids in that area (Hammer and Bridges 1987; Hammer et al. 1992, 1994).

In contrast to the detrimental effect of increased MPOA opioids on maternal behavior, increased opioid activity in other structures such as the ventral tegmental area (VTA), which is critical for motivation and reward, has the opposite effect. Morphine injection into the VTA facilitates the onset of maternal behavior in virgin rats, and intra-VTA treatment with quaternary naltrexone, a nonselective opioid antagonist that does not cross the blood-brain barrier, interferes with the onset of maternal behavior in parturient rats (Thompson and Kristal 1996). Recent data suggest that the ingestion of amniotic fluid (and thus of POEF) further enhances the positive effect of intra-VTA opioids on the onset of maternal behavior (unpublished results from our laboratory), and we hypothesize that POEF ingestion also reduces the negative effect of intra-MPOA opioids on the onset of maternal behavior.

[2]Abbreviations used in this article: MPOA, medial preoptic area; POEF, placental opioid-enhancing factor

High levels of systemic opioids can be deleterious to maternal behavior. Systemic morphine that is sufficient to produce a level of hypoalgesia comparable to that of pregnancy-induced analgesia interferes with the expression of maternal behaviors, elements of which the mother performs out of sequence or not at all (Mann et al. 1990). Thus higher opioid levels can produce more hypoalgesia but also negative cognitive and motoric side effects. However, with the systemic administration of a subthreshold dose of morphine in conjunction with the mother's ingestion of afterbirth material (and presumably POEF), the parturitional level of hypoalgesia is reached without any liability to maternal behavior (Tarapacki et al. 1995), suggesting that POEF is a mechanism for producing the effects of a higher level of endogenous opioids without the negative side effects associated with that higher level.

Injection of opioids into the periaqueductal gray area (PAG) also inhibits maternal behavior, but the action of cholecystokinin (CCK) in the PAG can reverse this effect (Miranda-Paiva et al. 2007). In that sense, the modulation by CCK of PAG opioid activity is analogous to the hypothesized effect of POEF on MPOA opioids. The authors of the CCK-PAG paper support a general hypothesis that opioids in the PAG switch the mother from a maternal behavior mode to a hunting behavior mode (Miranda-Paiva et al. 2007). However, μ- and κ-opioid agonists (and oxytocin; e.g., Ge et al. 2002) in the PAG, which forms a major part of the descending pain pathway, produce hypoalgesia. Antinociceptive substances in the PAG may therefore have an indirect impact on maternal behavior due to the reduction and subsequent restoration of intense mechanical sensory stimulation.

Neural Input and Circuitry

Numerous neural manipulations facilitate the onset of maternal behavior in virgins (they increase the sensitization rate), but for a variety of reasons do not produce maternal behavior latencies as short as those observed in parturient females. One explanation is that the stimuli presented to the virgins are usually clean pups, whereas parturient females encounter pups covered with afterbirth materials, to which they are intensely attracted, unlike virgins, which may show a fear response to placenta and amniotic fluid (Kristal and Graber 1976). The basis for the attraction at parturition and in late pregnancy is still unknown, but almost certainly represents a "specific hunger," a shift in motivation (e.g., for salt) based on a change in physiology during pregnancy: all rats in the late stages of pregnancy enthusiastically approach and eat placenta, regardless of the source, even those that avoided it as virgins (Kristal et al. 1981). Given the attraction to placenta and amniotic fluid shown by nearly all periparturient mammalian mothers (in conjunction with dynamic hormone changes representing pregnancy and pregnancy termination), these materials on the skin of the neonates further shorten the latency to onset of maternal responsiveness (Kristal et al. 1981; Steuer et al. 1987).

Another redundant system that facilitates the onset of maternal behavior, and is missing in studies that examine the effect of neural manipulations, is the uterine mechanical stimulation both from the accelerating fetal size and activity at the end of pregnancy and from cervical and vaginal stimulation and distortion during delivery (Figure 1). This activity stimulates mechanoreceptors in the uterus, vagina, and cervix and thus introduces peripheral neural stimulation into the process of sensitization. Experimentally, uterine distention and vaginocervical stimulation facilitate the onset of maternal behavior in rats (Graber and Kristal 1977) and in sheep (Keverne et al. 1983). The neural signals resulting from uterocervicovaginal stimulation, conducted to the spinal cord over the hypogastric and pelvic nerves (Peters et al. 1987), are also necessary for the release of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) from uterine tissue, which in turn produces luteolysis and a consequent decrease in progesterone (Figure 1).

Again, many of the factors involved in expelling the fetus and thereby presenting the female with objects to be mothered are the same as those that stimulate the rapid onset of mothering behavior itself. Uterocervicovaginal mechanical stimulation produces neural signals that cause nuclei in the hypothalamus to manufacture (and possibly secrete), and the posterior pituitary to secrete, oxytocin. Oxytocin enhances the sensitivity to, and effect of, mechanical stimulation of the uterus, cervix, and vagina. The uterocervicovaginal neural stimulation arrives at the hypothalamus, beginning the sensitization process. It is then coupled with olfactory stimulation and with perioral stimulation from self-licking and from birth materials during labor and delivery, and with perioral, auditory, and ventral tactile stimulation after the delivery of viable young has begun. Olfactory cues associated with afterbirth (which may disguise the aversive olfactory qualities of the clean pups used in concaveation) attract the female to the skin of the pup and induce pup licking and retrieval (for review, see Lévy et al. 2004). Perioral tactile stimulation (carried over the trigeminal nerve) is critical to the onset of maternal responsiveness, and then stimulation of the mother's ventrum by the pups has a critical effect on initiating nursing behaviors (González-Mariscal and Poindron 2002; Stern and Lonstein 2001). These incoming signals converge in the hypothalamus, as does the neural input from uterocervicovaginal mechanical stimulation, and activate the already sensitized "maternal neural substrate," which needs to be stimulated in order for appropriate maternal responses to occur at all and to occur in proper sequence.

In maternal behavior, hypothalamic structures, particularly the MPOA, are involved in processes that characterize hypothalamic function in many motivated behaviors. These processes entail the coordination of incoming chemical and neural signals with the monitoring and regulation of activity of other parts of the hypothalamus and many other brain structures. These processes involve the enlistment and coordination of necessary subroutines of maternal behavior such as motivation and reward, stress, pain and hypoalgesia, emotion, thermoregulation, feeding, drinking, motor output, and

learning and memory. Under experimental conditions, it is possible to dissociate some of these subroutines from one another. For example, lateral hypothalamic lesions eliminate placentophagia in female rats giving birth for the first time, just as they disrupt other oral behaviors involved in maternal behavior; but for rats with parturitional experience (i.e., multiparae), such lesions do not eliminate placentophagia at parturition, but do interfere with feeding (Kristal 1973). A further dissociation of components of maternal behavior, suggesting multiple mechanisms, was observed after lesions of the periventricular MPOA in rats (Noonan and Kristal 1979). Such lesions, produced just before parturition, produced either (1) a delay in the onset of placentophagia, pup retrieval, and nest building; or (2) an impairment of the latency and quality of nest building. None of the rats with lesions showed any disruption of pup licking.

Because so many subsystems are involved in the constellation of behaviors casually referred to as maternal behavior, it is difficult to make sense of the myriad brain manipulations that all affect the onset, quality, or maintenance of maternal behavior. Despite a wealth of studies involving the manipulation of neural structures and neurochemistry, a comprehensive understanding of the neural structures and mechanisms involved in the "maternal neural substrate" (see Numan 1994 for review), or even just the hypothalamic mechanisms involved (see Numan 2006 for review), has not been forthcoming. Because of behavioral subtleties and complexity, maternal behavior has eluded, and may not even be amenable to, a neuroethological analysis, which elaborates a linear series of excitations and inhibitions associated with specific neural components involved in the overall pattern of behavior (e.g., as has been accomplished with feeding behavior in mollusks; Elliott and Susswein 2002).

At a time when physiological psychology research focused primarily on the cortex, the cortex was found to be important, but not critical, for maternal behavior (Beach 1937, 1938), largely because of the cognitive association and integration functions necessary for performing such a complex nonreflexive behavior. More recently, studies have shown that the prefrontal cortex is involved in analyzing the olfactory cues that aid in recognition of individual young—not a key factor in mother-pup interactions in rats, but critical in ungulates such as sheep (e.g., Broad et al. 2002).

When the limbic system was a focus of study because of its perceived control of emotion, investigators found that limbic structures were important but not essential for maternal behavior (Lamb 1975; Slotnick 1967; Steele et al. 1979). Now that research has produced a clearer picture of the functions of various limbic structures and of the limbic system's interface function between motivation and motor output (Mogenson et al. 1980), more recent studies have elucidated the role of individual limbic structures in maternal behavior. For instance, the amygdala adds emotional valence to incoming olfactory and pheromonal stimuli (for review, see Numan 2006), the hippocampus participates in the recruitment of previous experience and the consolidation of new experiences (e.g., Pawluski et al. 2006), and the lateral habenula translates estrogen signals from the MPOA into dopamine activity in the mesolimbic dopamine system (Matthews-Felton et al. 1995).

The mesolimbic dopamine system, which includes the ventral tegmental area, the striatum, and the nucleus accumbens, is of major importance to maternal behavior, largely because of its role in motivation, reward, and the hedonic value of stimuli and behaviors (Bozarth 1983, 1987). Investigators have found that lesions of these structures, direct chemical modification of dopamine, and chemical modulation of opioids (Hansen 1991; Thompson and Kristal 1996), which likely indirectly results in changes in dopamine, are all important to the onset or maintenance (or both) of maternal behavior (Li and Fleming 2003; Stolzenberg et al. 2007). The fact that maternal rats will work (or overcome adversity) to obtain access to pups (Nissen 1930; Wansaw et al. 2008) is considered prima facie evidence that such access is rewarding. It is not surprising then that the mesolimbic dopamine system, critical for motivation and reward, is involved in various aspects of maternal behavior (e.g., Keer and Stern 1999; Stern and Keer 1999).

Individual differences in levels of maternal activity have even been associated with different levels of dopamine in the nucleus accumbens (Champagne et al. 2004) and of other neurotransmitters in different portions of the circuitry involved in maternal behavior (Olazábal et al. 2004). However, it is not yet clear whether these differences in dopamine and serotonin are a cause or a result of different levels of intensity of maternal behavior.

A caveat in interpreting the effects of brain manipulations on the onset or maintenance of maternal behavior is the indirect but strongly interactive negative effect of stress on the systems that underlie maternal behavior (Blanchard et al. 2001; Neumann 2003). It is impossible to overstate the pervasive effect of stress on neural (particularly hypothalamic) and neurochemical systems, and on the ability to sense and correctly analyze and interpret afferent information. Caged rodents under stress often show aberrant maternal behavior, resulting in pup death, or active pup killing, usually accompanied by cannibalism. Stress can cause such behavior through direct effects on the mother or indirect effects on fetal development resulting in weak or still-born neonates (e.g., Bale 2005; Malmkvist et al. 2007). Such stress is often attributable to changes in light cycle, caging, ambient noise level, olfactory stimuli, or ambient temperature, or to toxic agents in the environment, overcrowding, fear-inducing stimuli, difficult or painful delivery, or to a huge number of other negative or aversive stimuli. However, not all stimuli that human observers regard as "aversive" need be stressful. The determination of whether an agent is stressful depends on the effect of the stimulus on the subject, not on the nature of the stimulus (based on the expectations or opinions of the observer). Depending on the experiential and genetic background of individuals, factors that prove stressful to some will not necessarily be stressful to others (e.g., Champagne and Meaney 2006).

Conclusions

In mammals, the expression of maternal caretaking behaviors results from the activation of certain neural circuits (the "maternal neural substrate"). This activation occurs through a number of partly intersecting, but largely redundant, mechanisms. The redundancy in this system probably attests to the adaptive significance of these caretaking behaviors. At delivery, sensory modalities and the central circuits for processing and integrating birth- and neonate-related stimuli have been sensitized by the dynamic hormone changes of pregnancy and the precipitous hormone changes associated with the termination of pregnancy. In addition, mechanical stimulation associated with the growth, activity, and expulsion of the fetus produces neural and neurochemical signals that also sensitize and then activate the "maternal neural substrate." Upon delivery, the combination of hormonal, neural, and neuroendocrine effects have sensitized the central neural substrate such that only minutes of sensory stimulation from the neonate are sufficient to provoke intense and fully elaborated maternal caretaking behaviors in the new mother. Thereafter, neural and physiological process maintain these caretaking behaviors even under circumstances of dynamic hormone changes, periodic absences from the young, and changes in the demand characteristics of the young. Last, once the maternal behaviors have been initiated and maintained for some period, they can subsequently be reinitiated much more easily.

But the "maternal neural substrate" that underlies this complex behavior process is probably not a coherent circuit or set of circuits dedicated to maternal caretaking behavior. It is more likely that the arrangement and coordination of subunits that perform specific behavioral components (e.g., avoid, approach, inhibit attack, retrieve, lick, inhibit biting, hover) are recruited and sequenced in a way that makes them appear to belong to a coherent, purposive, complex task. It is also likely that what appears to be a "motivation to perform maternal behavior" is an epiphenomenon reflecting a sequence of more immediate, and simpler, motivations.

This conceptualization is similar to that used to understand how genes or enzymes work to bring about complex phenomena. Each step in the biochemical-physiological process is accomplished by an enzyme that does only one thing. When strung together and coordinated in one way or in one context, the end result is Phenomenon A; when strung together and coordinated in another way or in a different context, the result is Phenomenon B. Observers do not seem to be able to resist the temptation to erroneously label a gene for the enzyme that participates in Phenomenon A "the gene for Phenomenon A." Likewise, stimulation of the MPOA in one context (determined by sensory input and chemical signals) results in the recruitment of certain other brain systems (e.g., leading to Phenomenon A), and in another context (a different complex of sensory inputs and chemical signals), the recruitment of a different set of brain systems (e.g., leading to Phenomenon B). The action of the MPOA is recruitment—it has no intent or design to accomplish either Phenomenon A or B.

One can conceptualize the hypothalamus as the hub of a wheel-shaped complex (e.g., a "hub and spoke" communication system) for primary motivations, with the MPOA at the hub. The spokes are the various subunits that directly influence, or are influenced by, the hypothalamus: those involved in interpreting emotional valence, motivation, and the rewarding effect of engaging successfully in motivated behavior, cognitive analysis of and storage of experiential variables, and motor output for various active and passive or reflexive behaviors. A complete understanding of the "maternal neural substrate" will require much more detailed behavioral analysis of the specific acts and inhibitions that make up what is generally referred to as maternal caretaking behavior than is currently available.

Perhaps researchers should be more diligent about deconstructing the constellation of behaviors called "maternal behavior" into the various behavioral components and then analyzing the factors that produce those components and the neural substrates that underlie the behaviors. Such an approach would be more logical than trying to understand the myriad neural steps involved in the overall category—maternal behavior—which is like trying to build a jigsaw puzzle out of the pieces of several smaller jigsaw puzzles. Proper deconstruction of the "maternal behavior" pattern should produce a better tool with which to analyze how each subunit leads to the next subunit(s) in the sequence. Although some research has already focused on a few of the initiating factors of some of the subunits (e.g., pup licking, nursing, maternal aggression and defense), and although this approach was suggested more than 50 years ago (Birch 1956), there has been very little research on the physiological and neural mechanisms by which these and other actions of the maternal female are made to occur in a particular sequence. Only an understanding of such mechanisms will reveal the full complexity and elegance of mammalian maternal behavior.

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