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Hypothalamic Neural Circuits Regulating Maternal Responsiveness Toward Infants

Michael Numan
Boston College

A theoretical neural model is developed, along with supportive evidence, to explain how the medial preoptic area (MPOA) of the hypothalamus can regulate maternal responsiveness toward infant-related stimuli. It is proposed that efferents from a hormone-primed MPOA (a) depress a central aversion system (composed of neural circuits between the amygdala, medial hypothalamus, and midbrain) so that novel infant stimuli do not activate defensive or avoidance behavior and (b) excite the mesolimbic dopamine system so that active, voluntary maternal responses are promoted. The effects of oxytocin and maternal experience are included in the model, and the specificity of MPOA effects are discussed. The model may be relevant to the mechanisms through which other hypothalamic nuclei regulate other basic motivational states. In addition, aspects of the model may define a core neural circuitry for maternal behavior in mammals.

Key Words: maternal behavior, hypothalamus, mesolimbic dopamine system

It is generally accepted that the hypothalamus is involved in three major functions: autonomic regulation, pituitary gland regulation, and the regulation of behaviors that are essential for either personal survival or for reproductive success (Swanson, 1987). The focus of this review is on the hypothalamus's role in the latter process, which is usually referred to as its regulation of the primary motivational states. Although the emphasis will be on the mechanisms through which the hypothalamus regulates maternal responsiveness in mammals, the overall scheme that is developed is likely to be relevant to other basic behaviors controlled by the hypothalamus.

How should one define motivation? My view is that if I could present a sensible but simple (spare) definition, then the process would be amenable to a mechanistic anatomical and functional analysis. The following would be such a definition: Motivation refers to an internal process that modifies an organism's responsiveness to a certain class of external stimuli (Hinde, 1970). For example, a hungry animal shows increased responsiveness to food-related stimuli, whereas a maternally motivated organism shows increased responsiveness to infant-related stimuli. When such internal motivational states are not active, the associated external stimuli have much less impact on the organism's behavior: Food is not approached or eaten; infants are ignored. Note that this objective definition of motivation simply relates to the expression of behavior in response to external stimulation. Therefore, with this definition, one would state that the lordosis response (a measure of sexual receptivity) in the female rat is under motivational control because it occurs after estradiol priming in response to somatic sensory stimuli but does not occur in response to such stimuli in the absence of estradiol priming (Pfaff, 1980).

With respect to such motivational processes, one might conceive of the hypothalamus as operating in the following manner. Distinct nuclei in the hypothalamus respond to certain aspects of the internal environment (e.g., hormone levels, blood glucose levels, or electrolyte concentration [hypertonicity]) and to certain types of external stimuli. When a particular hypothalamic nucleus is effectively activated by specific events, its efferents ultimately interact with other brain mechanisms that actually regulate sensory-motor responsiveness. In a certain sense, hypothalamic output might be viewed as opening a gate in a sensory-motor integration apparatus, allowing a particular set of external stimuli to be effectively processed so that appropriate responsiveness

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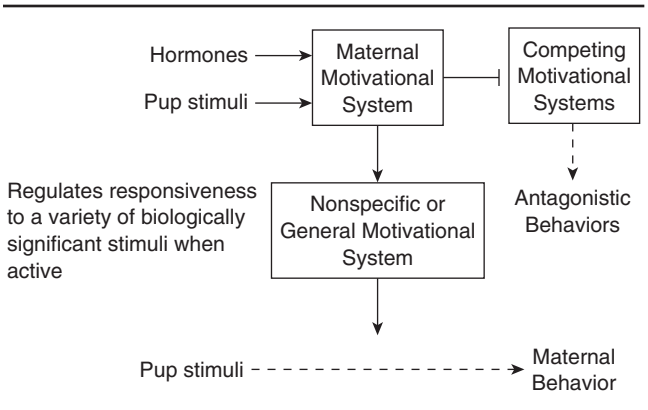

Figure 1: Conceptual Neural Model Relating Motivational Systems to Maternal Behavior.
NOTE: Neural regions controlling maternal responsiveness are shown as activating a nonspecific or general motivational system that acts to increase responsiveness to stimuli, which, in this case, are pup stimuli. Motivational systems specifically related to maternal behavior are also shown as inhibiting competing motivational systems that regulate responsiveness to stimuli that activate antagonistic behaviors. Lines ending in an arrow signify excitation, and those ending in a bar indicate inhibition.

occurs. This perspective suggests that the hypothalamus serves as a type of switch rather than as an integrator or organizer of the motor responses involved in a particular motivated behavior. In the case of maternal behavior in rodents, I present evidence that a "maternally relevant" hypothalamic nucleus is primed by pregnancy hormones, which then allow it to respond to certain pup stimuli. This activated hypothalamic nucleus then influences the operation of other brain regions that control sensory-motor integration, enabling infant-related stimuli to be processed by these latter structures so that appropriate maternal responses occur.

In further elaboration, I distinguish between specific and nonspecific motivational systems. With respect to the primary motivational states, we propose that separate and distinct hypothalamic nuclei regulate each state such that when the specific hypothalamic motivational system is active, it in turn increases responsiveness to a particular group of external stimuli. A hunger system would increase responsiveness to food-related stimuli, whereas a maternal system would increase responsiveness to infants. Nonspecific or general motivational systems (which in our model are not hypothalamic systems), permit the specific systems to perform their defined functions. That is, nonspecific motivational systems form an interface with, and can be stimulated by, each specific system. It is proposed that the nonspecific systems are capable of increasing responsiveness to a broad range of external stimuli. Importantly, however, behavioral reactivity at any one point in time would be determined by an interaction between the specific and nonspecific systems. That is, just which stimulus an organism responds to is the result of stimulation of the nonspecific system by a particular specific system.

Finally, it is also proposed that specific motivational systems, in addition to interfacing with general motivational systems, should act to inhibit competing specific motivational systems that would give rise to antagonistic behaviors.

Figure 1 shows a diagram outlining the mechanisms of motivational control that I have just described. This review presents evidence that will permit one to fill in this model with actual neural circuits that regulate maternal responsiveness. Whether other primary motivational states actually work in this manner remains to be determined, but the evidence for the maternal system operating in this manner is good, although not complete.

APPROACH V. AVOIDANCE TENDENCIES INFLUENCE THE OCCURRENCE OF MATERNAL BEHAVIOR IN RATS

Much of the research on the neural basis of maternal behavior in mammals has been done on rats (Numan & Insel, 2003), and this is the research that will be emphasized. The four major components of maternal behavior in postpartum rats are retrieval behavior (pup transport behavior), pup grooming, nursing behavior, and nest building. Maternal rats do not discriminate their own young from another female's young in the sense that they will care for all offspring to which they are exposed.

The primiparous puerperal female shows immediate maternal responsiveness at the time of parturition, and such behavior should be contrasted with the response of the nulliparous (virgin) female to pups. When naïve virgin females are presented with test pups they usually ignore them, although they sometimes attack the pups. If one is persistent, however, and cohabitates the virgin female with freshly nourished pups on a daily basis, then after a period of 5 to 7 days of continuous association, the virgin female begins to show all the essential components of maternal behavior (retrieval and pup grooming, nursing behavior, and nest building), even though she cannot lactate (Rosenblatt, 1967). This pup-induced maternal behavior has been called sensitized maternal behavior, and its occurrence indicates that the difference between the postpartum female and the nulliparous female is not that the latter cannot show maternal behavior but that the latency to onset of maternal behavior following initial pup presentation is much longer in the virgin female. Importantly, sensitized maternal behavior occurs in ovariectomized or hypophysectomized nulliparae, suggesting that the initiation of the behavior is not

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controlled by changes in hormone secretion that might be produced by prolonged pup stimulation (Rosenblatt, 1967).

In a detailed analysis of the sensitization process, Fleming and Luebke (1981) first noted that most virgin females slept or rested in the same area of their home cages each day, and they called this site the preferred quadrant. However, if pups were placed in this preferred area, the female would switch her sleeping/resting area, suggesting that she was actively avoiding the pups. When pups were presented in this manner over a series of days, the switching behavior persisted for 3 to 4 days. The female then began to show tolerance toward the pups for 1 to 2 days: She did not switch quadrants, but she also did not show maternal behavior. After this period of tolerance, the female began to show maternal behavior. This analysis of the sensitization process has led to approach-avoidance models of the onset of maternal behavior (Rosenblatt & Mayer, 1995): When a virgin female is first exposed to pups, both avoidance and approach tendencies are activated, but avoidance is the dominant behavior. As a result of continuous pup stimulation, neophobic avoidance responses habituate so that approach tendencies become dominant. Subsequently, proximal pup stimulation promotes further maternal responsiveness, allowing complete maternal behavior to occur. In other words, maternal behavior occurs when the tendency to approach and interact with pups is greater than the tendency to avoid pups.

The primiparous puerperal female, unlike the virgin, shows immediate maternal responsiveness upon her first exposure to pups because her brain has been influenced by the hormonal events of late pregnancy and pregnancy termination (Numan, 1994; Numan & Insel, 2003). These hormonal events include rising estradiol and lactogen (prolactin and placental lactogens) titers superimposed on a sharp drop in plasma progesterone levels. Significantly, one can administer a hormone regimen that simulates these endocrine changes to virgin females with the effect of stimulating a rapid onset of maternal behavior in these virgins.

Within an approach-avoidance motivational context, Figure 2 depicts several models to explain how hormones might act to stimulate maternal behavior in first-time mothers. Each model proposes that maternal behavior occurs when approach tendencies toward pups are greater than avoidance tendencies, but they differ in how this motivational change occurs. Model A proposes that hormones primarily decrease fear-related behaviors and avoidance of pups, Model B proposes that hormones act primarily to increase approach and attraction toward pups, and Model C argues that hormones both decrease avoidance of pup-related stimuli and increase attraction toward pups. Although the evidence is far from complete, it conforms best with Model C. Anosmia or deafferentation of the main or accessory olfactory bulbs facilitates maternal behavior in virgin female rats who have not been hormonally primed: Sensitization latencies fall from 7 to 8 days to 1 to 2 days (Fleming & Rosenblatt, 1974; Fleming, Vaccarino, Tambosso, & Chee, 1979). One interpretation of these results is that novel olfactory input from pups stimulates avoidance behavior in naïve virgins, and when such stimuli are eliminated, the onset of maternal behavior, although not immediate, occurs relatively quickly. On the basis of these findings, one might predict that pregnancy hormones render the puerperal female anosmic, but this is not the case: Toward the end of pregnancy (Day 22), pup odors become highly attractive to the primigravid female rat (Kinsley & Bridges, 1990), and treatment of naïve virgin females with a hormone regimen that is capable of stimulating maternal behavior increases the female's attraction toward pup odors (Fleming, Cheung, Myhal, & Kessler, 1989). Therefore, there appears to be a major switch in the valence of pup stimuli when one compares the virgin to the late pregnant female. In particular, olfactory pup stimuli switch from negative to positive. This switch is primarily involved in preventing avoidance and defensive behavior from occurring because anosmic females are perfectly capable of showing a normal onset of maternal behavior at parturition (Numan & Insel, 2003). Other pup stimuli must therefore serve as necessary and essential activators of maternal attraction toward pups, and such stimuli appear to be pup-related tactile inputs to the female's perioral and ventral regions (Numan & Insel, 2003; Stern, 1996). Olfactory input from pups, however, is still likely to serve an important subsidiary role in the maternal female's attraction toward her pups.

Please note how Model C in Figure 2 maps on to the motivational control system outlined in Figure 1: When a maternal motivational system is active, it should inhibit competing avoidance/defensive responses toward novel pup stimuli while also increasing maternal responsiveness toward such stimuli.

THE CORTICOMEDIAL AMYGDALA AND OLFACTORY INHIBITION AND MATERNAL BEHAVIOR

Figure 3A shows neural connections that would allow olfactory input to reach the cortical and medial nucleus of the amygdala. Note that input from both the main olfactory bulb and accessory olfactory bulb can converge on the medial nucleus (MeA). Because the amygdala is involved in the regulation of fear-related behaviors (LeDoux, 2000), this pathway may be the route through which novel olfactory input from pups

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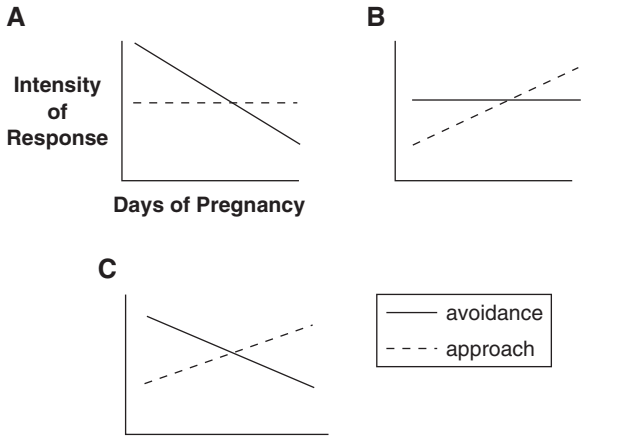

Figure 2: Three Alternative Approach-Avoidance Models of the Onset of Maternal Behavior at Parturition.

SOURCE: Adapted from Numan, M., & Sheehan, T. P. (1997). Neuroanatomical circuitry for mammalian maternal behavior. *Annals of the New York Academy of Sciences, 807*, 101-125. Copyright 1997 by the New York Academy of Sciences.

NOTE: Maternal behavior occurs when central neural approach systems are more active than central neural avoidance systems with respect to infant-related stimuli. The physiological events associated with late pregnancy could stimulate maternal behavior by decreasing avoidance (A), increasing approach (B), or causing both of these effects (C).

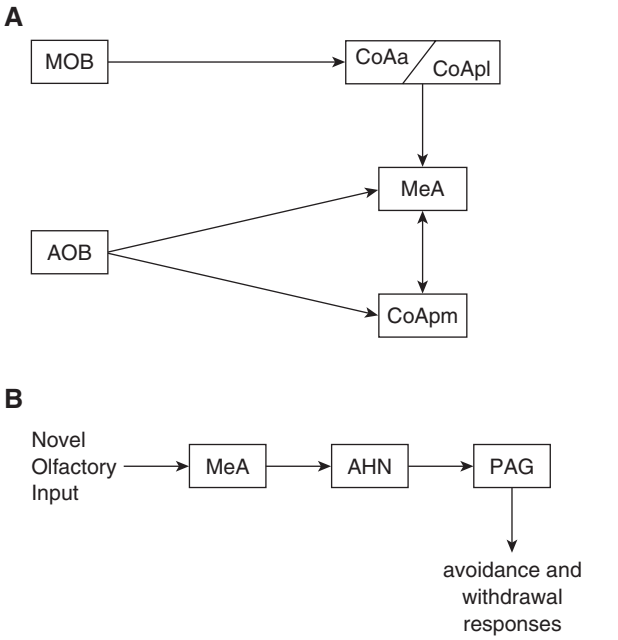

Figure 3: Diagram of the Neural Connections and Proposed Neural Circuit.

SOURCE: Part A is reproduced with permission from Numan, M., & Insel, T. R. (2003). *The neurobiology of parental behavior.* New York: Springer (Figure 4.4, p. 74). Copyright 2003 by Springer-Verlag.

NOTE: (A) Diagram of the neural connections between the main olfactory bulb (MOB), accessory olfactory bulb (AOB), and the corticomedial amygdala to show how olfactory input can converge on the medial amygdaloid nucleus (MeA). CoAa = anterior part of the cortical amygdaloid nucleus; CoApl = posterolateral part of the cortical amygdaloid nucleus; CoApm = posteromedial part of the cortical amygdaloid nucleus. (B) Proposed neural circuit through which novel olfactory input might act to suppress maternal responsiveness by activating avoidance behavior in naïve virgin rats. AHN = anterior hypothalamic nucleus; PAG = periaqueductal gray of midbrain.

causes avoidance behavior, which then delays the onset of maternal behavior in virgin rats. It has been shown that MeA lesions, in a manner similar to the induction of anosmia, facilitate the onset of pup-stimulated maternal behavior in naïve virgin rats that have not been treated with "maternal" hormones (Fleming, Vaccarino, & Luebke, 1980; Numan, Numan, & English, 1993). In further support, Fleming et al. (1980) have shown that virgins with corticomedial amygdaloid lesions do not go through an avoidance phase when first exposed to pups; they tolerate the pups' proximity, and after about 2 to 3 days of exposure, they express maternal behavior. It is as if the lesions disrupted fearfulness to novel pup stimuli but that a period of proximal pup stimulation was still needed to activate maternal responsiveness.

The efferents of the MeA project to many brain regions, one of which is the caudal part of the anterior hypothalamic nucleus (AHN; Canteras, Simerly, & Swanson, 1995). There is good reason to believe that the medial hypothalamic region that includes AHN is part of a central aversion system. Electrical or chemical stimulation of this region promotes defensive aggression and escape/flight responses (Fuchs, Edinger, & Siegel, 1985; Silveira & Graeff, 1992), and this medial hypothalamic region also has strong projections to the periaqueductal gray (PAG), a region that is also importantly involved in the regulation of fear-related behaviors (Bandler & Shipley, 1994; Risold, Canteras, & Swanson, 1994). Using this knowledge, Figure 3B proposes a more complete neural pathway through which novel olfactory pup stimuli might activate defensiveness, which then delays the onset of maternal behavior in naïve virgins. In partial support of this view, it has been shown that excitotoxic amino acid lesions of the caudal part of AHN, where it borders on the rostral part of the ventromedial hypothalamic nucleus, facilitate the onset of maternal behavior in rats that would normally avoid pups (Bridges, Mann, & Coppeta, 1999; Sheehan, Paul, Amaral, Numan, & Numan, 2001; also see Sheehan, Cirrito, Numan, & Numan, 2000). Finally, a recent report has shown that excitotoxic amino acid lesions of the rostral part of the lateral PAG also exerts a facilitatory effect on maternal behavior in rats (Sukikara, Mota-Ortiz, Baldo, Felicio, & Canteras, 2006). Therefore, damage at each level of the pathway from the olfactory bulbs to MeA to AHN and finally to PAG facilitates maternal behavior.

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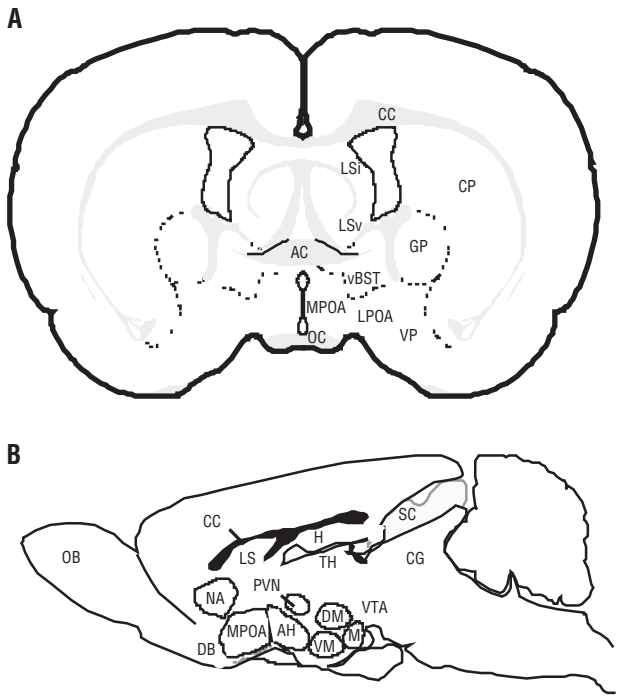

Figure 4: Frontal (A) and Sagittal (B) Sections of the Rat Brain at the Level of the Medial Proptic Area.

SOURCE: Adapted from Swanson's (1992) rat brain atlas. Reproduced with permission from Numan, M., & Insel, T. R. (2003). *The neurobiology of parental behavior*. New York: Springer (Figure 5.7, p. 130). Copyright 2003 by Springer-Verlag.

NOTE: AC = anterior commissure; AH = anterior hypothalamic nucleus; CC = corpus callosum; CG = central gray (periaqueductal gray); CP = caudate-putamen; DB = nucleus of the diagonal band of Broca; DM = dorsomedial hypothalamic nucleus; GP = globus pallidus; H = hippocampus; LPOA = lateral preoptic area; LS = lateral septum; LSi = intermediate nucleus of lateral septum; LSv = ventral nucleus of lateral septum; M = mammillary bodies; MPOA = medial preoptic area; NA = nucleus accumbens; OB = olfactory bulb; OC = optic chiasm; PVN = paraventricular hypothalamic nucleus; SC = superior colliculus; TH = thalamus; vBST = ventral bed nucleus of stria terminalis; VM = ventromedial hypothalamic nucleus; VP = ventral pallidum; VTA = ventral tegmental area.

Because the pathway described in Figure 3B appears to antagonize maternal behavior, elements of this pathway should be depressed in puerperal females to allow for the immediate onset of maternal behavior at parturition, and such inhibition might be orchestrated by neural regions which are also involved in increasing maternal responsiveness to pup stimuli.

THE MEDIAL PREOPTIC AREA AND VENTRAL BED NUCLEUS OF THE STRIA TERMINALIS (MPOA/vBST) AND MATERNAL BEHAVIOR

The MPOA/vBST plays an essential role in the control of maternal behavior. We want to make the case that neurons within this region comprise a specific maternal motivational system. Figure 4 shows coronal and sagittal sections through the rat brain indicating the location of the MPOA, which lies in the rostral hypothalamus, and the adjoining vBST (which is a telencephalic structure). MPOA/vBST neurons and their lateral connections with other neural regions must be intact for normal maternal behavior to occur in rats and other rodents (see Numan & Insel, 2003). It is important to note that MPOA/vBST lesions (electrical or excitotoxic) or lateral knife cuts need to be bilateral to disrupt maternal behavior; unilateral damage is not effective or results in transient deficits. Furthermore, although damage to the MPOA region usually also damages the adjoining vBST, studies have shown that discrete bilateral lesions to either the MPOA or vBST are capable of disrupting maternal behavior (Numan, Corodimas, Numan, Factor, & Piers, 1988; Numan & Numan, 1996). Finally, it is also clear that the deficits in maternal behavior resulting from MPOA/vBST damage are the result of a direct neurobehavioral effect and are not caused indirectly by a lesion-induced hormonal imbalance (Numan, 1994).

Concerning the nature of the maternal deficits that results from damage to MPOA/vBST neurons, all studies find that retrieval behavior (transporting displaced pups back to the nest site) is abolished or severely disrupted. Nursing behavior has been found to occur following such lesions, although at lower than normal levels. Several researchers have proposed that the MPOA/vBST may be most important for mother-initiated active/voluntary maternal responses, such as retrieving, and may be less involved in nursing behavior, which is more passive in nature and can be viewed as a somatic sensory reflex induced by suckling and other ventral somatic sensory stimulation from pups (Jacobson, Terkel, Gorski, & Sawyer, 1980; Numan & Insel, 2003; Stern, 1991, 1996; Terkel, Bridges, & Sawyer, 1979). In classic ethological terms, one might view retrieving behavior as an appetitive maternal response and nursing behavior as a consummatory maternal response (Hansen, Harthon, Wallin, Lofberg, & Svennson, 1991b).

Importantly, the maternal deficits resulting from MPOA/vBST damage are relatively specific; such females show normal body weight and temperature regulation, activity levels, female sexual behavior, and hoarding behavior (Numan, 1974; Numan & Callahan, 1980; Numan & Corodimas, 1985; Numan et al., 1988). Therefore, the females are clearly not debilitated by the MPOA lesions that disrupt maternal behavior. The intact hoarding behavior shows that the requisite motor responses that would be used to retrieve pups are intact, indicating that the retrieval deficit after such lesions cannot be explained on the basis of an MPOA lesion-induced oral motor deficit.

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In an important study, Lee, Clancy, and Fleming (2000) found that MPOA lesions not only disrupted retrieval behavior in postpartum rats but also disrupted an operant bar-press response if pups were used as a rewarding stimulus but not if palatable food was the reinforcing stimulus. These data suggest that although food is still rewarding for females with MPOA lesions, pup stimuli are not. In other words, for MPOA-lesioned postpartum females, pups are no longer an attractive goal object.

The MPOA/vBST is also one of the sites where hormones act to stimulate the onset of maternal behavior at parturition. MPOA/vBST neurons contain estrogen, progesterone, and prolactin receptors (Bakowska & Morrell, 1997; Numan et al., 1999; Shughrue, Lane, & Merchenthaler, 1997), and estradiol and prolactin/lactogens have been found to act locally at the level of the MPOA/vBST to activate the onset of maternal behavior in rats (Bridges et al., 1997; Bridges, Numan, Ronsheim, Mann, & Lupini, 1990; Numan, Rosenblatt, & Komisaruk, 1977). Therefore, while damage to MPOA neurons decreases maternal responsiveness to infant stimuli, hormonal stimulation of the MPOA increases such responsiveness.

The final piece of evidence indicates that MPOA/vBST neurons are activated during maternal behavior: The number of neurons in these regions that express Fos proteins increases during maternal behavior in rats and other species (see Numan & Insel, 2003). Because the promoter region of Fos genes (the genes that control the synthesis of Fos proteins) contains regulatory elements that allow Fos protein synthesis to be activated by a variety of extracellular signaling molecules (hormones, neurotransmitters; L. M. Robertson et al., 1995; Schuchard, Landers, Sandhu, & Spelsberg, 1993; Sheng & Greenberg, 1990; Xia, Dudek, Miranti, & Greenberg, 1996), the increased Fos expression in the MPOA/vBST during maternal behavior suggests that these neurons are being activated by extracellular signals. Research indicates that both the cFos and Fos B protein show increased expression in the MPOA and vBST for as long as females are with pups and engaging in maternal behavior; when pups are removed so that maternal behavior does not occur, the expression of these proteins declines (Stack & Numan, 2000). Some of these data are shown in Figure 5.

Because Fos proteins serve as transcription factors that activate the synthesis of additional proteins (Morgan & Curran, 1991), it can be proposed that the increased expression of Fos proteins in MPOA/vBST neurons during maternal behavior alters the phenotype of these neurons (by promoting neurotransmitter and/or neurotransmitter receptor synthesis, for example) and that this change in neuronal phenotype is essential for normal MPOA/vBST function and for maternal behavior. Some support for this view comes from the work of Brown, Ye, Bronson, Dikkes, and Greenberg (1996), who found that a transgenic mouse strain with a knockout mutation of the Fos B gene showed severe deficits in maternal behavior. Key goals for future research will be to determine whether Fos protein activity within MPOA/vBST neurons is indeed essential for maternal behavior, to determine the nature of the extracellular factors that activate Fos expression in MPOA/vBST, and, finally, to uncover the critical genes and gene products that are activated by Fos transcription factors and how these products, in turn, alter MPOA/vBST function to enable maternal responsiveness. It is worth pointing out that in addition to the activation of Fos protein expression in the MPOA/vBST during maternal behavior, cFos synthesis can also be activated in MPOA by treating female rats with hormones that are capable of stimulating the onset of maternal behavior, even if pups are not presented to these females (Sheehan & Numan, 2002; see Figure 6). It is as if pregnancy hormones activate Fos expression to change the phenotype of MPOA neurons and that this is one of the factors that allow for the immediate onset of maternal behavior at parturition. Subsequently, once maternal behavior occurs, the continued synthesis of Fos proteins during maternal behavior is proposed to maintain the functional integrity of MPOA/vBST neurons involved in maternal behavior control. Interestingly, the Fos expression response in the MPOA of females showing maternal behavior toward pups is slightly larger than the response induced by pregnancy hormones alone (see Sheehan et al., 2000).

Stack, Balakrishnan, Numan, and Numan (2002) have provided important evidence that Fos proteins may be contained within MPOA/vBST neurons that regulate maternal behavior. They took advantage of the fact the unilateral knife cuts that sever that lateral connections of the MPOA/vBST do not disrupt maternal behavior, whereas bilateral cuts are disruptive. When postpartum female rats received the unilateral cuts, they engaged in normal maternal behavior. However, when the brains of these females were subsequently immunocytochemically processed to detect Fos proteins, it was found that the number of cFos- and Fos B–expressing neurons was significantly reduced in the MPOA and vBST on the side of the brain ipsilateral to the knife cut, whereas normal high levels of the Fos proteins were expressed in the contralateral MPOA and vBST. Photomicrographs of this effect are shown in Figure 7. These results offer support for the view that Fos may serve as a marker of those MPOA and vBST neurons that contribute to circuits regulating maternal behavior.

In a recent study employing the conditioned place preference procedure, Mattson and Morrell (2005) found

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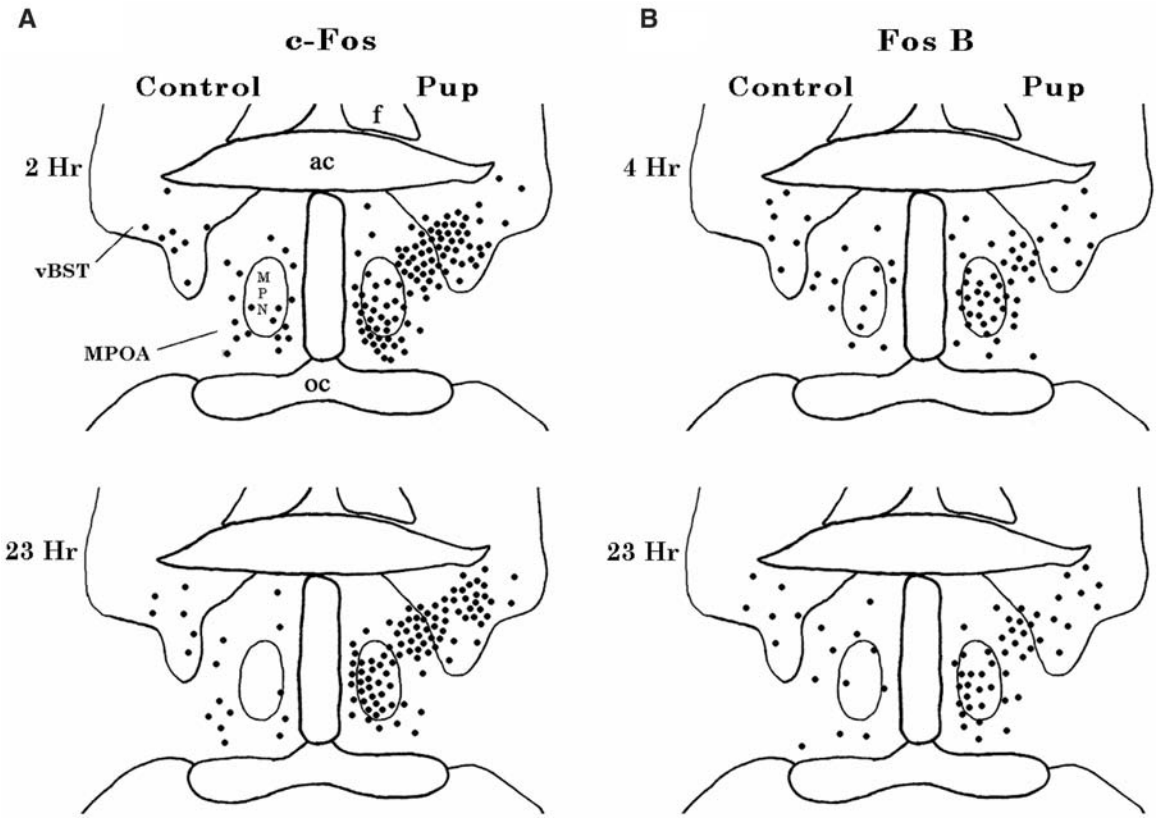

Figure 5: Representative Frontal Sections Through the Level of the Medial Preoptic Area (MPOA) on Which Is Plotted the Location of cFos (A) and Fos B Immunoreactive Cells (B) in Postpartum Primiparous Female Rats That Were Exposed to Pups and Showed Maternal Behavior for Either 2, 4, or 23 hr and for Control Females That Were Not Exposed to Pups.

SOURCE: Reproduced with permission from Stack, E. C., & Numan, M. (2000). The temporal course of expression of c-Fos and Fos B within the medial preoptic area and other brain regions of postpartum female rats during prolonged mother-young interactions. *Behavioral Neuroscience*, 114, 609-622. Copyright 2000 by the American Psychological Association, Inc.

NOTE: ac = anterior commissure; f = fornix; MPN = medial preoptic nucleus; oc = optic chiasm; vBST = ventral part of the bed nucleus of the stria terminalis.

that the MPOA not only becomes active, as indicated by Fos expression, during maternal behavior but also becomes active when females are searching for pups but the pups are actually not present. Postpartum females were trained in a conditioned place-preference apparatus in which one compartment contained pups and the other did not. On the test day, those females that showed a preference for the compartment that was previously associated with pups also showed increased expression of cFos in the MPOA. These important results indicate that stimuli that have been paired with pup stimuli can become conditioned appetitive stimuli and activate approach behavior in postpartum females and that these effects are associated with increased cFos expression in the MPOA. The MPOA appears to become activated when the postpartum female shows active responses aimed at achieving proximity to pups (for a related finding, see Fleming and Korsmit, 1996). It would be interesting to determine what effect MPOA lesions would have on the conditioned place-preference behavior.

Although most of the work on the involvement of the MPOA in parental behavior has been done on rodents (rats, mice, hamsters; Numan & Insel, 2003), other work has shown that this region controls parental behavior in birds (Buntin, 1996) and sheep (Levy, Ferreira, Keller, Meurisse, & Perrin, 2005). Levy et al. (2005) showed that the temporary inactivation of the MPOA with a local anesthetic disrupted maternal responsiveness in postpartum ewes.

MPOA/vBST EFFERENTS AND MATERNAL BEHAVIOR

In the context of Figure 1, I propose that neurons within the MPOA/vBST region are specifically involved in regulating maternal responsiveness to infant-related

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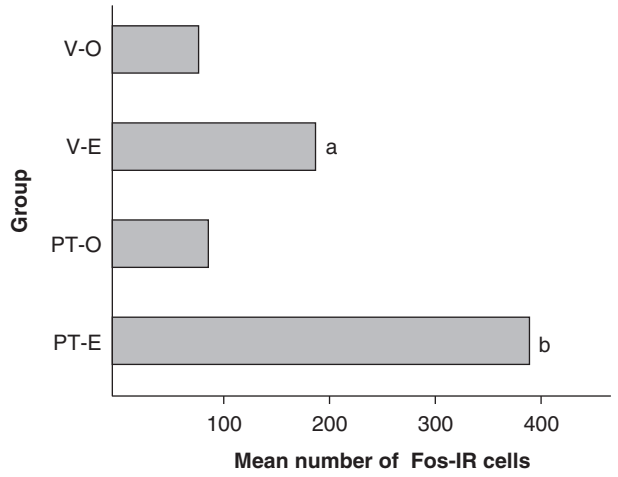

Figure 6: Mean Number of Fos-Immunoreactive (IR) Cells in the Medial Preoptic Area of Female Rats That Were Administered Various Treatments.

SOURCE: Data from Sheehan and Numan (2002).

NOTE: V-O = ovariectomized rats that received control subcutaneous (sc) injections of oil; V-E = ovariectomized rats injected sc with 20 µg/kg of estradiol benzoate (EB); PT-O = rats whose pregnancy was terminated on Day 12 (of a 22-day pregnancy) and received sc oil injections. These females would be exposed to progesterone withdrawal effects. PT-E = Rats whose pregnancy was terminated on Day 12 and received sc EB (20 µg/kg) injections. These females would be exposed to progesterone withdrawal effects superimposed on rising estradiol, which mimics the endocrine events that occur at the end of pregnancy when females would normally show maternal behavior. The females were not exposed to pups. a = significantly different from V-O and PT-O groups; b = significantly different from each of the other groups.

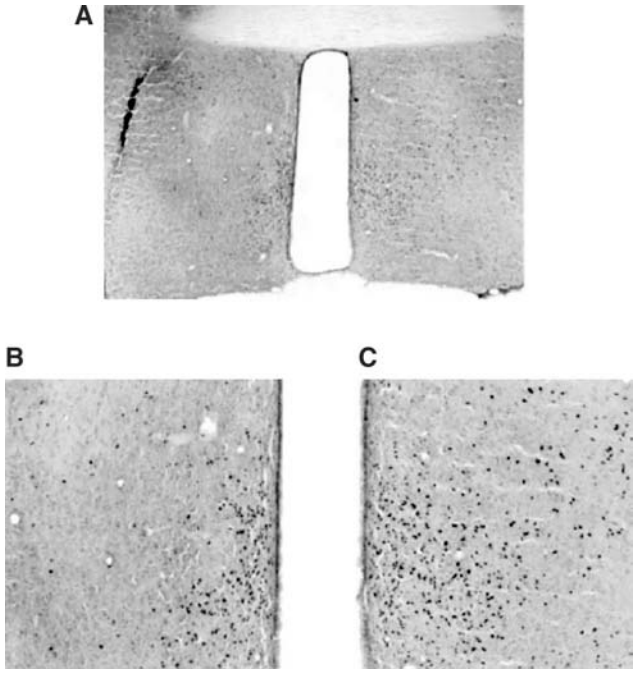

Figure 7: Photomicrographs Showing the Effect of a Unilateral Knife Cut Severing the Lateral Connections of the Medial Preoptic Area (MPOA) and Adjoining Ventral Bed Nucleus of the Stria Terminalis (vBST) on the Expression of cFos Within Cells in the Ipsilateral and Contralateral MPOA and vBST of Maternal Rats.

SOURCE: Reproduced with permission from Numan, M., & Insel, T. R. (2003). *The neurobiology of parental behavior.* New York: Springer (Figure 5.15, p. 158). Copyright 2003 by Springer-Verlag.

NOTE: (A) A low-power magnification showing both the ipsilateral and contralateral regions. The knife cut is visible on the left side, the anterior commissure is located dorsally, and the third ventricle is in the middle of the photomicrograph. B and C show high-power magnifications of the ipsilateral and contralateral regions, respectively. The knife cut clearly decreases cFos expression on the ipsilateral side. Modified from Stack, Balakrishnan, Numan, and Numan (2002).

stimuli. My view is that the MPOA/vBST is primed by hormones so that it is capable of responding to pup stimuli (which are primarily tactile in nature, with a secondary contribution of olfactory input; see Numan & Insel, 2003). As a result of this activation, MPOA/vBST efferents should do two things according to the model shown in Figure 1: (a) inhibit competing or antagonistic behavioral systems and (b) interact with a nonspecific motivational system so that the mother shows increased responsiveness to pup-related stimuli. Most of the remainder of this review concentrates on the latter process because that is where most of the evidence has accrued. However, I also briefly discuss the evidence for the first process.

To understand how MPOA/vBST neurons influence maternal behavior, one should first know where "maternally relevant" MPOA/vBST neurons project. In a series of two anatomical studies, my laboratory has investigated this question. In the first experiment, Numan and Numan (1996) iontophoretically injected the anterograde tracer PHAL into the region of the dorsal MPOA and adjoining vBST, which typically shows a strong Fos activation response during maternal behavior in rats. MPOA/vBST efferents terminated in several regions, which included the AHN, PAG, ventral tegmental area (VTA), and retrorubral field (RRF). The PHAL, of course, would most likely be taken up by a functionally heterogeneous group of MPOA/vBST neurons. Therefore, in a second study, Numan and Numan (1997) employed a double-labeling neuroanatomical analysis to gain insight into the neural regions to which MPOA and vBST neurons that express Fos during maternal behavior project. They found that MPOA/vBST neurons that are active during maternal behavior, as indicated by Fos expression, do indeed project to AHN, PAG, VTA, and RRF. As shown in Figure 8, I propose that MPOA/vBST projections to AHN and PAG are involved in inhibiting fear and withdrawal responses to novel pup stimuli, whereas MPOA/vBST projections to VTA and RRF are involved in exciting increased maternal responsiveness

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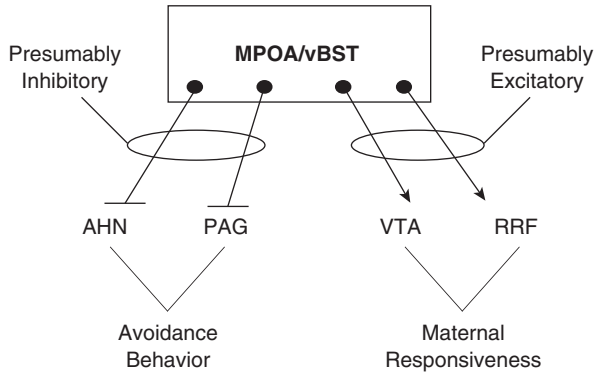

Figure 8: Some of the Efferent Projections of the Medial Preoptic Area (MPOA) and Ventral Bed Nucleus of the Stria Terminalis (vBST) Neurons That Express Fos During Maternal Behavior.

NOTE: Projections to the anterior hypothalamic nucleus (AHN) and periaqueductal gray (PAG) are presumed to inhibit avoidance behavior (axons end in a bar), whereas projections to the ventral tegmental area (VTA) and retrorubral field (RRF) are presumed to excite neural systems that increase positive responses to pup stimuli (axons end in an arrow).

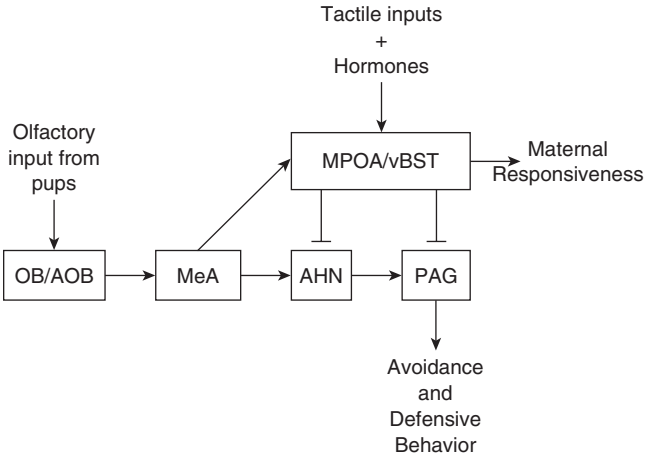

Figure 9: Olfactory Inputs That Arise From the Accessory Olfactory Bulb (AOB) and the Olfactory Bulb (OB) and Project to the Medial Amygdala (MeA) Can Reach Both the Medial Preoptic/Ventral Bed Nucleus of the Stria Terminalis (MPOA/vBST) Region and the Anterior Hypothalamic Nucleus (AHN).

NOTE: In a non-hormoned-primed female, inputs to AHN are dominant, and AHN projections to periaqueductal gray (PAG) are proposed to activate avoidance behavior. When MPOA/vBST is primed by pregnancy hormones, however, it responds to pup stimuli, and its efferents both promote maternal behavior and inhibit avoidance tendencies. Lines ending in an arrow signify excitation, and those ending in a bar indicate inhibition.

to pup stimuli. That is, the former projections are involved in depressing an antagonistic behavioral system, whereas the latter are involved in promoting maternal responsiveness to infant-related stimuli.

Figure 3B shows the central aversion system, which has been shown to depress maternal behavior in non-hormone-primed female rats. Because the MPOA projects to the AHN and the PAG, it makes sense to argue that when MPOA neurons are primed with estradiol, lactogens, and other stimulatory factors, one function of its efferents is to depress this central aversion system. Importantly, Lonstein and De Vries (2000) have reported that a significant proportion of MPOA and vBST neurons that express Fos during maternal behavior also contain glutamate decarboxylase, an enzyme necessary for gamma-aminobutyric acid (GABA) synthesis. Therefore, some maternally relevant MPOA/vBST neurons serve inhibitory functions.

Recall that virgin female rats initially find pup stimuli aversive, whereas the late pregnant and postpartum female finds such stimuli attractive. Also note that MeA efferents (through the stria terminalis) project to many regions in addition to AHN, which include major projections to MPOA and vBST (Canteras et al., 1995). In an important Fos immunocytochemical study, Sheehan et al. (2000) explored Fos expression in the brains of maternal and nonmaternal females, with the former group responding positively to pups and the latter group avoiding pups. Fos expression was high in the MPOA/vBST and low in the AHN of the maternal females. The reverse occurred in the nonmaternal females, who showed low expression of Fos in MPOA/vBST and high expression in AHN. Figure 9 outlines a possible neural system that might underlie this switch in responding to olfactory and other pup-related stimuli. The figure shows olfactory input reaching two populations of MeA neurons, one projecting to AHN with the potential of activating defensive behavior and the other projecting to MPOA/vBST, with the potential of stimulating maternal approach and attraction to pups (cf. Choi et al., 2005). I propose that in a non-hormone-primed female, the MPOA/vBST is less responsive to such pup stimuli and, therefore, inputs to the aversion system are dominant. However, the hormone-primed MPOA/vBST does respond to such signals, and its output performs two important functions: depression of the response of the aversion system to pup stimuli and activation of maternal responsiveness. Recall that anosmic postpartum rats show normal maternal behavior. Therefore, although olfactory input to the hormone-primed MPOA/vBST may promote maternal attraction toward pups, it is not essential for such responsiveness. In addition to olfactory inputs, the MPOA/vBST receives ventral somatic sensory and perioral somatic sensory inputs, which seem to be critical for maternal behavior in the postpartum female (Lonstein, Simmons, Swann, & Stern, 1998; Numan & Insel, 2003; Numan & Numan,

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1995). The significance of Figure 9 is that it proposes a mechanism to explain why pup stimuli do not activate avoidance and defensive responses when the primiparous hormone-primed puerperal female is initially exposed to novel pup stimuli.

It is important to note that in some species, such as mice, olfaction is essential for maternal behavior, and for other species, such as sheep, olfactory input from lambs becomes essential for the maternal behavior after a period of maternal experience with a specific lamb (Numan & Insel, 2003). Therefore, although in rats olfactory input to MPOA/vBST may play a secondary role in maternal attraction to young, in other species it may serve a primary role.

MPOA/vBST EFFERENTS TO VTA AND RRF AND MATERNAL RESPONSIVENESS

Dopamine (DA) neurons in the VTA and RRF give rise to the mesolimbic DA system, which ascends to the telencephalon, with a major projection to the nucleus accumbens (NA; Deutch, Goldstein, Baldino, & Roth, 1988; Pennartz, Groenewegen, & Lopes Da Silva, 1994; Swanson, 1982). It is well established that the mesolimbic DA system serves as a nonspecific motivational system involved in regulating behavioral responsiveness for a variety of motivated behaviors, although its exact role is still controversial. One group of researchers has emphasized the importance of VTA/RRF dopaminergic projections to NA in reinforcement processes (Wise, 2004), whereas another group has emphasized the role of this projection in appetitive motivational processes (processes that regulate attraction to particular stimuli; Berridge & Robinson, 1998). It is certainly possible that different neural circuits within NA, when affected by DA input, regulate each of these functions (Kelley & Berridge, 2002). I want to emphasize the role of VTA/RRF dopaminergic inputs to NA in the control of appetitive behavior. DA action on NA is proposed to increase an organism's responsiveness to those stimuli that are involved in causing such DA release. When pup stimuli, or stimuli that have been associated with primary pup stimuli, are involved in activating DA release into NA, the organism should show increased approach and attraction toward such pup-related stimuli, allowing such stimuli to activate proactive voluntary maternal responses. Finally, I present evidence that the activation of DA release into NA by pup-related stimuli may be mediated by pup stimuli–induced excitation of MPOA/vBST efferents to VTA/RRF. With respect to the model in Figure 1, I suggest that MPOA/vBST projections to VTA/RRF represent an interaction between a specific maternal motivational system (MPOA/vBST) and a nonspecific motivational system (VTA/RRF). The latter has the potential of increasing an organism's responsiveness to a broad range of external stimuli, but just which stimuli an organism actually responds to depends on the particular specific motivational system that activates the mesolimbic DA system.

The following additional findings are relevant to the proposal that maternally relevant MPOA neurons project to VTA/RRF: MPOA neurons that express Fos during maternal behavior contain estrogen receptors (Lonstein, Greco, De Vries, Stern, & Blaustein, 2000), and neurons in the MPOA and vBST that bind estradiol project to the VTA (Fahrbach, Morrell, & Pfaff, 1986). Interestingly, there is an important glutamatergic pathway between the vBST and the VTA that is capable of activating VTA DA neurons (Georges & Aston-Jones, 2002), suggesting that glutamate may be one of the neurotransmitters through which maternally relevant MPOA/vBST neurons activate the mesolimbic DA system.

There is a fairly large body of evidence that shows that VTA dopaminergic projections to NA are important for maternal responsiveness: (a) Fos expression increases in the shell region of the nucleus accumbens (NAs) during maternal behavior (Lonstein et al., 1998; Stack et al., 2002), (b) DA is released into the NA during maternal behavior (Champagne et al., 2004; Hansen, Bergvall, & Nyiredi, 1993), (c) electrical or 6-hydroxydopamine (6-HD) lesions of the VTA disrupt maternal behavior (Gaffori & Le Moal, 1979; Hansen et al., 1991b; Numan & Smith, 1984), and (d) 6-HD lesions of the nucleus accumbens (Hansen, Harthon, Wallin, Lofberg, & Svensson, 1991a) or injection of flupenthixol, a mixed DA receptor antagonist that blocks both D1-like and D2-like receptors, into NAs disrupts maternal behavior (Keer & Stern, 1999). The following additional points are worth noting. First, disruption of VTA DA input to NA does not disrupt all aspects of maternal behavior equally. Reflexive nursing behavior is less affected, whereas proactive voluntary responses such as retrieval behavior show a major disruption. Importantly, this matches the effects of MPOA lesions on maternal behavior, suggesting a functional connection. Second, other studies have shown that disruption of the mesolimbic DA system can impair aspects of male sexual behavior, female sexual behavior, and eating behavior (Becker, Rudnick, & Jenkins, 2001; Everitt, 1990; Pfaus & Phillips, 1991; Zhang, Balmadrid, & Kelley, 2003). These findings are exactly what one should expect from interfering with a nonspecific motivational system that regulates responsiveness to a variety of biologically significant stimuli.

Given that 6-HD lesions of NA or microinjections of a mixed D1/D2 antagonist into NAs disrupt maternal behavior, in a recent study (Numan, Numan, Pliakou, et al., 2005), I wanted to examine the relative importance of DA action on D1 and D2 receptors in NA for

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the maternal behavior of postpartum rats. I found that microinjection of relatively low doses (1, 2, and 3 μg) of a standard D1 antagonist (SCH 23390) into NA disrupted the retrieval response in postpartum rats while leaving nursing behavior intact. The injection sites were located in the shell (medial) region of NA (NAs). Injection of similar doses of eticlopride, a standard D2 antagonist, into NAs did not significantly depress any aspect of maternal behavior. However, the 3-μg dose of eticlopride did depress retrieval behavior in a few females, suggesting that higher doses of the D2 antagonist might have produced significant effects.

With respect to the severe retrieval deficit observed in the SCH 23390–injected females, it should be noted that all these females approached and sniffed their pups when they were placed outside the nest area at the beginning of each retrieval test, and they even retrieved some of the pups back to the nest. The primary deficit was an inability to completely retrieve the entire litter to the nest. Such females would retrieve one or two pups and begin nursing without returning for the others or would return after a delay. It took these females 1 to 2 hours to complete retrieval of their entire litter. In conclusion, although D2 receptors may also be involved, our results suggest the primary importance of DA action on D1 receptors in NAs for the control of the proactive voluntary maternal responses involved in retrieval behavior. This conclusion is important because Fos is expressed in NA during maternal behavior (Stack et al., 2002), and DA action of D1 receptors in NA is capable of activating Fos expression (Hunt & McGregor, 2002; Keefe & Gerfen, 1995; Moratalla, Xu, Tonegawa, & Graybiel, 1996).

In this study, I also established anatomical specificity for the inhibitory effects of SCH 23390 on the maternal retrieval response. Injection of 1 or 3 μg of SCH 23390 into the ventral pallidum (VP) or 1 or 2 μg of the drug into MPOA did not disrupt maternal behavior. This finding is important because NA, VP, and MPOA are anatomically located close to one another and the VP and MPOA also receive substantial DA input, that to the VP arising from the VTA (Klitenick, Deutch, Churchill, & Kalivas, 1992) and that to the MPOA arising for the incerto-hypothalamic DA system (Simerly, Gorski, & Swanson, 1986; Wagner, Eaton, Moore, & Lookingland, 1995). Therefore, the inhibitory effects of D1 receptor blockade in NA on retrieving cannot be explained on the basis of spread of the drug to VP or MPOA.

What are the mechanisms through which DA action on NA potentiates responsiveness to biologically significant stimuli? This issue is controversial, and research has suggested conflicting mechanisms. Important anatomical considerations include the following: The NA receives excitatory glutamate input from the prefrontal cortex (PFC), amygdala, and hippocampus (Pennartz et al., 1994). The major output neurons of NA are the GABAergic medium spiny neurons (MSNs), and although these neurons have diverse connections (Pennartz et al., 1994; Usuda, Tanaka, & Chiba, 1998), we will emphasize the MSN GABAergic projection to VP to simplify the following discussion and because the VP is involved in motivational processes (Gong, Neill, & Justice, 1997) and, as will be seen, maternal behavior (Numan, Numan, Schwarz, et al., 2005). Two contrasting views of the role of DA in NA function are shown in Figure 10. Early studies suggested that the primary action of DA on MSN output was inhibitory. On the basis of many important experiments, Mogenson (1987) proposed that DA acts to inhibit excitatory transmission in NA and that this effect releases VP from inhibition by NA efferents. According to Mogenson, increased output from VP then promotes behavioral reactivity. A contrasting view is described in an important review by Nicola, Surmeier, and Malenka (2000). This article presents evidence that NA output is essential for selective behavioral reactivity. It is proposed that DA functions in NA to inhibit weak excitatory inputs from the prefrontal cortex and limbic system while potentiating the effects of strong excitatory inputs. This effect would allow only strong sensory inputs to NA to drive its output, and then this GABAergic output to VP and other sites would allow behavioral responsiveness to selectively occur to strong stimulus inputs. A major difference between the two views is that Mogenson (1987) suggests that the NA is inhibitory and the VP is excitatory for behavioral reactivity, whereas the Nicola et al. (2000) view suggests that the reverse is true. Although most current views of striatal-pallidal function (which are primarily based on research findings on caudate/putamen-globus pallidus interactions) align themselves with the Nicola et al. (2000) perspective (see Grillner, Hellgren, Menard, Saitoh, & Wilkstrom, 2005), there has been a recent series of studies that suggests that inhibition of NA output plays a positive role in species-typic and goal-directed appetitive behaviors and reward-related process (Cheer, Heien, Garris, Carelli, & Wrightman, 2005; Reynolds & Berridge, 2002; Stratford & Kelley, 1997; Stratford, Kelley, & Simansky, 1999; Taha & Fields, 2006).

With respect to maternal behavior, our laboratory has recently produced data that are more consistent with Mogenson's (1987) view (Numan, Numan, Schwarz, et al., 2005). Lesions of NAs, which is the region where D1 antagonists exert inhibitory effects on maternal behavior, did not disrupt the maternal behavior of postpartum rats. These data fit with the view that NAs output is not essential for maternal behavior and that DA action on D1 receptors may normally function to inhibit NA, in this way releasing VP from inhibition and

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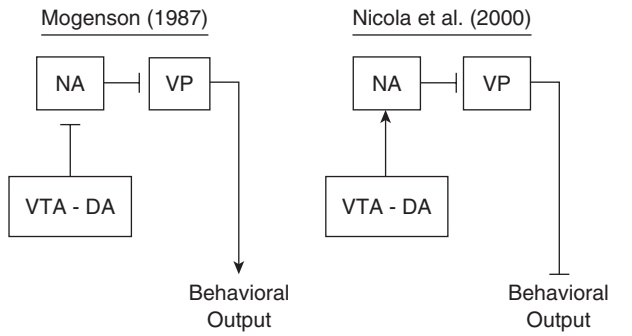

Figure 10: Two Contrasting Views of Mesolimbic Dopamine (DA) Function.

NOTE: Mogenson's (1987) perspective is that DA input from the ventral tegmental area (VTA) to the nucleus accumbens (NA) serves to inhibit NA output to the ventral pallidum, in this way disinhibiting VP, which then promotes behavioral reactivity. Nicola et al. (2000) proposed that DA input to NA excites NA output, which then inhibits VP, and that this inhibitory effect promotes behavioral reactivity. Lines ending in a bar are inhibitory, and those ending in an arrow signify excitatory projections.

allowing for the expression of proactive voluntary maternal responses. To provide additional support, we microinjected the drug muscimol into either NA or VP of postpartum rats and observed the effects on maternal behavior. Muscimol is a GABA-A receptor agonist, and it causes a reversible neural inhibition. Note that muscimol injections into VP would simulate the effects of an active NA because NA outputs to VP are GABAergic. Figure 11 shows the location of the NA and VP injection sites, and Figure 12 shows the effects of the injections on retrieving and nursing behavior. In support of the lesion data, muscimol injections into NA did not affect maternal behavior. In contrast, all doses of muscimol injected into VP depressed retrieval behavior, and the highest doses also depressed nursing behavior. Importantly, by 5 hr postinjection, this inhibitory effect wore off, supporting the contention that muscimol caused a reversible depression of neural activity.

To summarize, my evidence suggests that the output of the VP, but not that of NA, is important for maternal behavior. Because the mesolimbic DA system with an action of D1 NA receptors is also essential, the best conclusion is that DA functions to depress NA activity, which releases the VP from NA inhibition.

Up to this point, I have presented evidence that maternally relevant MPOA/vBST neurons project to VTA/RRF and that the mesolimbic DA system regulates maternal responsiveness. What is the evidence that MPOA/vBST actually interacts with the mesolimbic DA system to promote VP output in its control over maternal behavior? First, Numan and Smith (1984) showed that bilateral damage to a neural system that travels between the MPOA and VTA disrupts maternal behavior in postpartum rats (also see Numan & Numan, 1991). Using an asymmetrical lesion design, they found that a unilateral knife cut of the lateral MPOA connections paired with a contralateral electrical lesion of the VTA disrupted maternal behavior to a much larger extent than did a variety of control lesions, which included a group that had the knife cut and VTA lesion on the same side of the brain. Significantly, retrieving and nest building were more severely disrupted by the contralateral lesions of the MPOA and VTA than was nursing behavior. Second, based on the idea that MPOA activation of VTA/RRF releases DA into NA, which in turn disinhibits VP, we recently showed that an excitotoxic amino acid lesion of the MPOA/vBST on one side of the brain and an excitotoxic amino acid lesion of the VP on the contralateral side also disrupted maternal behavior in postpartum rats (Numan, Numan, Schwarz, et al., 2005). Control females received either sham lesions or ipsilateral MPOA/vBST and VP lesions. A contralateral lesion is shown in Figure 13. The contralateral lesions disrupted retrieval behavior while having only a minor effect on nursing behavior. The retrieval results are shown in Figure 14. Importantly, the effective contralateral lesions were found to depress retrieval behavior in a specific manner. The contralaterally lesioned females showed normal activity levels, and they were also able to pick up candy (which approximated the size and weight of pups) in their mouths, which they carried to other parts of the cage.

A final piece of evidence suggests an important interaction between the MPOA/vBST and the mesolimbic DA system during maternal behavior but also presents some complicating issues. Stack et al. (2002) asked whether unilateral excitotoxic amino acid lesions of the MPOA/vBST (recall that such unilateral lesions do not disrupt maternal behavior) would affect the Fos activation that occurs in the NAs during maternal behavior. They found that female rats with such lesions did in fact engage in normal maternal behavior. When the brains of these females were immunocytochemically processed, it was found that Fos activation was normal in the NAs that was contralateral to the MPOA/vBST lesion but that Fos activation in the ipsilateral NAs was reduced to baseline levels. Figure 15 shows this effect. These results clearly show that MPOA/vBST activity during maternal behavior influences NAs function. Equally important is the fact that DA action on D1 receptors can activate Fos expression in NA, suggesting that the MPOA effect may be mediated through D1 receptors, which we have shown to be critical for maternal behavior. A complicating factor, however, is that Fos activation is usually taken as a measure of an increase in neural activity, but I have suggested that NAs output activity should decrease during maternal behavior, in this way releasing VP from inhibition. One resolution

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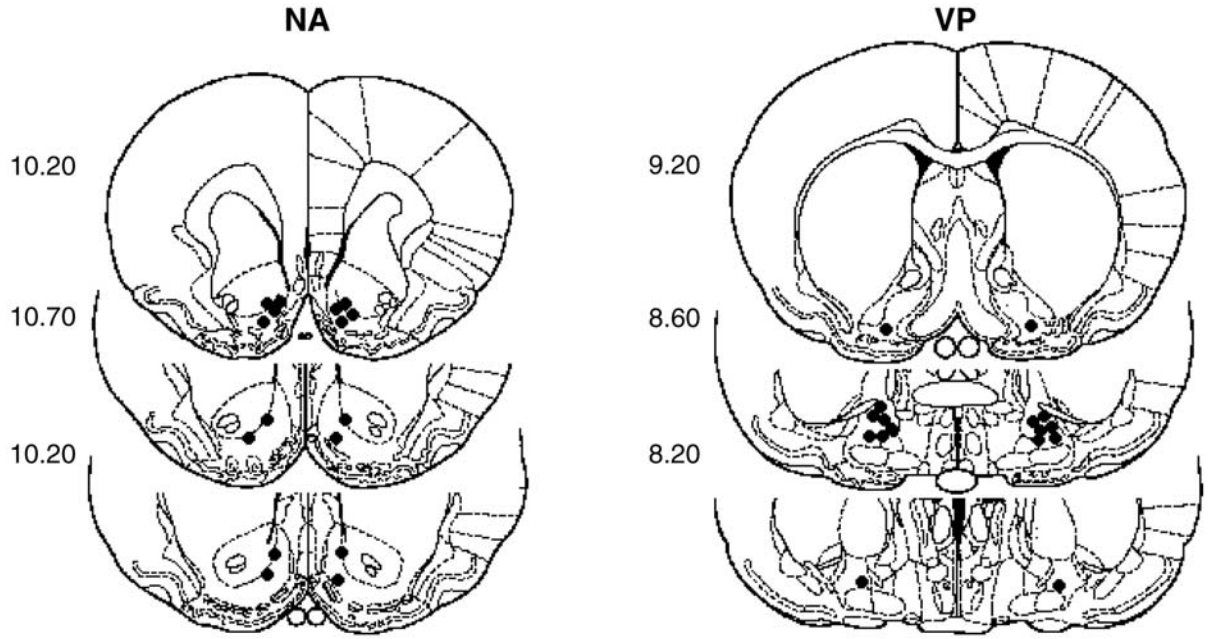

Figure 11: Reconstructions, Based on the Microscopic Analysis of Cresyl Violet–Stained Sections, of the Location of the Muscimol Injection Sites (Shown as Black Dots) Into Either the Medial Nucleus Accumbens (NA) or Ventral Pallidum (VP), Which Were Drawn on to Plates From the Paxinos and Watson (1997) Atlas.

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NOTE: The numbers to the left of each plate indicate the distance in millimeters anterior to the interaural plane.

of this conflict is that the Fos activation in NAs during maternal behavior may be expressed in inhibitory interneurons, which exert strong depressing effects of MSN output (Koos & Tepper, 1999; Trevitt, Morrow, & Marshall, 2005). Another interesting prospect is that Fos may actually be expressed in MSN NA projection neurons during maternal behavior, but such Fos expression may be a marker of an active inhibitory process wherein the MSNs become less responsive to glutamatergic inputs (Harvey & Lacey, 1997).

DA ACTION ON NAs D1 RECEPTORS FACILITATES MATERNAL BEHAVIOR

My proposal is that MPOA/vBST activation of the mesolimbic DA system increases maternal responsiveness to infant-related stimuli. For the MPOA/vBST, I have shown that lesions to this area disrupt whereas hormonal stimulation of this area facilitates maternal behavior. Most of the work on the mesolimbic DA system, however, has shown only that interference with this system disrupts proactive voluntary maternal responses.

My graduate student, Danielle Stolzenberg, has recently begun a research program to investigate whether stimulation of the mesolimbic DA system can facilitate maternal behavior (Stolzenberg & Numan, 2006). In the first experiment, which is now complete, naïve female rats (those who were never exposed to pups) were primed with a suboptimal hormone regimen and then exposed to pups over a 5-day test period. On the first 3 days of pup presentation (Days 0, 1, and 2 of testing), females received either bilateral injections of 0.5 μg of a D1 agonist (SKF 38393) into NAs or control vehicle injections. The cumulative percentage of females showing maternal behavior throughout the test period is shown in Figure 16 (females were presented with freshly nourished test pups on each day, and the pups remained with the females for 24 hours). Most of the females that received D1 agonist injections into NAs showed complete maternal behavior on either Day 0 or Day 1 of testing (82% were fully maternal by Day 1), whereas only 23% of the vehicle-injected females were maternal by the end of Day 1. These results show that when partially hormone-primed females are intracerebrally injected with a drug that stimulates D1 DA receptors in NAs, maternal behavior is facilitated. This work is the first step in a series of experiments that will provide important information on the operation of various parts of the mesolimbic DA system during maternal behavior.

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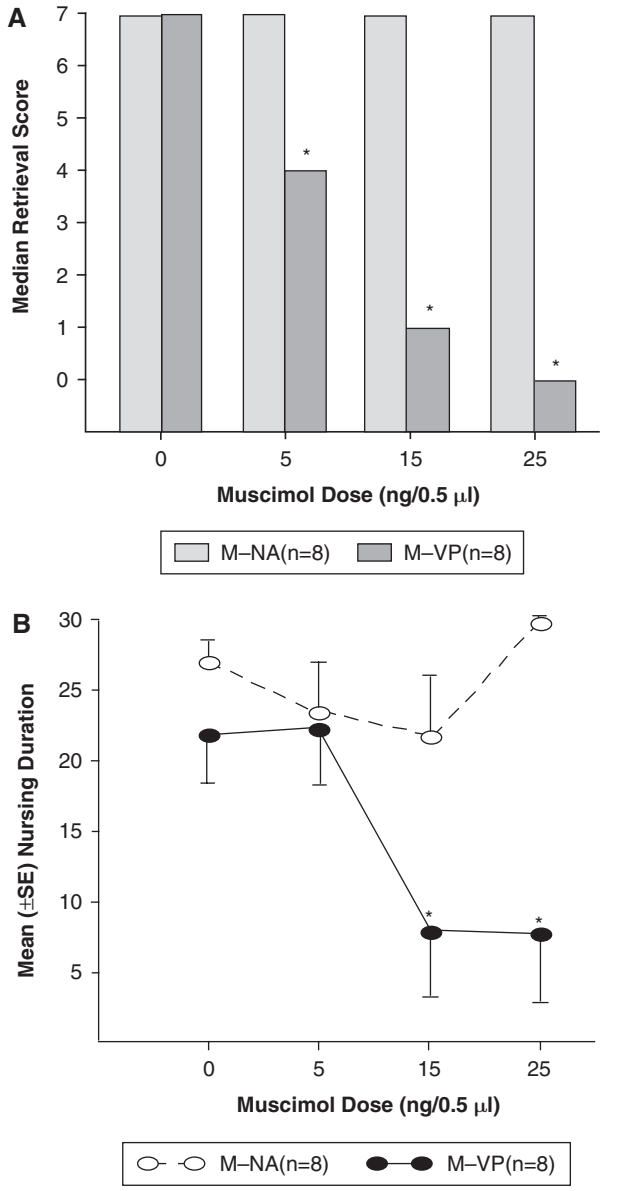

Figure 12: Median Retrieval Scores (A) and Mean Nursing Duration Scores (B) for Postpartum Rats That Received Various Doses of Muscimol Into Either the Medial Nucleus Accumbens (M-NA) or Ventral Pallidum (M-VP).

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*Significantly different from corresponding M-NA group.

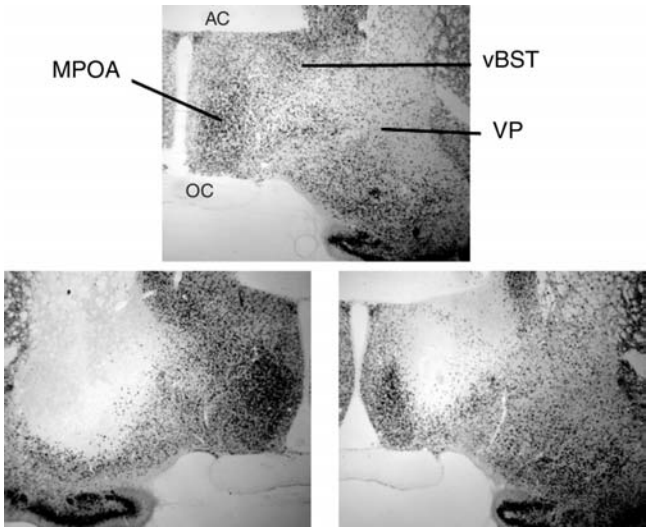

Figure 13: Frontal Sections Through the Preoptic Region Immunohistochemically Processed With Neu N Primary Antibody.

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NOTE: (Top) Normal morphology of the medial preoptic area (MPOA), ventral bed nucleus of the stria terminalis (vBST), and ventral pallidum (VP). (Bottom left) A unilateral N-methyl-D-aspartate (NMDA) lesion aimed at the VP. (Bottom right) A unilateral NMDA lesion aimed at the MPOA/vBST region. The Neu N antibody recognizes a neuronal-specific protein. If neurons are destroyed, the tissue appears white. AC = anterior commissure; OC = optic chiasm.

A NEURAL MODEL OF MPOA/vBST INTERACTION WITH THE MESOLIMBIC DA SYSTEM DURING MATERNAL BEHAVIOR

Based on the research and ideas presented in the previous two sections, I propose in Figure 17 a neural model showing how MPOA/vBST interactions with the mesolimbic DA system may increase a female's responsiveness to pup stimuli and pup-associated stimuli so that proactive voluntary maternal responses occur. When fully primed by maternal hormones, MPOA/vBST neurons respond to pup-related stimuli and send out efferent projections to VTA/RRF, which stimulate DA release into NA. It is proposed that DA action on D1 receptors has the primary effect of inhibiting MSN output to VP, in this way releasing VP from inhibitory control. Note also that external stimuli, including pup stimuli, are shown as activating both NA and VP, which is a critical aspect of the model. If the MPOA/vBST were not active, as would be presumed to be the case in nonmaternal females, these stimulatory (glutamatergic) inputs to NA and VP would oppose each other, and VP would not show a strong response to pup stimuli. However, in maternal females, the MPOA/vBST is active, and it would inhibit NA responsiveness to pup stimuli through stimulation of DA release into NA, which would enhance VP responsiveness to pup stimuli. The resultant VP activation is viewed as a first step in the occurrence of appetitive

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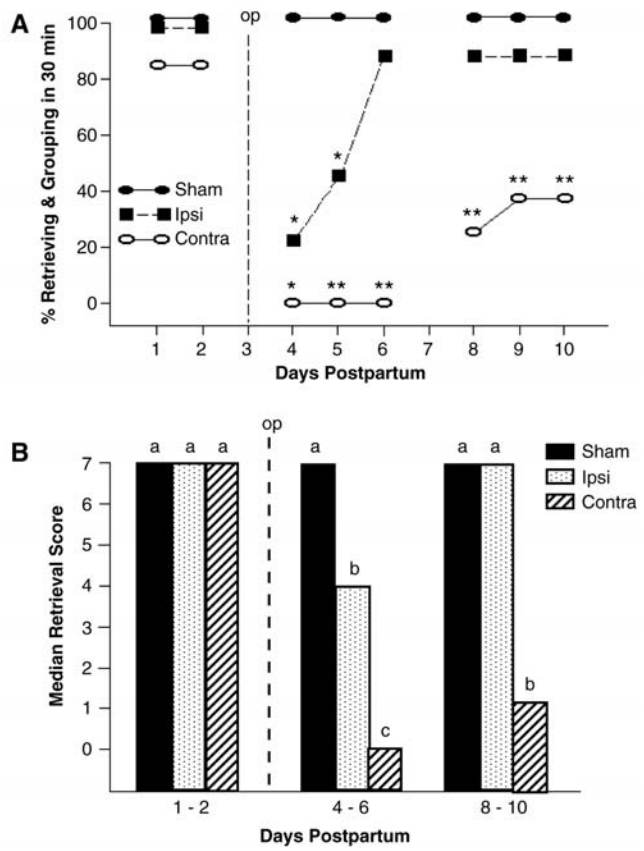

Figure 14: Retrieval Results.
SOURCE: Reproduced with permission from Numan, M., Numan, M. J., Schwarz, J. M., Neuner, C. M., Flood, T. F., & Smith, C. D. (2005). Medial preoptic area interactions with the nucleus accumbens-ventral pallidum circuit and maternal behavior in rats. *Behavioural Brain Research*, *158*, 53-68. Copyright 2005 by Elsevier.
NOTE: (A) Percentage of females retrieving all their pups to a single nest site within 30 min of pup presentation pre- and postoperatively, during the postpartum period. Retrieval tests were not administered on day 7 postpartum. Females received one of the following: unilateral excitotoxic amino acid lesions of the medial preoptic area (MPOA) and ventral pallidum (VP) that were either contralateral or ipsilateral to one another or sham lesions. The lesions were performed on Day 3 postpartum (op). *Significantly different from Sham group. **Significantly different from sham and ipsi groups. (B) For the same groups, median retrieval scores averaged over Days 1 to 2 preoperatively and 4 to 6 and 8 to 10 postoperatively. Within each time interval, groups that do not share a common letter differ significantly from one another.

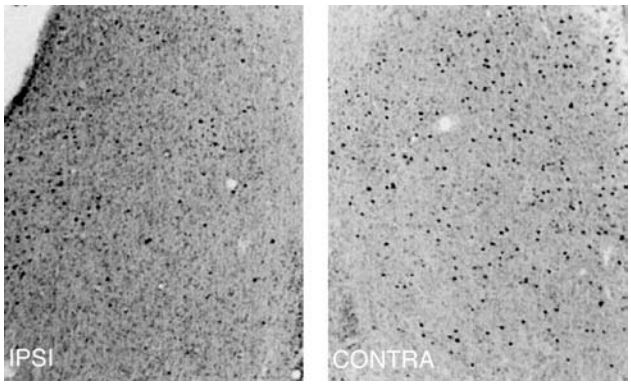

Figure 15: Photomicrographs Showing the Expression of cFos Within Cells of the Nucleus Accumbens Shell Region (NAs).
SOURCE: Reproduced with permission from Numan, M., Fleming, A. S., & Levy, F. (2006). Maternal behaviors. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (3rd ed.). San Diego, CA: Academic Press. Copyright 2006 by Elsevier.
NOTE: Postpartum female rats received a unilateral lesion of the medial preoptic area and adjoining ventral bed nucleus of the stria terminalis and continued to show maternal behavior (bilateral lesions are needed to disrupt the behavior). The lesion decreased cFos expression in the ipsilateral (IPSI) NAs but not in the contralateral (CONTRA) NAs. Data from Stack et al. (2002).

maternal responses. It is as if NA inhibition opens a gate that allows the VP to pass on pup-related stimuli to other brain regions, which then respond to such stimuli in an appropriate and adaptive manner.

An important question with respect to this model is what determines the particular stimuli that gain access to NA and VP at any one point in time. I tentatively propose that attentional mechanisms determine stimulus input to NA and VP. However, such stimuli are processed further by neural centers downstream from VP only if DA acts to inhibit NA. Future research, of course, should be aimed at determining the critical regions downstream from VP that are essential for maternal behavior and the essential neural pathways through which pup stimuli gain access to VP (and NA).

Additional support for this model can be outlined as follows: (a) The NA and VP receive excitatory glutamatergic afferents from the prefrontal cortex and amygdala (Brog, Salyapongse, Deutch, & Zahm, 1993; Fuller, Russchen, & Price, 1987; Maslowski-Cobuzzi & Napier, 1994; Petrovich, Risold, & Swanson, 1996; Sesack, Deutch, Roth, & Bunney, 1989; Wright & Groenewegen, 1995; Zaborszky, Gaykema, Swanson, & Cullinan, 1997). It is aspects of these inputs that presumably carry pup stimuli–induced neural activity to NA and VP. (b) DA action on D1 receptors in NA has been found to inhibit excitatory inputs carried by the prefrontal cortex and amygdala (Charara & Grace, 2003; Maeda et al., 2004; Pennartz, Dolleman-Van Der Weel, Kitai, Lopes Da Silva, 1992). (c) D1 receptors are located on NAs neurons that project to VP (Lu, Ghasemzadeh, & Kalivas, 1998; G. S. Robertson & Jian, 1995).

A recent study from Nicola's group has actually presented evidence consistent with the model shown in Figure 17 (Yun, Nicola, & Fields, 2004). They trained rats on a variable interval (VI) operant bar-press response for a food reward. The operant chamber contained an active lever and an inactive lever, and

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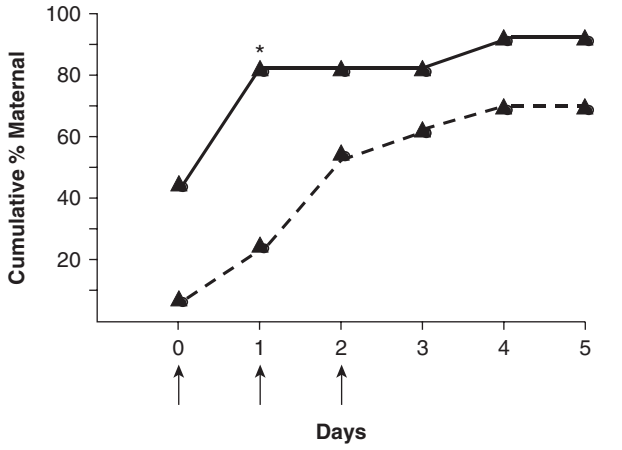

Figure 16: Cumulative Percentage of Females Showing Maternal Behavior Over a 5-Day Period of Pup Exposure.

NOTE: All females were primed with a suboptimal hormone regimen that would shorten sensitization latencies but that would not stimulate immediate maternal behavior. One group received microinjections of 0.5 µg of a D1 DA receptor agonist into the medial nucleus accumbens on Days 0, 1, and 2 of testing (solid line), whereas the control group received injections of the vehicle solution (dashed line). Arrows on the abscissa indicate days on which intracerebral injections took place. *A significantly higher proportion of females in the DA agonist group showed complete maternal behavior by Day 1 of testing (Fisher exact probability test, $P = .02$; Stolzenberg & Numan, 2006).

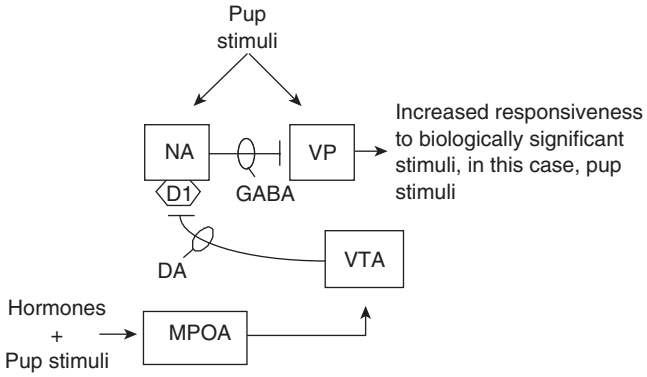

Figure 17: Neural Model Showing How the Medial Preoptic Area (MPOA), Ventral Tegmental Area (VTA), Nucleus Accumbens (NA), and Ventral Pallidum (VP) Might Interact to Regulate Maternal Responsiveness.

SOURCE: Reproduced with permission from Numan, M., Numan, M. J., Pliakou, N., Stolzenberg, D. S., Mullins, O. J., Murphy, J. M., et al. (2005). The effects of D1 or D2 receptor antagonism in the medial preoptic area, ventral pallidum, or nucleus accumbens on the maternal retrieval response and other aspects of maternal behavior in rats. *Behavioral Neuroscience, 119*, 1588-1604. Copyright 2005 by the American Psychological Association, Inc.

NOTE: Connections ending in a bar are inhibitory, and those ending in an arrow are excitatory. In a nonmaternal female, pup stimuli, arriving over pathways from the amygdala and prefrontal cortex, activate both NA and VP, resulting in low VP activity. In a maternal female with a hormone-primed MPOA, pup stimuli also activate MPOA, which in turn stimulates VTA dopamine (DA) projections to NA. DA acting on NA D1 receptors is hypothesized to depress NA output, which results in increased VP activity, promoting proactive voluntary maternal responses.

pressing the former would result in food reward under certain conditions, whereas pressing the latter was always ineffective. The availability of reward was signaled by a 20-s discriminative stimulus (DS; a tone), and the first response on the active lever during the DS terminated the DS and resulted in delivery of a food pellet. A light above the inactive lever was also illuminated on an independent VI schedule, but responses on the inactive lever were never rewarded. Based on the Nicola et al. (2000) model presented in Figure 10, they hypothesized two things: that DA input to NA would be necessary for selective active lever responding to DS and that NA output would be essential for responding appropriately to DS. Their results, some of which are shown in Figure 18, supported the first hypothesis but not the second. When they injected saline into NA, the animals pressed at a high level on the active lever and at a low level on the inactive lever. Injection of a D1 antagonist (SCH 23390) into NA (at a dose level that also inhibits maternal retrieving) significantly depressed responses on the active lever in response to DS. Surprisingly, injection of glutamatergic antagonists (or a sodium channel blocker) into NA did not depress responses on the active lever in response to DS but instead increased the number of responses performed on the inactive lever. Although these authors present their own model to explain these results, please note how our model presented in Figure 17 could also explain these results. The only change that would have to be made would be that hunger-related hypothalamic nuclei (rather than MPOA/vBST maternal circuits) would have to interact with the mesolimbic DA system (see Harris, Wimmer, & Aston-Jones, 2005). By inactivating NA with glutamatergic antagonists or sodium channel blockers, the VP would be tonically released from NA inhibition, and therefore, VP would respond to relevant and irrelevant stimuli.

There is one finding in the maternal literature that is somewhat similar to these results. Recall that it was found that NAs lesions or muscimol injections into NAs did not disrupt postpartum retrieving (Numan, Numan, Schwarz, et al., 2005). However, when we injected SCH 23390 into NAs, retrieving was disrupted for 1 to 2 hours (Numan, Numan, Pliakou, et al., 2005). Interestingly, Li and Fleming (2003b) reported that NAs lesions caused a mild disruption of retrieval behavior in postpartum rats. Whereas control females retrieved all their pups to the nest in about 2 min, the NAs-lesioned females took about 10 min. Their NAs-lesioned females

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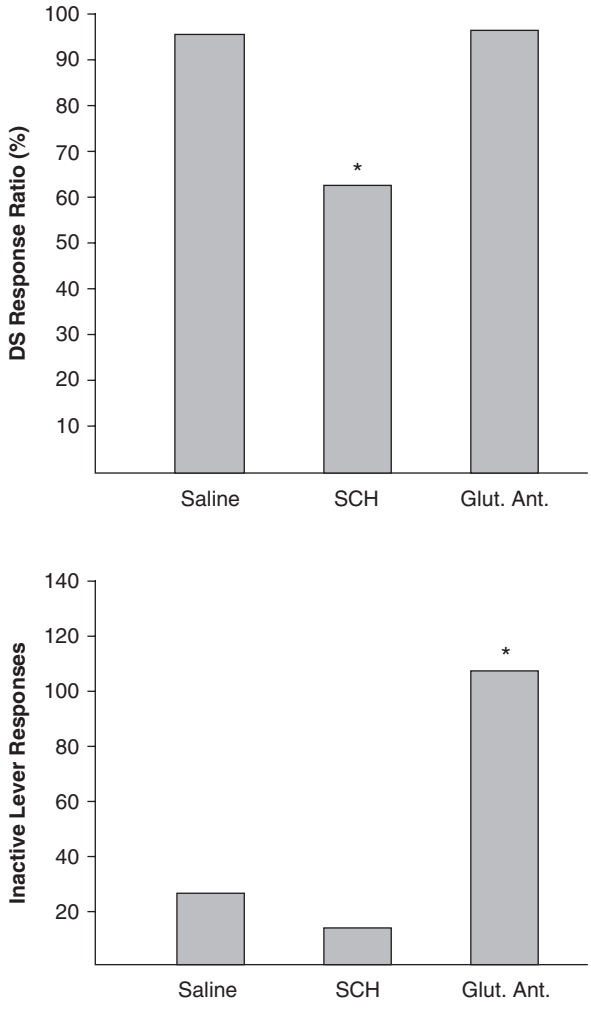

Figure 18: Rats Were Trained to Perform an Operant Bar-Press Response.

SOURCE: Data adapted from Yun, Nicola, and Fields (2004).

*Significantly different from the remaining groups.

NOTE: Pressing on an active lever during the occurrence of a discriminative stimulus (DS; tone) resulted in a food reward. An inactive lever was also present in the operant chamber, but responses on this lever were not rewarded. (A) The DS ratio is the number of active lever responses divided by the number of DS presentations. Control saline injections into nucleus accumbens (NA) were associated with a high DS ratio. The DS ratio was significantly depressed by the injection of SCH 23390 (a D1 antagonist) into NA but was not affected the injection of glutamate antagonists (Glut. Anat.) into NA, which would depress NA output. (B) The injection of Glut. Anat. into NA significantly increases operant responses on the inactive lever.

were slightly delayed because they appeared to be distracted by extraneous stimuli. Such females would retrieve some pups and then would engage in sniffing, rearing, and feeding before completing the retrieval of the remaining pups. It is as if by lesioning NAs, relevant and less relevant stimuli were capable of gaining access to VP response regulatory mechanisms.

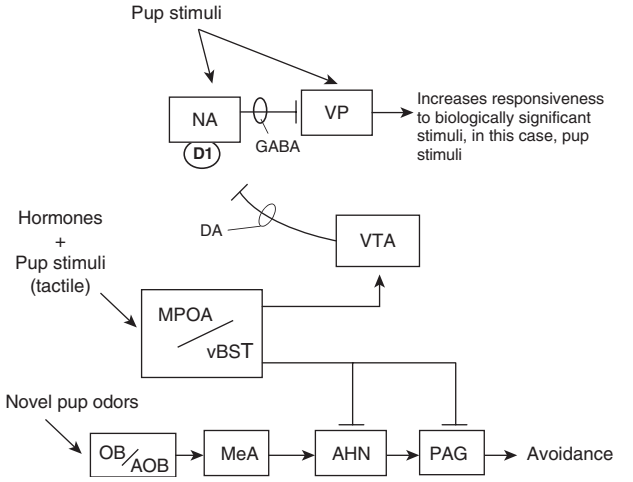

Figure 19: Overall Hypothetical Neural Model of the Regulation of Maternal Behavior.

NOTE: A hormonally primed medial preoptic area (MPOA)/ventral bed nucleus of the stria terminalis (vBST) is proposed to have two main effects. The first effect is to suppress the avoidance circuit defined in Figure 9. The second effect is to activate the mesolimbic dopamine (DA) system as outlined in Figure 17. See previous figure captions for definitions of all terms.

AN OVERALL VIEW

Figure 1 proposed a neural model whereby specific motivational systems should do two things: inhibit antagonist behavioral systems while increasing the organism's responsiveness to external stimuli relevant to the specific motivational state. Up to this point, I have tried to develop two strands of research findings that have fleshed out the model depicted in Figure 1. The full model of how hypothalamic maternal motivational systems perform these two important functions is shown in Figure 19. Future research, of course, is needed to further support and verify aspects of this model.

Within this model, I have referred to the mesolimbic DA system as a nonspecific motivational system. All that is meant by this is that the system is involved in regulating behavioral responsiveness to a wide variety of biologically significant stimuli. I do not rule out the possibility, however, that subcircuits within the NA-VP system may be involved in controlling particular sensory-motor linkages that are potentiated by DA; this would simply be the result of certain limbic and/or PFC inputs synapsing on particular NA and VP neurons, which in turn have different outputs (see Grillner et al., 2005; Pennartz et al., 1994).

OXYTOCIN AND MATERNAL BEHAVIOR

Oxytocin is a neuropeptide that is importantly involved in social behaviors, including maternal behavior.

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With respect to maternal behavior, this section describes the evidence that shows that oxytocin may exert facilitatory effects by acting at critical nodes in the neural circuitry (Figure 19) that I have just outlined.

Oxytocin, as a hormone, is released from the neural lobe of the pituitary into the general blood supply, and its physiological actions include stimulation of uterine contractions near the time of parturition and stimulation of the contractile elements in the mammary glands, which causes milk ejection in response to infant suckling during the postpartum period (Challis & Lye, 1994; Wakerley, Clarke, & Summerlee, 1994). In addition, oxytocin serves as a neurotransmitter/neuromodulator, being released at synapses in a variety of neural circuits within the brain; the main source, but not the only source, of oxytocinergic neural pathways arises from the paraventricular nucleus of the hypothalamus (PVN; Numan & Insel, 2003). Because oxytocin's peripheral functions are related to parturition and milk ejection, it is not surprising that its central functions included a role in parental responsiveness.

Electrical lesions of the PVN, when performed during pregnancy, disrupt the onset of maternal behavior at parturition, but when similar lesions are performed during the postpartum period, after maternal behavior has become established, they do not have a disruptive effect (Insel & Harbaugh, 1989; Numan & Corodimas, 1985). Therefore, PVN oxytocinergic neural circuits may be essential for the onset of maternal behavior but not its maintenance. In further support, intracerebroventricular (ICV) injection of oxytocin facilitates the onset of maternal behavior in rats that have been primed with estradiol (Fahrbach, Morrell, & Pfaff, 1984; Pedersen, Ascher, Monroe, & Prange, 1982), whereas ICV injection of oxytocin antagonists disrupts the onset of maternal behavior (but not the maintenance of established maternal behavior) in hormone-primed female rats and naturally parturient females (Fahrbach, Morrell, & Pfaff, 1985; Pedersen, Caldwell, Fort, & Prange, 1985; van Leengoed, Kerker, & Swanson, 1987). In addition to rats, it is also well established that central oxytocin is essential for the onset of maternal behavior in sheep at parturition (see Numan & Insel, 2003, for a review).

The current consensus is that one of the mechanisms through which the hormonal changes that occur at the end of pregnancy (declining progesterone levels and rising estradiol levels) stimulate the onset of maternal behavior is through the activation of oxytocinergic neural systems: These steroidal changes have been shown to stimulate oxytocin synthesis in the PVN and the synthesis of oxytocin receptors in diverse brain regions (Numan & Insel, 2003). Indeed, oxytocin receptors have been located in many brain regions that are involved in maternal behavior control, including MPOA, vBST, VTA, and NA (Champagne, Diorio, Sharma, & Meaney, 2001; Kremarik, Freund-Mercier, & Stoeckel, 1995; Pedersen, Caldwell, Walker, Ayers, & Mason, 1994; Veinante & Freund-Mercier, 1997). Importantly, Pedersen et al. (1994) have provided evidence that oxytocin binding sites in MPOA and VTA are necessary for the normal onset of maternal behavior at parturition in rats: Microinjection of an oxytocin antagonist into either region disrupted the onset of maternal behavior. Finally, in prairie voles, preliminary evidence suggests the involvement of NA oxytocin receptors in the maternal behavior of this species (Olazabal & Young, 2005). A likely possibility is that the hormonal events of late pregnancy set up a functional central oxytocinergic system near the time of parturition and that subsequent oxytocin release at diverse neural sites promotes the onset of maternal behavior by actions on these critical neural areas so that approach and attraction toward infant-related stimuli are enhanced while avoidance tendencies and defensive behavior are reduced. Because oxytocin appears most important for the onset of maternal behavior in rats, it can be suggested that once maternal behavior becomes established, these effects of oxytocin are no longer absolutely necessary.

An action of oxytocin on the MPOA/vBST, VTA, and NA in the stimulation of the onset of maternal behavior fits nicely with the work I have reviewed with respect to the interaction between the MPOA/vBST and the mesolimbic DA system in the regulation of attraction to pups and proactive voluntary maternal responses. It should be noted, however, that additional work suggests that oxytocin may modulate the processing of olfactory input by the olfactory bulb (Osako, Otsuka, Taniguchi, Oka, & Kaba, 2001; Yu, Kaba, Okutani, Takahashi, & Higuchi, 1996a, 1996b) in its regulation of the onset of maternal behavior in rats, and other work suggests that oxytocinergic neural pathways may influence the function of the amygdala to depress fear-related behaviors (Bale, Davis, Auger, Dorsa, & McCarthy, 2001). Therefore, in addition to an action on MPOA, NA, and VTA, oxytocin might directly influence olfactory processing and fearfulness, in this way promoting the onset of maternal behavior not only by increasing appetitive responses but also by decreasing avoidance responses to novel pup stimuli. In other words, oxytocin may not only decrease avoidance responses by promoting the MPOA output that has been hypothesized to depress a central aversion system but also by directly affecting elements within the central aversion system itself.

Some caveats are in order with respect to the statement that oxytocin neural pathways are important for the onset, but not the maintenance of, maternal behavior. This statement is based on the evidence that PVN lesions disrupt the onset, but not the maintenance of,

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maternal behavior and that the same results are observed if one administers an oxytocin antagonist ICV (Fahrbach et al., 1985; Pedersen, 1997). However, more recent evidence suggests that the administration of such antagonists during the postpartum period, although not preventing maternal behavior, can have subtle modulatory influences on the behavior, affecting the quantity and quality of nursing behavior and maternal grooming of pups (Champagne et al., 2001; Pedersen & Boccia, 2003). For example, ICV administration of an oxytocin antagonist decreases the incidence of the crouch-type nursing posture (an arched back and quiescent/immobile posture during which the dam is relatively unresponsive to external stimuli) in postpartum rats (Pedersen & Boccia, 2003), and this is significant because this particular nursing posture is induced by suckling stimulation (Stern & Johnson, 1990), which would also be expected to release oxytocin into a variety of brain regions. Furthermore, the effects of ICV administration of oxytocin antagonists on established maternal behavior have been examined only after acute intracerebral injections, and it is possible that the chronic administration of oxytocin antagonists during the postpartum period might have more profound effects on maternal responsiveness toward pups. Finally, although the PVN is the main source of oxytocinergic neural pathways, other nuclear groups also contain oxytocin neurons, and these may also be important for maternal behavior. Indeed, in a preliminary anatomical study, Shahrokh, Cameron, and Meaney (2005) have identified an oxytocinergic pathway between the MPOA and VTA of postpartum rats. One possibility is that this pathway is critical for the onset of maternal behavior (and might be activated by PVN oxytocinergic input to MPOA) and then plays a subsidiary role during the postpartum maintenance phase. Perhaps a glutamatergic MPOA/vBST projection to VTA is essential for both the onset and maintenance of maternal behavior in rats. It would be interesting to determine whether glutamate is colocalized with oxytocin in some MPOA-to-VTA circuits.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI) RECORDINGS OF MPOA ACTIVITY DURING NURSING BEHAVIOR IN RATS: ACTIVATION BY OXYTOCIN

A recent report on fMRI recordings of brain activity during suckling stimulation in postpartum rats is relevant to the issues discussed in the previous section (Febo, Numan, & Ferris, 2005). Between Days 4 and 8 postpartum, awake rats were placed in a magnet and through the use of blood oxygen level–dependent (BOLD) magnetic resonance imaging, the effects of the following stimuli on functional brain activity were measured: suckling stimulation, ICV oxytocin administration, and suckling stimulation in conjunction with ICV injection of an oxytocin receptor antagonist (OTA). In the MPOA, a positive BOLD response was induced by suckling stimulation. This positive response was abolished by concurrent ICV OTA administration, and ICV oxytocin administration in the absence of suckling also caused a positive BOLD response. These results make it highly likely that suckling stimulation-induced oxytocin release into the brain affects the MPOA so that the activity of this region is modified during maintenance phase of maternal behavior (ie, after the full establishment of maternal behavior).

An important issue is what is being measured by the BOLD signal. A positive BOLD signal is a direct measure of increased cerebral blood flow into a neural region (an increase in oxygenated hemoglobin), but the controversial issue is the question of the neural correlate of this increased blood flow (Attwell & Iadecola, 2002; Mukamel et al., 2005; Nair, 2005). A positive BOLD response could be due to increases in neural input to a brain nucleus, increases in the neural output of a nucleus, or increased neural processing within a nucleus that occurs without a concurrent increase in the output of the area. The latter possibility has clearly been shown from animal work on the cerebellum (Caesar, Gold, & Lauritzen, 2003; Caesar, Thomsen, & Lauritzen, 2003; Yang, Huard, Beitz, Ross, & Iadecola, 2000). In particular, increased activity in inhibitory interneurons, which suppress the output of a region of interest, could result in a positive BOLD response.

With these points in mind, it is difficult to interpret the MPOA BOLD response observed in the rat during suckling and oxytocin administration. The increased BOLD response in the MPOA may indicate that chronic suckling-induced intracerebral oxytocin release is directly or indirectly promoting functional changes in the MPOA, which are important for maintaining the mother-infant bond (see Febo et al., 2005). Another possibility is related to the fact that the interaction between the MPOA and the mesolimbic DA system is most important for proactive, voluntary maternal responses and is less involved in nursing behavior. Perhaps suckling-induced oxytocin release within the brain during the postpartum period is actually affecting inhibitory interneurons within MPOA so that its output is relatively suppressed and that such suppression would allow for the expression of the suckling-induced quiescent crouch nursing posture. Yet a third possibility is that the increased BOLD response in MPOA in response to suckling and oxytocin administration is not related to neuronal systems influencing maternal behavior but instead reflects activation of a neuroendocrine response, the milk ejection reflex, by a particular subset

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of MPOA neurons. However, the fact that oxytocin action on MPOA is known to influence maternal behavior suggests that this fMRI data may indeed be relevant to behavioral systems.

An interesting fMRI study on human mothers, which did not investigate the involvement of oxytocin, measured the BOLD response to the sound of an infant crying (Lorberbaum et al., 2002) and an increased BOLD signal in response to this stimulus was observed in the BST, hypothalamus, VTA, and NA-VP region (the striatum and pallidum were not spatially differentiated). Importantly, postscan emotional ratings indicated that the mothers felt an urge to help upon hearing the infant cry. These data might be interpreted as measuring brain correlates of active maternal states, and the increased BOLD response may be measuring increased hypothalamic (MPOA), vBST, and VP output and increased activity in NA inhibitory interneurons.

THE SPECIFICITY OF MPOA CIRCUITS REGULATING MATERNAL MOTIVATION

The hypothalamus is involved in the regulation of a variety of motivational states, which include hunger, thirst, aggression, male and female sexual motivation, and maternal motivation (Swanson, 1987). I have argued that there are neural circuits from the MPOA that are specific to (i.e., dedicated to) regulating maternal behavior. These neurons are proposed to be responsive to pup stimuli and to hormones, and through their projections to the mesolimbic DA systems and to the AHN/PAG, they are hypothesized to increase proactive voluntary maternal responses while decreasing defensive behavior and avoidance. This section examines in more detail the proposition that the MPOA contains neurons that are dedicated to maternal motivation.

An attractive hypothesis, derived from Stellar's (1954) early theoretical model of the physiology of motivation, is that there are separate hypothalamic nuclei that regulate each motivational state. Based on the theoretical model (see Figure 17), it could be argued that that separate and specific hypothalamic nuclei respond to the cues relevant to the motivational state that they regulate, and then, through interactions with the mesolimbic DA system, these nuclei control appetitive voluntary responses appropriate to the specific motivational state (through the gating of the relevant stimuli through the NA-VP circuit). For example, specific neurons in the MPOA, dedicated to maternal behavior, may respond to estradiol, prolactin, oxytocin, and pup stimuli, and through projections to the mesolimbic DA system, this network would control appetitive responses toward pup-related stimuli. I have already described, in detail, the evidence for this proposal. With respect to hunger and appetitive behavior related to the acquisition of food, a separate and distinct set of hypothalamic nuclei (e.g., neurons in the lateral hypothalamus [LH] and the arcuate nucleus [ARC]) would respond to food-related stimuli and the internal environment (leptin levels, glucose levels), and then, through projections to the mesolimbic DA system, these nuclei would control the occurrence of proactive voluntary responses relevant to the acquisition of food. These examples describe what I have referred to as an interaction between specific and nonspecific motivational systems.

There is evidence that distinct neural circuits may regulate different basic motivational states, and importantly, in some cases, these separate neural circuits may reside within a larger general nucleus. For example, separate subnuclei within the MeA may project to separate subnuclei within the ventromedial hypothalamic nucleus (and other hypothalamic nuclei) to regulate responses to distinct pheromonal cues that are relevant to either defensive aggression or reproduction (Choi et al., 2005). This finding is extremely important because it suggests that separate microcircuits could exist within a hypothalamic nucleus, which in turn regulate separate behavioral states. In addition, there is recent evidence that LH and ARC neurons may project to parts of the mesolimbic DA system to regulate appetitive food-seeking behaviors (Harris et al., 2005; Kelley, Baldo, & Pratt, 2005).

In apparent opposition to the view that there are distinct hypothalamic circuits that regulate different motivational states is the perspective of Newman (1999), who emphasized the large amount of overlap in the neural circuits that regulate a diverse set of social behaviors (male and female sexual behavior, offensive aggression, parental behavior) in mammals. In partial support of this view, she noted that Fos expression is activated in the MPOA and other hypothalamic nuclei during each of these social behaviors. She proposed that there may be a common central network that regulates a variety of social behaviors, and just which behavior occurs may be determined by the stimuli that have access to this circuit.

The best evidence for the statement that the MPOA may contain general social behavior neurons that influence the motivational aspects of more than one social behavior comes from a comparison of the neural regulation of maternal behavior and male sexual behavior in rodents. It has long been known that there is a striking similarity in the neural control of male sexual behavior and maternal behavior in rodents (Numan, 1974, 1985): Lesions of the MPOA and knife cuts severing the lateral connections of the MPOA disrupt, and estradiol action on the MPOA facilitates, both behaviors. More recent studies have reported that the microinjection of L-NAME into the MPOA of postpartum female rats or male rats disrupts the maternal retrieval response

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(Popeski & Woodside, 2004; Service & Woodside, 2005) and male sexual behavior (Dominguez & Hull, 2005), respectively. L-NAME is a nitric oxide synthase inhibitor and therefore would interfere with nitric oxide (NO) production. These results suggest that NO may serve as an important neuromodulator controlling the function of MPOA neurons that influence both male sexual behavior and maternal behavior. Finally, the injection of DA antagonists into MPOA, which would disrupt incerto-hypothalamic DA input to MPOA neurons, has been found to disrupt both male sexual behavior (Dominguez & Hull, 2005) and maternal behavior (Miller & Lonstein, 2005) in rats. It is possible that NO interaction with DA within MPOA regulates both behaviors (see Domiguez & Hull, 2005, for evidence on this interaction with respect to male sexual behavior).

I have presented evidence that the MPOA interacts with the mesolimbic DA system in the control of appetitive maternal responses. Similar evidence is not available for male sexual behavior (or other social behaviors). However, the following points are worth considering: (a) The mesolimbic DA system is involved in the appetitive aspects of male sexual behavior (Damsma, Pfaus, Wenkstern, Phillips, & Fibiger, 1992; Everitt, 1990; Pfaus & Phillips, 1991) and other social behaviors (see Numan & Insel, 2003), which is what one would expect from a nonspecific motivational system, and (b) MPOA efferents project to VTA (Numan & Numan, 1996; Simerly & Swanson, 1988). Therefore, it makes sense to argue that MPOA projections to the mesolimbic DA system influence the motivational aspects of male sexual behavior.

If MPOA projections to the VTA are involved in both male sexual behavior and maternal behavior (and other social behaviors), an important question is whether the same MPOA neurons are involved in different social behaviors. Gray and Brooks (1984) examined this issue. They found that lesions of the rostral or middle MPOA, but not the caudal MPOA, disrupted maternal behavior in rats, whereas lesions of the rostral, middle, or caudal MPOA disrupted male sexual behavior. From these data, they suggested that different neural circuits in the MPOA regulate the two behaviors. However, an alternative interpretation is possible, which is based on the distinction between appetitive and consummatory aspects of behavior.

The appetitive component of a goal directed behavior is composed of those behaviors which bring an organism in contact with a desired stimulus, whereas the consummatory component is made up of those behaviors that are performed once contact with the attractive stimulus is attained (Ikemoto & Panksepp, 1999). The MPOA is involved in the appetitive aspects of maternal behavior. The major effect of MPOA lesions is a disruption of retrieval behavior, which can be considered an appetitive maternal response: it allows females to return pups to a nest site where the consummatory response of nursing can take place. In addition, Fos expression is activated in the MPOA when a female is searching for her pups (Mattson & Morrell, 2005). Finally, MPOA lesions disrupt the ability of postpartum females to perform an operant bar press response when pups, but not food, are used as a reward (Lee et al., 2000). An interesting study on MPOA involvement in the male sexual behavior of quails was performed by Balthazart, Absil, Gerard, Appeltants, and Ball (1998). They examined the consummatory phase by examining copulatory activity. The appetitive aspect was examined through the use of a learned social proximity procedure that measured the time spent by a male in front of a window with a view of the female prior to the female's release into the male's cage. They found that lesions to the rostral MPOA disrupted both the appetitive and consummatory aspects of male sexual behavior, whereas lesions to the caudal MPOA disrupted only consummatory responses.

One conclusion from all these data is that there may be a pool of neurons in the rostral–to-middle MPOA that regulates the appetitive aspects of both male sexual behavior and maternal behavior. The important question, which future research will need to tackle, is whether such appetitive maternal neurons and appetitive male sexual behavior neurons are the same or different. Following Choi et al. (2005), I suggest that separate microcircuits within the rostral-to-middle MPOA may regulate the two behaviors. However, if Newman's (1999) view is correct, and the same neural elements in MPOA control the appetitive aspects of maternal behavior, male sexual behavior, and other social behaviors, then I will have to determine how I arrive at behavioral specificity. One possibility is that hormonal, genetic, and other factors may prepare a general appetitive MPOA neural pool to be activated by certain types of stimuli and not others at a particular point in time (Newman, 1999; Numan & Insel, 2003).

MATERNAL MEMORY

Recall that in first-time mothers of many species, the hormonal events of late pregnancy are critically involved in stimulating the onset of maternal behavior at parturition. Maternal memory, or the maternal experience effect, refers to the fact that adult maternal experience in rats and other species can render the onset of future maternal behavior less dependent on hormonal stimulation (Numan & Insel, 2003). The classic studies were done by Bridges (1975, 1977, 1978), who allowed primiparous mother rats to care for their young for the first 1 or 2 days postpartum and then removed the pups. An additional group of primiparous females had

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each of their pups removed as soon as they were born, in this way denying the mothers any maternal experience. Twenty-five days later, all females were exposed to foster test pups, and sensitization latencies to the onset of maternal behavior were recorded. The onset latencies of the experienced females averaged 1 to 2 days, which were significantly shorter than the 5-day onset latencies shown by the females who were not allowed postpartum maternal experience. The latencies of these latter females did not differ from those shown by naïve virgin females. These findings were confirmed by Orpen and Fleming (1987), who also showed that full interaction with pups was necessary for the development of maternal memory: Females who were exposed only to exteroceptive or distal stimuli from pups (they could see, hear, and smell the pups but could not interact with them) on the day of parturition did not show a heightened maternal responsiveness to full pup presentation when tested 10 days later.

These results indicate that maternal experience in primiparous females partly emancipates future maternal behavior from the control of the hormonal events associated with pregnancy termination. I use the term *partial emancipation* because the maternally experienced females still require a day or two of pup stimulation before they show complete maternal behavior. The maternal experience effect implies that some sort of synaptic plasticity may underlie maternal memory. There is a significant literature on this issue (see Numan & Insel, 2003), and several neural changes that mediate this effect may occur at many levels of the nervous system. In reference to Figure 19, one or more of the following mechanisms may be involved. There may be (a) a down-regulation of synaptic strength in the central aversion system that connects olfactory input to MeA and AHN/PAG (in fact, some sort of olfactory learning may take place that permanently suppresses the aversive characteristics of pup odors so that they no longer promote withdrawal or avoidance responses), (b) a synaptic reorganization of the MPOA so that it can be effectively activated by pup stimuli in the absence of hormonal effects, and (3) a modification of different components of the mesolimbic DA system so that it functions effectively despite decreased activation by MPOA efferents.

I want to focus on the last possibility in reference to some relatively recent work from Fleming's lab (Lee, Watchus, & Fleming, 1999; Li & Fleming, 2003a) and in the context of the model presented in Figure 17. These investigators found that electrical lesions of NAs, performed during pregnancy, did not disrupt the onset of maternal behavior at parturition but did disrupt maternal memory mechanisms. NAs-lesioned females and sham-lesioned females, with both groups showing normal maternal behavior, were allowed 12 to 24 hours of maternal experience after parturition before their pups were removed. Ten days later, they were given a retention test to examine maternal memory. Whereas the sham-lesioned females showed short sensitization latencies, averaging 1 to 3 days, when testing was initiated on Day 10, the NAs-lesioned females showed long sensitization latencies (about 7 days), which was similar to the level of responsiveness shown by naïve virgin females. Importantly, if females received NAs lesions 24 hr after the maternal experience (rather than before the experience), maternal memory was intact, and such females showed heightened maternal responsiveness on the retention sensitization test. These results suggest that the nucleus accumbens is involved in the consolidation of maternal memory but that the synaptic modifications that underlie this memory occur at a neural site outside NAs.

In considering the neural model shown in Figure 17, how can I account for these results? First, I have argued that the NAs needs to be inhibited, with a concomitant disinhibition of VP, for maternal behavior to occur. The finding from Fleming's group that NAs lesions do not disrupt the onset of maternal behavior at parturition clearly fits with this view and previous work (Numan, Numan, Schwarz, et al., 2005). But why should such lesions disrupt the formation of maternal memory, and how could I describe the mechanism wherein the NAs would not be necessary for maternal behavior per se but would be involved in the formation of maternal memory? At this point, I can only offer a very preliminary hypothesis, which is based on the possibility that a low level of NAs activity during maternal behavior is in some way involved in the strengthening of synaptic connections within the VP. Before I describe this hypothetical model, additional information on the anatomy of the NA-VP circuit and on the maternal experience effect is reviewed.

D1 and D2 receptors are located on separate groups of GABAergic medium spiny neurons that project from NAs to VP: D1 receptors are located on GABAergic neurons that also contain substance P, and D2 receptors are located on those GABAergic neurons that colocalize with enkephalin (Lu et al., 1998; G. S. Robertson & Jian, 1995). In the context of this anatomy, the following findings are relevant: Systemic treatment with a D2 dopamine receptor antagonist has been found to interfere with the formation of maternal memory in rats (Byrnes, Rigero, & Bridges, 2002), and ICV administration of a μ opioid receptor antagonist, although not interfering with the onset of maternal behavior at parturition, has similarly been found to interfere with the formation of maternal memory (Byrnes & Bridges, 2000). Although these two studies did not localize the neural sites of action of the injected drugs, it is intriguing to

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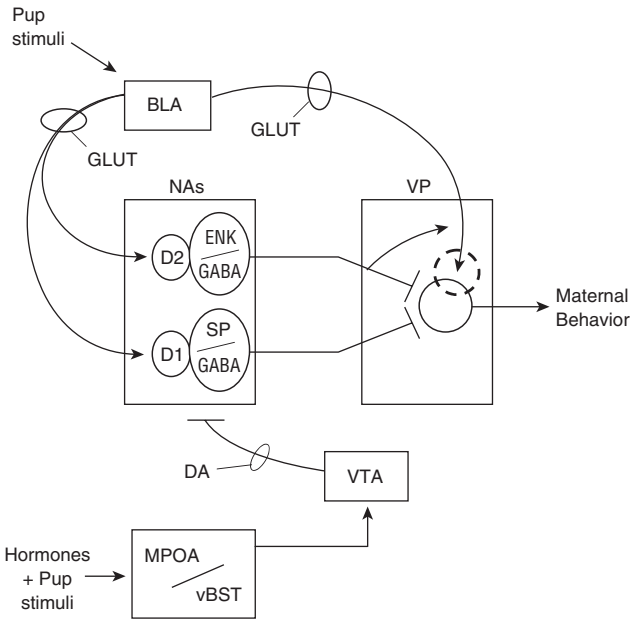

Figure 20: Hypothetical Neural Model to Explain How Nucleus Accumbens Shell (NAs) D2 Dopamine Receptors and NAs Enkephalinergic Efferents Might Be Necessary for Maternal Memory Even Though NAs Lesions Do Not Disrupt Maternal Behavior in Hormone-Primed Postpartum Females.

NOTE: The basolateral amygdala (BLA) is shown as receiving input from pup stimuli (which could arise for the cortex or thalamus) and sending excitatory projections to both NAs and ventral pallidum (VP). Inhibitory NAs outputs to VP are shown as arising from two sources: gamma-aminobutyric acid (GABA) neurons that also contain enkephalin (Enk) and D2 receptors and GABA neurons that also contain substance P (SP) and D1 receptors. It is proposed that when a hormone-primed medial preoptic/ventral bed nucleus region (MPOA/vBST) activates ventral tegmental area (VTA) dopamine (DA) input to NAs, the output of NA is depressed, and this facilitates maternal responses because the VP is disinhibited. It is further hypothesized that low levels of enkephalin release into VP may play a role in strengthening BLA-to-VP synapses so that in the future, even if the MPOA/vBST projection to VTA is less active because the MPOA/vBST is no longer hormone primed, pup stimuli might still be capable of eliciting maternal responsiveness (maternal memory). See the text for additional details.

speculate that they are acting within NA-VP circuitry. Because we have emphasized the importance for DA acting on D1 receptors in NAs for the display of maternal behavior, these results suggest that separate circuits within the NA-VP network may be involved in maternal motivation and maternal memory. It is worth pointing out that studies on prairie voles investigating the synaptic plasticity changes that underlie the formation of long-lasting social attachments between mates has also emphasized the positive involvement of DA action on D2 receptors in NAs (Gingrich, Liu, Cascio, Wang, & Insel, 2000; Liu & Wang, 2003).

Although separate neural circuits may be involved in maternal motivation and maternal memory, one would expect that they should interact in some way because the formation of maternal memory involves a heightened maternal responsiveness at a later point in time. In other words, as a result of maternal memory, females respond quickly to pups without hormonal stimulation. A study by Mitrovic and Napier (1998) may be relevant to such an interaction in the context of the neural model shown in Figure 17. First, they provide evidence that some neurons in VP receive inputs from both substance P– and enkephalin-containing NA neurons. Next, they recorded the electrical activity of VP neurons that were excited by electrical stimulation of a basolateral amygdala (BLA) glutamatergic input to VP. Most important, they found that iontophoretic injections of low doses of DAMGO, a μ opioid receptor agonist, into VP facilitated the excitatory effects produced by amygdaloid stimulation. In contrast, high doses of DAMGO inhibited VP neurons. Before we present our speculative model, it should be noted that work on the dorsal striatum (caudate putamen) shows that DA action on D2 receptors depresses enkephalin synthesis (Gerfen, 1992). The maternal memory model is shown in Figure 20. During the onset of maternal behavior at parturition, the MPOA is primed by hormones and responds to pup stimuli so that efferents to the VTA are strongly activated. Increased DA input to the NA acts to depress GABAergic input to VP through an action of both D1 and D2 receptors, although my work suggests the primary importance of an action on D1 receptors. This depression of GABAergic input to VP allows the VP to respond to pup stimuli inputs carried by the amygdala and prefrontal cortex as already described. In addition, I argue that DA action on D2 receptors decreases enkephalin synthesis to low levels so that only a small amount of enkephalin is released into VP. In the model, this low-level release of enkephalin is shown to facilitate the excitatory effects of glutamate from BLA synapses on to VP neurons. Although I have drawn this as a presynaptic facilitatory effect, the actual mechanism has not been clearly defined (Mitrovic & Napier, 1998). This enkephalinergic facilitation of BLA glutamatergic activation of VP might contribute to the long-term strengthening of the BLA-to-VP synapse, possibly by recruiting N-methyl-D-aspartate receptor-activated synaptic strengthening mechanisms. Similar mechanisms may occur at PFC-to-VP synapses. At subsequent points in time, when the effects of hormonal activation of MPOA have waned, these strengthened synapses may be one of the elements involved in maternal memory. According to this very speculative model, the enkephalin-induced amygdala-to-VP strengthened synapse would have to play a very important role in maternal memory because NA lesions block this memory formation despite the fact that such lesions would also decrease GABAergic inhibition of VP.

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This model, along with the experimental results discussed, also makes one realize that the MPOA must be doing more than just depressing NA output to VP and regulating enkephalin release into VP in its control of maternal behavior. Two facts highlight this statement: NA lesions do not appear to facilitate maternal behavior in non-hormone-primed rats, even though such lesions should decrease NA GABAergic inhibition of VP (Li & Fleming, 2003a) and MPOA lesions disrupt maternal behavior in primiparous and multiparous rats (Franz, Leo, Steuer, & Kristal, 1986; Numan & Insel, 2003). Clearly, MPOA interactions with the mesolimbic DA system may be just one element in a complicated MPOA circuitry involved in maternal behavior control. As already reviewed, MPOA suppression of avoidance responses may be important during all phases of maternal behavior. In addition, some MPOA efferents may directly regulate the consummatory (as opposed to the appetitive) aspects of maternal behavior through connections with brainstem motor mechanisms (see Numan & Insel, 2003, for a more comprehensive discussion of these issues).

CONCLUSIONS

A theoretical neural model of the regulation of maternal motivation in mammals has been presented. Although a substantial body of evidence has been used to create the model, it is clear that much more research will be needed to validate it. In fact, because the present model has evolved from earlier ones (Numan, 1985, 1988), it should be viewed as a work in progress that will be updated as new findings accrue.

The importance of the model is that it integrates current research on the neural basis of maternal behavior into a coherent scheme that should stimulate and focus future research. Significantly, the model is not only relevant to maternal behavior but also has important implications for a general understanding of hypothalamic involvement in motivation (see Risold, Thompson, & Swanson, 1997, which influenced aspects of the current model).

The model is also relevant to an understanding of the operations of the NA-VP circuit and its control by DA in the regulation of general appetitive processes. In this regard, it should be noted that much more research is available on the mechanistic operations of the dorsal striatum (caudate-putamen) when compared to the ventral striatum (nucleus accumbens), and it is not clear whether the two systems share the same exact operating principles. Although it might make sense to use research on the dorsal striatal system as a template for understanding NA function, my research suggests that differences may exist in the way the two systems work. Finally, research on the dorsal striatum has identified direct and indirect output circuits that have opposing influences on motor control (Gerfen, 1992). It is not clear whether analogous output circuits emanate from NA, but if such circuits are uncovered, they may provide important insights into the way in which general appetitive processes are neurally regulated.

Finally, elements of the model may be defining a core neural circuitry for maternal behavior in mammals. Species may differ in the degree to which pregnancy hormones stimulate maternal behavior and in the degree to which inexperienced females exhibit avoidance responses toward infants. However, the neural circuits that regulate proactive voluntary maternal responses, which are located, in part, in the phylogenetically older parts of the brain, are likely to contribute to maternal responsiveness in most mammals, including primates. A disruption in the operation of these circuits may contribute to pathological disorders associated with maternity in humans (see Numan & Insel, 2003).

REFERENCES

Attwell, D., & Iadecola, C. (2002). The neural basis of functional brain imaging signals. *Trends in Neurosciences*, *25*, 621-625.

Bakowska, J. C., & Morrell, J. I. (1997). Atlas of the neurons that express mRNA for the long form of the prolactin receptor in the forebrain of the female rat. *Journal of Comparative Neurology*, *386*, 161-177.

Bale, T. L., Davis, A. M., Auger, A. P., Dorsa, D. M., & McCarthy, M. M. (2001). CNS region-specific oxytocin receptor expression: Importance in regulation of anxiety and sex behavior. *Journal of Neuroscience*, *21*, 2546-2552.

Balthazart, J., Absil, P., Gerard, M., Appeltants, D., & Ball, G. F. (1998). Appetitive and consummatory male sexual behavior in Japanese quail are differentially regulated by subregions of the preoptic medial nucleus. *Journal of Neuroscience*, *18*, 6512-6527.

Bandler, R., & Shipley, M. T. (1994). Columnar organization of the midbrain periaqueductal gray: Modules for emotional expression. *Trends in Neurosciences*, *17*, 379-389.

Becker, J. B., Rudnick, C. N., & Jenkins, W. J. (2001). The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. *Journal of Neuroscience*, *21*, 3236-3241.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*, 309-369.

Bridges, R. S. (1975). Long-term effects of pregnancy and parturition upon maternal responsiveness in the rat. *Physiology & Behavior*, *14*, 245-249.

Bridges, R. S. (1977). Parturition: Its role in the long term retention of maternal behavior in the rat. *Physiology & Behavior*, *18*, 487-490.

Bridges, R. S. (1978). Retention of rapid onset of maternal behavior during pregnancy in primiparous rats. *Behavioral Biology*, *24*, 113-117.

Bridges, R. S., Mann, P. E., & Coppeta, J. S. (1999). Hypothalamic involvement in the regulation of maternal behavior in the rat: Inhibitory roles for the ventromedial hypothalamus and the dorsal/anterior hypothalamic areas. *Journal of Neuroendocrinology*, *11*, 259-266.

Bridges, R. S., Numan, M., Ronsheim, P. M., Mann, P. E., & Lupini, C. E. (1990). Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. *Proceedings of the National Academy of Sciences of the United States of America*, *87*, 8003-8007.

Bridges, R. S., Robertson, M. C., Shiu, R. P. C., Sturgis, J. D., Henriquez, B. M., & Mann, P. E. (1997). Central lactogenic regulation of maternal behavior in rats: Steroid dependence, hormone specificity, and behavioral potencies of rat prolactin and rat placental lactogen 1. *Endocrinology*, *138*, 756-763.

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Brog, J. S., Salyapongse, A., Deutch, A. Y., & Zahm, D. S. (1993). The pattern of afferent innervation of the core and shell of the "accumbens" part of the rat ventral striatum: Immunohistochemical detection of retrogradely transported fluoro-gold. *Journal of Comparative Neurology, 338*, 255-278.

Brown, J. R., Ye, H., Bronson, R. T., Dikkes, P., & Greenberg, M. E. (1996). A defect in nurturing in mice lacking the immediate early gene *fosB*. *Cell, 86*, 297-309.

Buntin, J. D. (1996). Neural and hormonal control of parental behavior in birds. In J. S. Rosenblatt & C. T. Snowdon (Eds.), *Advances in the study of behavior* (Vol. 25, pp. 161-213). San Diego, CA: Academic Press.

Byrnes, E. M., & Bridges, R. S. (2000). Endogenous opioid facilitation of maternal memory in rats. *Behavioral Neuroscience, 114*, 797-804.

Byrnes, E. M., Rigero, B. A., & Bridges, R. S. (2002). Dopamine antagonists during parturition disrupt maternal care and the retention of maternal behavior in rats. *Pharmacology, Biochemistry, and Behavior, 73*, 869-875.

Caesar, K., Gold, L., & Lauritzen, M. (2003). Context sensitivity of activity-dependent increases in cerebral blood flow. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 4239-4244.

Caesar, K., Thomsen, K., & Lauritzen, M. (2003). Dissociation of spikes, synaptic activity, and activity-dependent increments in rat cerebellar blood flow by tonic synaptic inhibition. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 16000-16005.

Canteras, N. S., Simerly, R. B., & Swanson, L. W. (1995). Organization of projections from the medial nucleus of the amygdala: A PHAL study in the rat. *Journal of Comparative Neurology, 360*, 213-245.

Challis, J. R. G., & Lye, S. J. (1994). Parturition. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (Vol. 2, pp. 985-1031). New York: Raven Press.

Champagne, F., Diorio, J., Sharma, S., & Meaney, M. J. (2001). Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proceedings of the National Academy of Sciences of the United States of America, 98*, 12736-12741.

Champagne, F. A., Chretien, P., Stevenson, C. W., Zhang, T. Y., Gratton, A., & Meaney, M. J. (2004). Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *Journal of Neuroscience, 24*, 4113-4123.

Charara, A., & Grace, A. A. (2003). Dopamine receptor subtypes selectively modulate excitatory afferents from the hippocampus and amygdala in rat nucleus accumbens neurons. *Neuropsychopharmacology, 28*, 1412-1421.

Cheer, J. F., Heien, M. A. L. V., Garris, P. A., Carelli, R. M., & Wrightman, R. M. (2005). Simultaneous dopamine and single-unit recordings reveal accumbens GABAergic responses: Implications for intracranial self-stimulation. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 19150-19155.

Choi, G. B., Dong, H., Murphy, A. J., Valenzuela, D. M., Yancopoulus, G. D., Swanson, L. W., et al. (2005). Lhx6 delineates a pathway mediating innate reproductive behaviors from the amygdala to the hypothalamus. *Neuron, 46*, 647-660.

Damsma, G., Pfaus, J. G., Wenkstern, D., Phillips, A. G., & Fibiger, H. C. (1992). Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: Comparison with novelty and locomotion. *Behavioral Neuroscience, 106*, 181-191.

Deutch, A. Y., Goldstein, M., Baldino, F., & Roth, R. H. (1988). Telencephalic projections of the A8 dopamine cell group. *Annals of the New York Academy of Sciences, 537*, 27-50.

Dominguez, J. M., & Hull, E. M. (2005). Dopamine, the medial preoptic area, and male sexual behavior. *Physiology & Behavior, 86*, 356-368.

Everitt, B. J. (1990). Sexual motivation: A neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats. *Neuroscience and Biobehavioral Reviews, 14*, 214-232.

Fahrbach, S. E., Morrell, J. I., & Pfaff, D. W. (1984). Oxytocin induction of short-latency maternal behavior in nulliparous, estrogen-primed female rats. *Hormones and Behavior, 18*, 267-286.

Fahrbach, S. E., Morrell, J. I., & Pfaff, D. W. (1985). Possible role for endogenous oxytocin in estrogen-facilitated maternal behaviour in rats. *Neuroendocrinology, 40*, 526-532.

Fahrbach, S. E., Morrell, J. I., & Pfaff, D. W. (1986). Identification of medial preoptic neurons that concentrate estradiol and project to the midbrain in the rat. *Journal of Comparative Neurology, 247*, 364-382.

Febo, M., Numan, M., & Ferris, C. F. (2005). Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. *Journal of Neuroscience, 25*, 11637-11644.

Fleming, A. S., Cheung, U. S., Myhal, N., & Kessler, Z. (1989). Effects of maternal hormones on "timidity" and attraction to pup-related odors in female rats. *Physiology & Behavior, 46*, 449-453.

Fleming, A. S., & Korsmit, M. (1996). Plasticity in the maternal circuit: Effects of maternal experience on Fos-Lir in hypothalamic, limbic, and cortical structures in the postpartum rat. *Behavioral Neuroscience, 110*, 567-582.

Fleming, A. S., & Luebke, C. (1981). Timidity prevents the nulliparous female from being a good mother. *Physiology & Behavior, 27*, 863-868.

Fleming, A. S., & Rosenblatt, J. S. (1974). Olfactory regulation of maternal behavior in rats: II. Effects of peripherally induced anosmia and lesions of the lateral olfactory tract in pup-induced virgins. *Journal of Comparative and Physiological Psychology, 86*, 233-246.

Fleming, A. S., Vaccarino, F., & Luebke, C. (1980). Amygdaloid inhibition of maternal behavior in the nulliparous female rat. *Physiology & Behavior, 25*, 731-743.

Fleming, A. S., Vaccarino, F., Tambosso, L., & Chee, P. (1979). Vomeronasal and olfactory system modulation of maternal behavior in the rat. *Science, 203*, 372-374.

Franz, J. J., Leo, R. J., Steuer, M. A., & Kristal, M. B. (1986). Effects of hypothalamic knife cuts and experience on maternal behavior in the rat. *Physiology & Behavior, 38*, 629-640.

Fuchs, S. A. G., Edinger, H. M., & Siegel, A. (1985). The organization of the hypothalamic pathways mediating affective defense behavior in the cat. *Brain Research, 330*, 77-92.

Fuller, T. A., Russchen, F. T., & Price, J. L. (1987). Sources of presumptive glutamatergic/aspartergic afferents to rat ventral striatopallidal region. *Journal of Comparative Neurology, 258*, 317-338.

Gaffori, O., & Le Moal, M. (1979). Disruption of maternal behavior and the appearance of cannibalism after ventral mesencephalic tegmentum lesions. *Physiology & Behavior, 23*, 317-323.

Georges, F., & Aston-Jones, G. (2002). Activation of ventral tegmental area cells by the bed nucleus of the stria terminalis: A novel excitatory amino acid input to midbrain dopamine neurons. *Journal of Neuroscience, 22*, 5173-5187.

Gerfen, C. R. (1992). The neostriatal mosaic: Multiple levels of compartmental organization. *Trends in Neurosciences, 15*, 133-138.

Gingrich, B., Liu, Y., Cascio, C., Wang, Z., & Insel, T. R. (2000). Dopamine D2 receptors in the nucleus accumbens are important for social attachment in female prairie voles (*Microtus ochrogaster*). *Behavioral Neuroscience, 114*, 173-183.

Gong, W., Neill, D., & Justice, J. B. (1997). 6-Hydroxydopamine lesion of the ventral pallidum blocks acquisition of place preference conditioning to cocaine. *Brain Research, 754*, 103-112.

Gray, P., & Brooks, P. J. (1984). Effect of lesion location within the medial preoptic-anterior hypothalamic continuum on maternal and male sexual behaviors in female rats. *Behavioral Neuroscience, 98*, 703-711.

Grillner, S., Hellgren, J., Menard, A., Saitoh, K., & Wikstrom, M. A. (2005). Mechanisms for selection of basic motor programs—Roles for the striatum and pallidum. *Trends in Neurosciences, 28*, 364-370.

Hansen, S., Bergvall, A. H., & Nyiredi, S. (1993). Interaction with pups enhances dopamine release in the ventral striatum of maternal rats: A microdialysis study. *Pharmacology, Biochemistry and Behavior, 45*, 673-676.

Hansen, S., Harthon, C., Wallin, E., Lofberg, L., & Svensson, K. (1991a). The effects of 6-OHDA-induced dopamine depletions in the ventral and dorsal striatum on maternal and sexual behavior in the female rat. *Pharmacology, Biochemistry and Behavior, 39*, 71-77.

Hansen, S., Harthon, C., Wallin, E., Lofberg, L., & Svensson, K. (1991b). Mesotelencephalic dopamine system and reproductive behavior

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in the female rat: Effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. *Behavioral Neuroscience, 105*, 588-598.

Harris, G. C., Wimmer, M., & Aston-Jones, G. (2005). A role for the lateral hypothalamic orexin neurons in reward seeking. *Nature, 437*, 556-559.

Harvey, J., & Lacey, M. G. (1997). A postsynaptic interaction between dopamine D1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. *Journal of Neuroscience, 17*, 5271-5280.

Hinde, R. A. (1970). *Animal behaviour*. New York: McGraw-Hill.

Hunt, G. E., & McGregor, I. S. (2002). Contrasting effects of dopamine antagonists and frequency induction of Fos expression induced by lateral hypothalamic stimulation. *Behavioural Brain Research, 132*, 187-201.

Ikemoto, S., & Panksepp, J. (1999). The role of nucleus accumbens dopamine in motivated behavior: A unifying interpretation with special reference to reward-seeking. *Brain Research Reviews, 31*, 6-41.

Insel, T. R., & Harbaugh, C. R. (1989). Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. *Physiology & Behavior, 45*, 1033-1041.

Jacobson, C. D., Terkel, J., Gorski, R. A., & Sawyer, C. H. (1980). Effects of small medial preoptic area lesions on maternal behavior: Retrieving and nestbuilding in the rat. *Brain Research, 194*, 471-478.

Keefe, K. A., & Gerfen, C. R. (1995). D1-D2 dopamine receptor synergy in striatum: Effects of intrastriatal infusions of dopamine agonists and antagonists on immediate early gene expression. *Neuroscience, 66*, 903-913.

Keer, S. E., & Stern, J. M. (1999). Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieving and licking, but enhances nursing behavior in lactating rats. *Physiology & Behavior, 67*, 659-669.

Kelley, A. E., Baldo, B. A., & Pratt, W. E. (2005). A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. *Journal of Comparative Neurology, 493*, 72-85.

Kelley, A. E., & Berridge, K. C. (2002). The neuroscience of natural rewards: Relevance to addictive drugs. *Journal of Neuroscience, 22*, 3306-3311.

Kinsley, C. H., & Bridges, R. S. (1990). Morphine treatment and reproductive condition alter olfactory preferences for pup and adult male odors in female rats. *Developmental Psychobiology, 23*, 331-347.

Klitenick, M. A., Deutch, A.Y., Churchill, L., & Kalivas, P. W. (1992). Topography and functional role of dopaminergic projections from the ventral mesencephalic tegmentum to the ventral pallidum. *Neuroscience, 50*, 371-386.

Koos, T., & Tepper, J. M. (1999). Inhibitory control of neostriatal projection neurons by GABAergic interneurons. *Nature Neuroscience, 2*, 467-472.

Kremarik, P., Freund-Mercier, M. J., & Stoeckel, M. E. (1995). Oxytocin and vasopressin binding sites in the hypothalamus of the rat: Histautoradiographic detection. *Brain Research Bulletin, 36*, 195-203.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155-184.

Lee, A., Clancy, S., & Fleming, A. S. (2000). Mother rats bar-press for pups: Effects of lesions of the MPOA and limbic sites on maternal behavior and operant responding for pup–reinforcement. *Behavioural Brain Research, 108*, 215-231.

Lee, A., Watchus, J., & Fleming, A. S. (1999). Neuroanatomical basis of maternal memory in postpartum rats: Selective role for the nucleus accumbens. *Behavioral Neuroscience, 113*, 523-538.

Levy, F., Ferreira, G., Keller, M., Meurisse, M., & Perrin, G. (2005). Neural substrates involved in the control of maternal responsiveness and maternal selectivity are different in sheep. *Developmental Psychobiology, 47*, 436.

Li, M., & Fleming, A. S. (2003a). The nucleus accumbens shell is critical for the normal expression of pup-retrieval in postpartum female rats. *Behavioural Brain Research, 145*, 99-111.

Li, M., & Fleming, A. S. (2003b). Differential involvement of the nucleus accumbens shell and core subregions in maternal memory in postpartum female rats. *Behavioral Neuroscience, 117*, 426-445.

Liu, Y., & Wang, Z. X. (2003). Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience, 121*, 537-544.

Lonstein, J. S., & De Vries, G. J. (2000). Maternal behavior in lactating rats stimulates *c-fos* in glutamate decarboxylase-synthesizing neurons of the medial preoptic area, ventral bed nucleus of the stria terminalis, and ventrocaudal periaqueductal gray. *Neuroscience, 100*, 557-568.

Lonstein, J. S., Greco, B., De Vries, G. J., Stern, J. M., & Blaustein, J. D. (2000). Maternal behavior stimulates c-fos activity within estrogen receptor alpha-containing neurons in lactating rats. *Neuroendocrinology, 72*, 91-101.

Lonstein, J. S., Simmons, D. A., Swann, J. M., & Stern, J. M. (1998). Forebrain expression of c-Fos due to active maternal behavior in lactating rats. *Neuroscience, 82*, 267-281.

Lorberbaum, J. P., Newman, J. D., Horwitz, A. R., Dubno, J. R., Lydiard, R. B., Hamner, M. B., et al. (2002). A potential role for the thalamocingulate circuitry in human maternal behavior. *Biological Psychiatry, 51*, 431-445.

Lu, X. Y., Ghasemzadeh, M. B., & Kalivas, P. W. (1998). Expression of D1 receptor, D2 receptor, substance P and enkephalin messenger RNAs in neurons projecting from the nucleus accumbens. *Neuroscience, 82*, 767-780.

Maeda, T., Fukazawa, Y., Shimizu, N., Ozaki, M., Yamamoto, H., & Kishioka, S. (2004). Electrophysiological characteristic of corticoaccumbens synapses in rat mesolimbic system reconstructed using organotypic slice cultures. *Brain Research, 1015*, 34-40.

Maslowski-Cobuzzi, R. J., & Napier, T. C. (1994). Activation of dopaminergic neurons modulates ventral pallidal responses evoked by amygdala stimulation. *Neuroscience, 62*, 1103-1120.

Mattson, B. J., & Morrell, J. I. (2005). Preference for cocaine- versus pup-associated cues differentially activates neurons expressing either Fos or cocaine- and amphetamine-regulated transcript in lactating maternal rodents. *Neuroscience, 135*, 315-328.

Miller, S. M., & Lonstein, J. S. (2005). Dopamine D1 and D2 receptor antagonism in the preoptic area produces different effects on maternal behavior in lactating rats. *Behavioral Neuroscience, 119*, 1072-1083.

Mitrovic, I., & Napier, T. C. (1998). Substance P attenuates and DAMGO potentiates amygdala glutamatergic neurotransmission within the ventral pallidum. *Brain Research, 792*, 193-206.

Mogenson, G. J. (1987). Limbic-motor integration. *Progress in Psychobiology and Physiological Psychology, 12*, 117-167.

Moratalla, R., Xu, M., Tonegawa, S., & Graybiel, A. M. (1996). Cellular responses to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 14928-14933.

Morgan, J. I., & Curran, T. (1991). Stimulus-transcription coupling in the nervous system: Involvement of the inducible proto-oncogenes *fos* and *jun*. *Annual Review of Neuroscience, 14*, 421-451.

Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science, 309*, 951-954.

Nair, D. G. (2005). About being BOLD. *Brain Research Reviews, 50*, 229-243.

Newman, S. W. (1999). The medial extended amygdala in male reproductive behavior. *Annals of the New York Academy of Sciences, 877*, 242-257.

Nicola, S. M., Surmeier, D. J., & Malenka, R. C. (2000). Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annual Review of Neuroscience, 23*, 185-215.

Numan, M. (1974). The medial preoptic area and maternal behavior in the female rat. *Journal of Comparative and Physiological Psychology, 87*, 746-759.

Numan, M. (1985). Brain mechanisms and parental behavior. In N. Adler, D. Pfaff, & R. W. Goy (Eds.), *Handbook of behavioral neurobiology* (Vol. 7, pp. 537-605). New York: Plenum.

Numan, M. (1988). Maternal behavior. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (Vol. 2, pp. 1569-1645). New York: Raven Press.

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Numan, M. (1994). Maternal behavior. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (Vol. 2, pp. 221-302). New York: Raven Press.

Numan, M., & Callahan, E. C. (1980). The connections of the medial preoptic region and maternal behavior in the rat. *Physiology & Behavior*, *25*, 653-665.

Numan, M., & Corodimas, K. P. (1985). The effects of paraventricular hypothalamic lesions on maternal behavior in rats. *Physiology & Behavior*, *35*, 417-425.

Numan, M., Corodimas, K. P., Numan, M. J., Factor, E. M., & Piers, W. D. (1988). Axon-sparing lesions of the preoptic region and substantia innominata disrupt maternal behavior in rats. *Behavioral Neuroscience*, *102*, 381-396.

Numan, M., & Insel, T. R. (2003). *The neurobiology of parental behavior*. New York: Springer-Verlag.

Numan, M., & Numan, M. J. (1991). Preoptic-brainstem connections and maternal behavior in rats. *Behavioral Neuroscience*, *105*, 1013-1029.

Numan, M., & Numan, M. J. (1995). Importance of pup-related sensory inputs and maternal performance for the expression of Fos-like immunoreactivity in the preoptic area and ventral bed nucleus of the stria terminalis of postpartum rats. *Behavioral Neuroscience*, *109*, 135-149.

Numan, M., & Numan, M. J. (1996). A lesion and neuroanatomical tract-tracing study of the role of the bed nucleus of the stria terminalis in retrieval behavior and other aspects of maternal responsiveness in rats. *Developmental Psychobiology*, *29*, 23-51.

Numan, M., & Numan, M. J. (1997). Projection sites of medial preoptic and ventral bed nucleus of the stria terminalis neurons that express Fos during maternal behavior in female rats. *Journal of Neuroendocrinology*, *9*, 369-384.

Numan, M., Numan, M. J., & English, J. B. (1993). Excitotoxic amino acid injections into the medial amygdala facilitate maternal behavior in virgin female rats. *Hormones and Behavior*, *27*, 56-81.

Numan, M., Numan, M. J., Pliakou, N., Stolzenberg, D. S., Mullins, O. J., Murphy, J. M., et al. (2005). The effects of D1 and D2 dopamine receptor antagonism in the medial preoptic area, ventral pallidum, or nucleus accumbens on the maternal retrieval response and other aspects of maternal behavior in rats. *Behavioral Neuroscience*, *119*, 1588-1604.

Numan, M., Numan, M. J., Schwarz, J. M., Neuner, C. M., Flood, T. F., & Smith, C. D. (2005). Medial preoptic area interactions with the nucleus accumbens-ventral pallidum circuit and maternal behavior in rats. *Behavioural Brain Research*, *158*, 53-68.

Numan, M., Roach, J. K., del Cerro, M. C. R., Guillamon, A., Segovia, S., Sheehan, T. P., et al. (1999). Expression of intracellular progesterone receptors in the rat brain during different reproductive states, and involvement in maternal behavior. *Brain Research*, *830*, 358-371.

Numan, M., Rosenblatt, J. S., & Komisaruk, B. R. (1977). Medial preoptic area and onset of maternal behavior in the rat. *Journal of Comparative and Physiological Psychology*, 91, 146-164.

Numan, M., & Sheehan, T. P. (1997). Neuroanatomical circuitry for mammalian maternal behavior. *Annals of the New York Academy of Sciences*, *807*, 101-125.

Numan, M., & Smith, H. G. (1984). Maternal behavior in rats: Evidence for the involvement of preoptic projections to the ventral tegmental area. *Behavioral Neuroscience*, *98*, 712-727.

Olazabal, D. E., & Young, L. J. (2005). Alloparental behavior in juvenile rodents is associated with higher oxytocin receptor density in the nucleus accumbens and the caudate putamen. Program No. 419.3. In *2005 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience.

Orpen, B. G., & Fleming, A. S. (1987). Experience with pups sustains maternal responding in postpartum rats. *Physiology & Behavior*, *40*, 47-54.

Osako, Y., Otsuka, T., Taniguchi, M., Oka, T., & Kaba, H. (2001). Oxytocin enhances presynaptic and postsynaptic glutamatergic transmission between rat olfactory bulb neurones in culture. *Neuroscience Letters*, *299*, 65-68.

Paxinos, G., & Watson, C. (1997). *The rat brain in stereotaxic coordinates*. San Diego, CA: Academic Press.

Pedersen, C. A. (1997). Oxytocin control of maternal behavior. *Annals of the New York Academy of Sciences*, *807*, 126-145.

Pedersen, C. A., Ascher, J. A., Monroe, Y. L., & Prange, A. J. (1982). Oxytocin induces maternal behaviour in virgin female rats. *Science*, *216*, 648-649.

Pedersen, C. A., & Boccia, M. L. (2003). Oxytocin antagonism alters rat dams' oral grooming and upright nursing posture over pups. *Physiology & Behavior*, *80*, 233-241.

Pedersen, C. A., Caldwell, J. D., Fort, S. A., & Prange, A. J. (1985). Oxytocin antiserum delays onset of ovarian steroid-induced maternal behaviour. *Neuropeptides*, *6*, 175-182.

Pedersen, C. A., Caldwell, J. D., Walker, C., Ayers, G., & Mason, G. A. (1994). Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental area and medial preoptic area. *Behavioral Neuroscience*, *108*, 1163-1171.

Pennartz, C. M. A., Dolleman-Van Der Weel, M. J., Kitai, S. T., & Lopes Da Silva, F. H. (1992). Presynaptic dopamine D1 receptors attenuate excitatory and inhibitory limbic inputs to the shell region of the rat nucleus accumbens studied in vitro. *Journal of Neurophysiology*, *67*, 1325-1334.

Pennartz, C. M. A., Groenewegen, H. J., & Lopes Da Silva, F. H. (1994). The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioural, electrophysiological and anatomical data. *Progress in Neurobiology*, *42*, 719-761.

Petrovich, G. D., Risold, P. Y., & Swanson, L. W. (1996). Organization of projections from the basomedial nucleus of the amygdala: A PHAL study in the rat. *Journal of Comparative Neurology*, *374*, 387-420.

Pfaff, D. W. (1980). *Estrogens and brain function: Neural analysis of a hormone-controlled mammalian reproductive behavior*. New York: Springer-Verlag.

Pfaus, J. G., & Phillips, A. G. (1991). Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. *Behavioral Neuroscience*, *105*, 727-743.

Popeski, N., & Woodside, B. (2004). Central nitric oxide synthase inhibition disrupts maternal behavior in the rat. *Behavioral Neuroscience*, *118*, 1305-1316.

Reynolds, S. M., & Berridge, K. C. (2002). Positive and negative motivation in nucleus accumbens shell: Bivalent rostrocaudal gradients for GABA-elicited eating, "liking"/"disliking" reactions, place preference/avoidance and fear. *Journal of Neuroscience*, *22*, 7308-7320.

Risold, P. Y., Canteras, N. S., & Swanson, L. W. (1994). Organization of projections from the anterior hypothalamic nucleus: A *Phaseolus vulgaris*–leucoagglutinin study in the rat. *Journal of Comparative Neurology*, *348*, 1-40.

Risold, P. Y., Thompson, R. H., & Swanson, L. W. (1997). The structural organization of connections between hypothalamus and cerebral cortex. *Brain Research Reviews*, *24*, 197-254.

Robertson, G. S., & Jian, M. (1995). D1 and D2 dopamine receptors differentially increase Fos-like immunoreactivity in accumbal projections to the ventral pallidum and midbrain. *Neuroscience*, *64*, 1019-1034.

Robertson, L. M., Kerppola, T. K., Vendrell, M., Luk, D., Smeyne, R. J., Bocchiaro, C., et al. (1995). Regulation of c-fos expression in transgenic mice requires multiple independent transcription control elements. *Neuron*, *14*, 241-252.

Rosenblatt, J. S. (1967). Nonhormonal basis of maternal behavior in the rat. *Science*, *156*, 1512-1514.

Rosenblatt, J. S., & Mayer, A. D. (1995). An analysis of approach/withdrawal processes in the initiation of maternal behavior in the laboratory rat. In K. E. Hood, G. Greenberg, & E. Tobach (Eds.), *Behavioral development* (pp. 177-230). New York: Garland Press.

Schuchard, M., Landers, J. P., Sandhu, N. P., & Spelsberg, T. C. (1993). Steroid hormone regulation of nuclear proto-oncogenes. *Endocrinology Reviews*, *14*, 659-669.

Service, G. O., & Woodside, B. C. (2005). Administration of a nitirc oxide synthase inhibitor into the medial preoptic area (MPOA) impairs retrieval behavior but not maternal aggression in lactating rats. Program No. 322.10. In *2005 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience.

Sesack, S. R., Deutch, A. Y., Roth, R. H., & Bunney, B. S. (1989). Topographical organization of the efferent projections from the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. *Journal of Comparative Neurology*, *290*, 213-242.

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Shahrokh, D. K., Cameron, N., & Meaney, M. J. (2005). Oxytocin projections from the medial preoptic area to the ventral tegmental area in high- and low-licking/grooming female rats. Program No. 419.4. In *2005 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience.

Sheehan, T., Paul, M., Amaral, E., Numan, M. J., & Numan, M. (2001). Evidence that the medial amygdala projects to the anterior/ventromedial nuclei to inhibit maternal behavior in rats. *Neuroscience*, *106*, 341-356.

Sheehan, T. P., Cirrito, J., Numan, M. J., & Numan, M. (2000). Using c-Fos immunocytochemistry to identify forebrain regions that may inhibit maternal behavior in rats. *Behavioral Neuroscience*, *114*, 337-352.

Sheehan, T. P., & Numan, M. (2002). Estrogen, progesterone, and pregnancy termination alter neural activity in brain regions that control maternal behavior in rats. *Neuroendocrinology*, *75*, 12-23.

Sheng, M., & Greenberg, M. E. (1990). The regulation and function of *c-fos* and other immediate early genes in the nervous system. *Neuron*, *4*, 477-485.

Shughrue, P. J., Lane, M. V., & Merchenthaler, I. (1997). Comparative distribution of estrogen receptor-α and-β mRNA in the rat central nervous system. *Journal of Comparative Neurology*, *388*, 507-525.

Silveira, M. C. L., & Graeff, F. G. (1992). Defense reaction elicited by microinjection of kainic acid into the medial hypothalamus of the rat: Antagonism by a GABA-A receptor agonist. *Behavioral and Neural Biology*, *57*, 226-232.

Simerly, R. B., Gorski, R. A., & Swanson, L. W. (1986). Neurotransmitter specificity of cells and fibers in the medial preoptic nucleus: An immunohistochemical study in the rat. *Journal of Comparative Neurology*, *246*, 343-363.

Simerly, R. B., & Swanson, L. W. (1988). Projections of the medial preoptic nucleus: A *Phaseolus vulgaris* leucoagglutinin anterograde tract-tracing study in the rat. *Journal of Comparative Neurology*, *270*, 209-242.

Stack, E. C., Balakrishnan, R., Numan, M. J., & Numan, M. (2002). A functional neuroanatomical investigation of the role of the medial preoptic area in neural circuits regulating maternal behavior. *Behavioural Brain Research*, *131*, 17-36.

Stack, E. C., & Numan, M. (2000). The temporal course of expression of c-Fos and Fos B within the medial preoptic area and other brain regions of postpartum female rats during prolonged mother-young interactions. *Behavioral Neuroscience*, *114*, 609-622.

Stellar, E. (1954). The physiology of motivation. *Psychological Review*, *61*, 5-21.

Stern, J. M. (1991). Nursing posture is elicited rapidly in maternally naïve, haloperidol-treated female and male rats in response to ventral trunk stimulation from active pups. *Hormones and Behavior*, *25*, 504-517.

Stern, J. M. (1996). Somatosensation and maternal care in Norway rats. In J. S. Rosenblatt & C. T. Snowdon (Eds.), *Advances in the study of behavior* (Vol. 25, pp. 243-294). San Diego, CA: Academic Press.

Stern, J. M., & Johnson, S. K. (1990). Ventral somatosensory determinants of nursing behavior in Norway rats. I. Effects of variations in the quality and quantity of pup stimuli. *Physiology & Behavior*, *47*, 993-1011.

Stolzenberg, D. S., & Numan, M. (2006). *Microinjection of a dopamine D1 receptor agonist into the nucleus accumbens stimulates maternal behavior in pregnancy-terminated female rats*. Manuscript in preparation.

Stratford, T. R., & Kelley, A. E. (1997). GABA in the nucleus accumbens shell participates in the central regulation of feeding. *Journal of Neuroscience*, *17*, 4434-4440.

Stratford, T. R., Kelley, A. E., & Simansky, K. J. (1999). Blockade of GABA-A receptors in the medial ventral pallidum elicits feeding in satiated rats. *Brain Research*, *825*, 199-203.

Sukikara, M. H., Mota-Ortiz, S. R., Baldo, M. V., & Felicio, L. F., Canteras, N. S. (2006). A role for the periaqueductal gray in switching adaptive behavioral responses. *Journal of Neuroscience*, *26*, 2583-2589.

Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Research Bulletin*, *9*, 321-353.

Swanson, L. W. (1987). The hypothalamus. In A. Bjorklund, T. Hokfelt, & L. W. Swanson (Eds.), *Handbook of chemical neuroanatomy* (Vol. 5, pp. 1-124). Amsterdam: Elsevier.

Swanson, L. W. (1992). *Brain maps: Structure of the rat brain*. Amsterdam: Elsevier.

Taha, S. A., & Fields, H. L. (2006). Inhibitions of nucleus accumbens neurons encode a gating signal for reward-directed behavior. *Journal of Neuroscience*, *26*, 217-222.

Terkel, J., Bridges, R. S., & Sawyer, C. H. (1979). Effects of transecting the lateral neural connections of the medial preoptic area on maternal behavior in the rat: Nest building, pup retrieval, and prolactin secretion. *Brain Research*, *169*, 369-380.

Trevitt, J. T., Morrow, J., & Marshall, J. F. (2005). Dopamine manipulation alters immediate-early gene response of striatal parvalbumin interneurons to cortical stimulation. *Brain Research*, *1035*, 41-50.

Usuda, I., Tanaka, K., & Chiba, T. (1998). Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: Biotinylated dextran amine study. *Brain Research*, *797*, 73-93.

van Leengoed, E., Kerker, E., & Swanson, H. H. (1987). Inhibition of postpartum maternal behaviour in the rat by injecting an oxytocin antagonist into the cerebral ventricles. *Journal of Endocrinology*, *112*, 275-282.

Veinante, P., & Freund-Mercier, M. (1997). Distribution of oxytocin- and vasopressin-binding sites in the rat extended amygdala: A histoautoradiographic study. *Journal of Comparative Neurology*, *383*, 305-325.

Wagner, C. K., Eaton, M. J., Moore, K. E., & Lookingland, K. J. (1995). Efferent projections from the region of the medial zona incerta containing A13 dopaminergic neurons: A PHA-L anterograde tract-tracing study in the rat. *Brain Research*, *677*, 229-237.

Wakerley, J. B., Clarke, G., & Summerlee, A. J. S. (1994). Milk-ejection and its control. In E. Knobil & J. D. Neill (Eds.), *The physiology of reproduction* (Vol. 2, pp. 1131-1177). New York: Raven Press.

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews: Neuroscience*, *5*, 483-494.

Wright, C. I., & Groenewegen, H. J. (1995). Patterns of convergence and segregation in the medial nucleus accumbens of the rat: Relationships of prefrontal cortical, midline thalamic, and basal amygdaloid afferents. *Journal of Comparative Neurology*, *361*, 383-403.

Xia, Z., Dudek, H., Miranti, C. K., & Greenberg, M. E. (1996). Calcium influx via the NMDA receptor induces immediate early gene transcription by a MAP kinase/ERK-dependent mechanism. *Journal of Neuroscience*, *16*, 5425-5436.

Yang, G., Huard, J. M. T., Beitz, A. J., Ross, M. E., & Iadecola, C. (2000). Stellate neurons mediate functional hyperemia in the cerebellar molecular layer. *Journal of Neuroscience*, *20*, 6968-6973.

Yu, G. Z., Kaba, H. Okutani, F., Takahashi, S., Higuchi, T., & Seto, K. (1996a). The action of oxytocin originating in the hypothalamic paraventricular nucleus on mitral and granule cells in the rat main olfactory bulb. *Neuroscience*, *72*, 1073-1082.

Yu, G. Z., Kaba, H., Okutani, F., Takahashi, S., & Higuchi, T. (1996b). The olfactory bulb: A critical site of action for oxytocin on the induction of maternal behavior. *Neuroscience*, *72*, 1083-1088.

Yun, I. A., Nicola, S. M., & Fields, H. L. (2004). Contrasting effects of dopamine and glutamate receptor antagonist injection in the nucleus accumbens suggest a neural mechanism underlying cue-evoked goal-directed behavior. *European Journal of Neuroscience*, *20*, 249-263.

Zaborszky, L., Gaykema, R. P., Swanson, D. J., & Cullinan, W. E. (1997). Cortical input to the basal forebrain. *Neuroscience*, *79*, 1051-1078.

Zhang, M., Balmadrid, C., & Kelley, A. E. (2003). Nucleus accumbens opioid, GABAergic, and dopaminergic modulation of food motivation: Contrasting effects revealed by a progressive ratio study in the rat. *Behavioral Neuroscience*, *117*, 202-211.

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