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Neural mechanisms of mother-infant bonding and pair bonding: Similarities, differences, and broader implications

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Abstract

Mother-infant bonding is a characteristic of virtually all mammals. The maternal neural system may have provided the scaffold upon which other types of social bonds in mammals have been built. For example, most mammals exhibit a polygamous mating system, but monogamy and pair bonding between mating partners occurs in ~5% of mammalian species. In mammals, it is plausible that the neural mechanisms that promote mother-infant bonding have been modified by natural selection to establish the capacity to develop a selective bond with a mate during the evolution of monogamous mating strategies. Here we compare the details of the neural mechanisms that promote mother-infant bonding in rats and other mammals with those that underpin pair bond formation in the monogamous prairie vole. Although details remain to be resolved, remarkable similarities and a few differences between the mechanisms underlying these two types of bond formation are revealed. For example, amygdala and nucleus accumbens-ventral pallidum (NA-VP) circuits are involved in both types of bond formation, and dopamine and oxytocin action within NA appears to promote the synaptic plasticity that allows either infant or mating partner stimuli to persistently activate NA-VP attraction circuits, leading to an enduring social attraction and bonding. Further, although the medial preoptic area is essential for maternal behavior, its role in pair bonding remains to be determined. Our review concludes by examining the broader implications of this comparative analysis, and evidence is provided that the maternal care system may have also provided the basic neural foundation for other types of strong social relationships, beyond pair bonding, in mammals, including humans.

Keywords

oxytocin; vasopressin; dopamine; medial preoptic area; nucleus accumbens; ventral pallidum; amygdala; social attachment; monogamy

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Introduction

The two most common prosocial behaviors in mammals are the sexual interactions that occur during mating and mother-infant interactions. In most mammals, sexual interactions are short lasting, while the mother-infant bond is long-term, persisting, at least, through weaning. The mother-infant bond, therefore, is the most common enduring social bond in mammals.

More specifically, about 95% of mammalian species exhibit a polygamous mating system (Kleiman, 1977), and although the two sexes are attracted to each other during mating, once mating is complete the two sexes leave each other. In these cases, the pregnant female gives birth and cares for her offspring by herself, giving rise to the typical mammalian maternal care system. In contrast, about 5% of mammalian species exhibit a monogamous mating system where one male engages in sexual activity preferentially with one female, and then the male-female pair remains together and both parents contribute to raising offspring (McGraw & Young, 2010; Young et al., 2011). Such a pair bond represents the formation of a selective and a long-term social attraction between two specific adults who recognize each other and remain together after sexual activity has terminated. Monogamy usually evolves under conditions where biparental care is necessary for infant survival (Brown, 1975).

Since the strong attraction between a mother and her infant(s) is common to all mammals, while the enduring pair bond in monogamy is rare in mammals, it can be suggested that the neural circuitry and mechanisms that underpin the long-term mother-infant attraction may have provided a primordial neural scaffold upon which other types of strong social bonds, such as pair bonds, have been built. Although many researchers have made this point (for a review, see Numan, 2015), the purpose of this paper is to compare the *details* of the neural circuitry and mechanisms that contribute to the formation of the mother-infant bond and the pair bond, where remarkable similarities (and some important differences) exist. In particular, in this review we will show that the amygdala and nucleus accumbens-ventral pallidum (NA-VP) circuits are involved in both types of bond formation, and that dopamine (DA) and oxytocin (OT) action within NA appears to promote the synaptic plasticity that allows either infant or mating partner stimuli to persistently activate NA-VP attraction circuits, leading to an enduring social attraction and bonding. Further, we will present evidence that OT effects on the connections between the olfactory bulbs and the amygdala may play a role in the selective recognition processes that occur during maternal bonding in certain species and during pair bond formation. Such processes would allow for individual recognition of one's offspring or mating partner.

Most of the research we will review concerns maternal behavior in rats and sheep and pair bond formation in prairie voles. We will analyze the maternal bonding system first and then follow with the pair bond system because the former is proposed to be the primordial system. We will conclude with a comparative analysis of the two systems, along with broader implications.

Maternal Behavior and Mother-Infant Attachment

The development of a mother-infant bond consists of a two-step process: a recognition process and a persistent attraction process (Numan, 2015). The recognition process allows infant stimuli to gain access to those neural mechanisms that promote attraction and maternal care rather than rejection and avoidance of infant stimuli, while the persistent attraction process is the result of brain plasticity mechanisms that cause an enduring or long-lasting attraction to develop between a mother and her infant(s).

With respect to the recognition process, it can be either nonselective or selective. A nonselective recognition process typically occurs in mothers that give birth to altricial young, such as rats and many other rodents: maternal care is directed toward a generic infant stimulus rather than to particular infants, and mothers will care for any conspecific infant throughout the postpartum period. As a result, general infant stimuli are recognized as positive, rather than negative, social stimuli. In contrast, a selective recognition process operates in mothers that give birth to precocial young, such as sheep and other ungulates, or semi-mobile young, such as primates, where selective maternal care is ultimately directed toward the particular offspring that the mother gives birth to, while other (alien) young are rejected (Insel & Young, 2001; Nowak et al., 2011; Numan & Insel, 2003). *Experimental* manipulations show that postpartum rats will care for their own pups or pups from another mother, while sheep learn the olfactory characteristics of their lamb at the time of birth and will subsequently care for their own lamb while rejecting the advances of alien young. This difference in the selectivity of the recognition mechanism and the mother-infant bond is the result of evolutionary forces: selective recognition mechanisms are adaptive for sheep but have no adaptive significance for most rodents (Numan & Insel, 2003). However, the long-term attraction of a mother toward her infant(s) is an essential component of the mother-infant bond in all mammals.

It is worth pointing out that when one compares the mother-infant bond with the pair bond in monogamous species, the overall characteristics of the pair bond closely match the selective maternal bond that forms in such species as sheep. In both cases, a selective and long-term attraction is formed to a particular individual. However, please note that two processes are occurring during bond formation: one governing the nature of the stimuli that are relayed to an attraction mechanism (specific or generic stimuli), and one controlling the operation and modification of the attraction mechanism so that a persistent attraction develops to the relevant stimuli. Research on the maternal bond in species with precocial young, when compared to those with altricial young, will be shown to inform us about both processes. In particular, research on sheep has highlighted the mechanisms underlying the selective recognition process, while research on rats has provided significant insights into the mechanisms that underpin the development of an enduring attraction between a mother and her young. The research on pair bond formation in prairie voles, in the context of the maternal bonding data, provides hypotheses on how these two mechanisms are combined so that a selective and enduring attraction develops between mating partners.

In most mammals, the endocrine events associated with the end of pregnancy and parturition, in conjunction with OT release into the brain that results from the vaginocervical

stimulation associated with the birth process, act on the brain to stimulate the immediate onset of maternal behavior at parturition, but after maternal behavior becomes established during the early postpartum hours, its maintenance until weaning becomes independent of hormonal control (Numan et al., 2006). Therefore, hormonal action on the brain, in conjunction with an initial maternal experience with infants, results in a long-lasting modification of brain function so that an enduring attraction between a mother and her infant(s) persists after the hormonal events that activated the behavior have waned. This process shares similarities with pair bond formation, where gonadal hormones trigger sexual motivation and attraction, but then the attraction between mating partners persists after sexual behavior and the hormonal events that triggered it have waned.

Maternal Behavior in Rats: The Response of Virgin Females

Given that pregnancy hormones trigger the onset of maternal behavior, it is not surprising that naive virgin female rats initially avoid young pups. However, the classic research of Rosenblatt (1967) showed that when virgins are continuously exposed to healthy pups (obtained from lactating donor females), pup-stimulated or sensitized maternal behavior occurs: the virgin will begin to retrieve pups to a single location and adopt a nursing posture over them, even though the virgin cannot lactate. This sensitization process occurs after about seven days of pup exposure, and the exact number of days of pup exposure needed to induce maternal behavior in a particular female is referred to as the female's sensitization latency. Therefore, although maternal behavior can occur in virgins, the hormonal events occurring at the end of pregnancy allow for immediate maternal responsiveness at parturition. If such immediate responsiveness did not occur, infant pups would die of neglect. Research indicates that hormonal and neuropeptide (OT) factors act on the brain near the time of parturition to depress neural circuits that promote avoidance and rejection of infant stimuli while at the same time stimulating those neural circuits which promote attraction and prosocial responses toward infant stimuli (Numan, 2015; 2007; 2006; Sheehan et al., 2001). In other words, parturient physiological events promote a critical shift in the processing of infant stimuli, allowing such stimuli to gain access to attraction mechanisms while depressing their access to avoidance mechanisms. The focus of this review will be on the former process. Since postpartum rats give birth to altricial young and will care for any rat pup, this process would be an example of a nonselective recognition mechanism.

Maternal Memory in Rats

Maternal memory refers to the fact that although primiparous rats require hormonal stimulation to initiate prompt maternal behavior, once a critical duration of maternal experience occurs, subsequent episodes of maternal behavior, even after long periods of mother-infant separation, become emancipated from hormones (Bridges, 1975; Orpen & Fleming, 1987). In a typical experiment, one group of primiparous parturient rats is allowed to interact with pups for 1 hr after birth and then the pups are removed, while a second group has its pups removed immediately at birth. A retention test is then conducted 10 or more days later, at which time all females are continuously exposed to young foster pups until sensitized maternal behavior occurs. The parturient females with the 1-hr maternal experience exhibit sensitization latencies of 1-2 days during the retention test (even when such females are ovariectomized: Bridges, 1975), while the parturient females without

maternal experience show the typical naïve virgin sensitization latency of about 7 days. The processes underlying maternal memory formation are likely similar to those that underpin the maintenance of maternal behavior during the postpartum period, both representing the formation of an enduring bond between a mother and a general pup stimulus. These processes indicate that maternal neural mechanisms can be modified by hormonal events, OT, and maternal experience in first time mothers, allowing the maternal circuit to subsequently be activated relatively easily by pup stimuli alone.

An important question relates to the exact mechanisms that modify particular neural circuits so that an enduring attraction forms between a mother and her infant(s). A guiding principle is that sites of neural plasticity should be located within the circuits that regulate maternal behavior and maternal attraction to infant stimuli (Numan, 2015). Certain circuits that are active during the hormonally stimulated onset of maternal behavior in primiparous females might become strengthened, resulting in the formation of a persistent mother-infant attraction that remains intact without an essential continuance of hormonal involvement. Given this perspective, the neural circuits regulating maternal motivation will be presented first, followed by research that shows that maternal memory likely results from experience-induced modifications within this circuitry.

Brain Circuits Regulating Maternal Motivation in Rats

The medial preoptic area (MPOA) and the adjoining ventral bed nucleus of the stria terminalis (vBST) are essential components of the neural circuitry regulating maternal behavior (Bridges et al., 1990; Numan, 2015; Numan et al., 1988; Numan & Numan, 1996; Numan et al., 1977; Numan & Stolzenberg, 2009). Lesions of MPOA/vBST disrupt maternal behavior and estradiol and prolactin action on MPOA promotes the onset of maternal behavior. OT action on the MPOA, presumably derived from neural inputs from the paraventricular nucleus of the hypothalamus (PVN) that are activated by vaginocervical and suckling stimulation (Numan et al., 2006), is also essential for the onset of maternal behavior at parturition in rats (Insel & Harbaugh, 1989; Pedersen et al., 1994). Indeed, one of the functions of estradiol action within MPOA neurons may be to stimulate the expression of oxytocin receptors (OTRs) so that the critical neurons become responsive to OT, allowing OT to activate MPOA efferents that regulate maternal motivation (Numan & Stolzenberg, 2009). Significantly, MPOA neural activity is necessary for all phases of maternal behavior in rats: its onset and maintenance in primiparous and multiparous females and its occurrence in sensitized virgins (Numan, 2015; Numan & Stolzenberg, 2009).

Research has indicated that MPOA/vBST efferents regulate maternal motivation by interacting with the mesolimbic DA system (Numan & Stolzenberg, 2009; Stack et al., 2002). Within the mesolimbic DA system, activation of ventral tegmental area (VTA) DA inputs to the NA facilitates an organism's behavioral reactivity to a variety of biologically significant sensory stimuli that are relayed to the NA and adjoining ventral pallidum (VP) by afferents from the amygdala, hippocampus, and allocortical parts of the prefrontal cortex (Numan, 2015; Stolzenberg & Numan, 2011). MPOA stimulation of the mesolimbic DA system appears to trigger the ability of the NA-VP circuit to respond to infant-related stimuli.

Mogenson (1987) presented a model of how the mesolimbic DA system operates: DA action on NA was proposed to depress the activity of NA, and since the GABAergic medium spiny output neurons (MSNs) of NA send inhibitory projections to VP, the action of DA on NA MSNs would release VP from inhibition. It was the output of VP that was proposed to promote goal-directed motivated responses. Recent research has affirmed the involvement of VP in motivational processes (Smith et al., 2009). In contrast to Mogenson, other research suggests that DA action stimulates the output of NA GABAergic MSNs in order to facilitate goal-directed responses (Ambroggi et al., 2008). The organization of the NA, composed of a medial shell (NAs) and lateral core (NAc), is complex: NAs and NAc GABAergic efferents project to areas other than VP, and some MSNs contain the D1-type DA receptor while others contain the D2-type DA receptor (Humphries & Prescott, 2010; Smith et al., 2013). It is probably best to conceive of the NA as containing functionally discrete modules, each with unique inputs and outputs, with these modules regulating different motivational processes via different and specialized operating mechanisms (Nelson & Kreitzer, 2014; Pennartz et al., 1994).

Given these caveats, the involvement of the mesolimbic DA system in maternal motivation is very consistent with Mogenson's (1987) model. A simplified model of the interaction between the MPOA/vBST and the mesolimbic DA system in the regulation of maternal motivation in rats is shown in Fig. 1 (Numan, 2015; Numan & Stolzenberg, 2009). It is proposed that when MPOA/vBST is primed by hormones and OT it becomes responsive to multimodal pup stimuli derived from the medial prefrontal cortex [mPFC] (see Balfour, Brown, Yu, & Coolen, 2006; Mattson & Morrell, 2005), which activate MPOA/vBST projections to VTA, resulting in DA release into NAs. DA is presumed to depress the inhibitory GABAergic projections from NAs to VP, resulting in VP being more easily excitable. In the model, glutamatergic excitatory efferents from the basomedial and basolateral amygdala (BMA/BLA) relay sensory inputs from pups to *both* NA and VP. Such stimuli are conceived as representing a generic pup stimulus. In the absence of DA release triggered by pup stimuli, as would occur in naive nulliparous females (see Afonso et al., 2013), the responsiveness of VP is suppressed by NA inhibition and appetitive maternal responses, such as retrieval of pups, do not occur. Due to the proposed depressing action of DA on NA, triggered by pup stimuli at the level of the hormone-primed MPOA/vBST in parturient rats, VP becomes more easily excited by BMA/BLA glutamate input, and the stimulated output of VP then promotes maternal behavior. The site(s) to which VP projects to influence maternal motivation is an important question for future research.

Some evidence supporting the model shown in Fig. 1 is: (a) MPOA/vBST neurons project to VTA (Numan & Numan, 1997; 1996), and VTA neural activity is necessary for the occurrence of the appetitive aspects of maternal behavior (Numan et al., 2009); (b) DA is released into NAs during maternal behavior (Afonso et al., 2009; Champagne et al., 2004); (c) DA receptor antagonist action on NAs disrupts, and DA receptor agonist action on NAs stimulates, maternal behavior (Keer & Stern, 1999; Numan et al., 2005a; Stolzenberg et al., 2007; Stolzenberg et al., 2010); (d) Asymmetrical lesion disconnection studies show that MPOA/vBST is linked to mesolimbic DA system in the control of maternal behavior (Numan et al., 2005b; Numan & Smith, 1984); (e) Suppression of VP activity disrupts

maternal behavior in postpartum rats while similar suppression of NA activity has negligible effects, which fits with the idea that NA activity needs to be depressed and VP activity needs to be upregulated for normal maternal responsiveness to occur (Numan et al., 1988, Numan et al., 2005b); (f) BMA/BLA is anatomically positioned to relay olfactory, gustatory, and somatic sensory stimuli (which are important types of stimuli that a mother receives from her infants) to both the NA and VP (Perry & McNally, 2013; Petrovich et al., 1996), and suppression of BMA/BLA neural activity and its input to VP disrupts maternal behavior (Numan, 2015; Numan et al., 2010); (g) Depression of mPFC neural activity interferes with the appetitive aspects of maternal behavior in postpartum rats (Febo et al., 2010; Pereira & Morrell, 2011).

Research shows that it is DA action on D1 receptors in NAs that stimulates the onset of maternal behavior and is also necessary for the maintenance of maternal motivation, when examined over postpartum days 3-7 (Numan et al., 2005a; Stolzenberg et al., 2007; Stolzenberg et al., 2010). Interestingly, research on the dorsal striatum (caudate nucleus and putamen) indicates that DA action of D1 receptors located on MSNs stimulates these neurons (Humphries & Prescott, 2010). If this occurred in the NAs module that regulates maternal motivation, DA would act to suppress the VP, which would contradict the mechanism depicted in Fig 1. However, in comparison to the dorsal striatum, in the NA (ventral striatum) of rats, D1 receptors are not only located on MSNs, but are also located on the axon terminals of glutamatergic inputs to NAs (Dumartin et al., 2007), and DA action on such receptors results in presynaptic inhibition of glutamate release, which can act to selectively depress BMA/BLA excitation of NAs MSNs, while leaving such input to the VP intact (Charara & Grace, 2003). As a hypothesis, we propose that this may be the mechanism of action of DA within the NA-to-VP module that regulates maternal behavior, which would decrease the excitatory drive on NAs inhibitory input to VP (refer to Fig. 3).

Significantly, OT not only acts on MPOA to stimulate the onset of maternal behavior in rats, but also stimulates VTA-DA neurons to influence maternal behavior (Pedersen et al., 1994; Shahrokh et al., 2010). Interestingly, in female prairie voles, OT acts on OTRs in NA to stimulate allomaternal behavior (Olazabal & Young, 2006a). Since MPOA/vBST projects to PVN (Csaki et al., 2000; Numan & Numan, 1996; Simerly & Swanson, 1988), and since PVN OT neurons project to MPOA, VTA, and NA (as well as other sites such as the amygdala) (Bosch et al., 2010; Knobloch et al., 2012; Ross et al., 2009a; Shahrokh et al., 2010), it is possible that during the onset of maternal behavior the MPOA participates in the activation of OT input to each node in the crucial MPOA-to-VTA-to-NAs pathway that is necessary for maternal motivation. This process, of course, would occur in conjunction with OT release in the brain that is triggered by vaginocervical and suckling stimulation near the time of parturition.

Although much data support the proposed model shown in Fig.1, it is still a work in progress and needs to be further validated by future research.

The Mechanisms of Maternal Memory in Rats

Using the occurrence of maternal memory as a model for the long-term persistence of a mother-infant bond, in conjunction with the principle that maternal memory should be

related to synaptic plasticity within the neural circuit that regulates maternal behavior, it is significant that Fleming's group has shown that essential neurochemical inputs to NAs during an initial maternal experience in primiparous parturient rats are involved in maternal memory formation (D'Cunha et al., 2011; Li & Fleming, 2003; Parada et al., 2008). Some of these results are shown in Fig. 2, which indicate that DA and OT action on NAs are each necessary for maternal memory formation (as we will subsequently show, a similar process is also essential of pair bond formation in prairie voles). In these studies, primiparous rats were allowed 1 hr of postpartum maternal experience and then the pups were removed. Immediately after this 1 hr experience, DA receptor antagonists, an OTR antagonist (OTA), or control solutions were injected into NAs. Ten days later, females were re-exposed to young foster pups on a daily basis and sensitization latencies for the re-initiation of maternal behavior were recorded. Fig. 2A shows that blockade of *both* D1 and D2 receptors in NAs effectively disrupted maternal memory, while the blockade of either receptor alone was relatively ineffective (cf. Byrnes et al., 2002). Fig. 2B shows that blockade of OT action on OT receptors in NAs also effectively disrupted maternal memory formation.

Research on the onset and maintenance of maternal motivation has shown that DA action on D1, but not D2 receptors, in NAs is essential for maternal behavior (Numan et al., 2005a; Stolzenberg et al., 2007). But Parada et al. (2008) have shown that DA action on D1 and D2 receptors in NAs is involved in maternal memory formation. Therefore, the DA mechanisms involved in the synaptic plasticity that underpins maternal memory are not necessarily identical to those that regulate ongoing maternal motivation. That is, DA motivational mechanisms within NAs may be at least partially distinct from DA reinforcement mechanisms (that is, mechanisms that strengthen synapses). Finally, with respect to OT action at the level of NAs and maternal memory, the OTA used by D'Cunha et al. (2011) is relatively nonselective and also blocks V1a vasopressin receptors (Manning et al., 2008), leaving open the possibility that these receptors might also be involved in maternal memory formation (see Nephew & Bridges, 2008).

Based on these very preliminary data, a hypothetical model of maternal memory formation in rats, which has been influenced by the research on pair bond formation in prairie voles, is presented in Fig. 3 (Numan, 2015). This speculative model represents a proposed mechanism for the development of a persistent attraction by an experienced mother to general pup stimuli and is meant to serve as a foundation for future research, which will test its various elements. The rat NAs contains OTRs (Olazabal & Young, 2006b; Veinante & Freund-Mercier, 1997), but their exact cellular location has not been specified in detail. Recent research suggests that OTRs may form heteromers with D2 receptors on MSNs and that OT binding to such OTRs increases the affinity of DA to the associated D2 receptor (Romero-Fernandez et al., 2013). Based on the assumption, derived from research on the dorsal striatum, that DA action of D2 receptors depresses the activity of MSNs (Humphries & Prescott, 2010), the findings of Romero-Fernandez et al. suggest that OT could potentiate such inhibitory effects. The model shown in Fig. 3 incorporates this mechanism of OT action. The model shows that during an initial maternal experience in parturient rats, DA action on D1 and D2 receptors and OT action on OTRs in NAs all act to depress MSN inhibitory output to VP. Note that *both* DA and OT inputs to NAs are shown as being

directed, in part, by active MPOA efferent projections. According to this hypothetical NA-VP module, D1 receptors are located presynaptically on glutamatergic axon terminals within NAs that are derived from BMA/BLA, while D2-OTR heteromers are located on MSN projections to VP. The resultant depression of NAs inhibitory input to VP by each of these factors allows for a supernormal excitation of BMA/BLA inputs to VP, which then strengthens those particular synapses (shown by a dashed circle) via a Hebbian-like activity-dependent facilitation. Subsequently, when pregnancy hormones are no longer acting on MPOA, and even after long periods of mother-infant separation, it is proposed that a lower-level activation of the MPOA by pup stimuli (presumably due to the absence of hormonal stimulation of MPOA) is compensated for by the strengthened BMA/BLA-to-VP synapses so that MPOA output can still effectively activate mesolimbic DA stimulation of VP output.

Much more research is needed to lend support to the model shown in Fig. 3. (a) Are D2-OTR heteromers actually present in NAs of parturient rats, and if one were to selectively disrupt such heteromer formation, would maternal memory be disrupted? (b) Is the action of DA on presynaptic D1 receptors the actual mechanism by which D1 DA receptors promote maternal motivation and memory? (c) Further, it would be important to provide evidence that BMA/BLA inputs to VP are indeed strengthened by maternal experience, with such a process being necessary for maternal memory formation.

In addition to the hypothesized synaptic plasticity within the NA-VP circuit, it is likely that maternal memory is mediated by experience-induced modifications at other neural sites. For example, maternal experience-induced modifications within MPOA neurons may allow such neurons to be more easily activated by pup stimuli in the absence of hormonal priming (Stolzenberg et al., 2012). As another example, maternal experience may not only cause an enduring potentiation of the ability of pup stimuli to access prosocial circuits, but may also cause a long-term attenuation of the ability of infant stimuli to access those neural circuits which mediate avoidance and rejection responses toward pups (Numan & Insel, 2003).

Moderate numbers of OTRs are located in the NA of rats (Olazabal & Young, 2006b). Further, Stolzenberg and Numan (2011) have reviewed the evidence that MPOA interactions with the mesolimbic DA system are not only involved in maternal motivation, but also appear to contribute to the appetitive aspects of male and female sexual behaviors in rats. Therefore, why do rats form enduring mother-infant bonds but not pair bonds? One possibility is that the hormonal and OT changes associated with the end of pregnancy coupled with maternal interaction with pups in some way boosts the number of OTRs in NAs to levels much higher than those that are typically expressed in nonpregnant females and males. Perhaps epigenetic mechanisms are involved in this effect (Stolzenberg et al., 2014; 2012; cf. Wang et al., 2013). This is certainly an important area for future research.

Maternal Motivation and Maternal Selectivity in Sheep

Research on maternal behavior in sheep indicates that at parturition a selective recognition mechanism and an enduring bond is formed between a maternal ewe and her lamb (Levy & Keller, 2008; Nowak et al., 2011; Numan, 2015). Relevantly, these dual characteristics are similar to the bond that forms between monogamous mating partners. As in naïve virgin rats, estrous cycling ewes avoid and reject the advances of lambs. As in rats, the hormonal

events occurring at the end of pregnancy coupled with the central release of OT, derived from PVN projections that are activated by parturition-induced vaginocervical stimulation, stimulate the onset of maternal behavior, and recently parturient ewes will accept and nurture *any* newborn lamb. However, as a result of interacting with a particular lamb during the first few postpartum hours, the mother learns its specific olfactory characteristics, and subsequently she will only care for this lamb while rejecting the advances of other lambs. Further, the MPOA is essential for maternal motivation in ewes as depression of MPOA activity blocks the onset and maintenance of maternal behavior (Perrin et al., 2007). In contrast to rats, it is not yet known whether MPOA interacts with the mesolimbic DA system and the NA-VP circuit to influence the appetitive aspects of maternal responsiveness in sheep.

Concerning the neural mechanisms regulating selective maternal recognition, research indicates that neural plasticity within both the olfactory bulbs and the amygdala are involved. The vaginocervical stimulation that occurs during parturition in sheep activates norepinephrine (NE) and OT release into the olfactory bulbs, which may influence the particular types of lamb stimuli that are relayed to the amygdala (Levy et al., 1995; Numan & Insel, 2003). Although NE release into the olfactory bulbs has been shown to be necessary for the development of maternal selectivity, such data is not yet available with respect to the role of OT release at this site. Note that the olfactory bulbs have significant projections to the cortical and medial amygdala [CoA, MeA, respectively], and that CoA and MeA are reciprocally connected to one another, and also project to the BMA/BLA and to MPOA (Meurisse et al., 2009). Importantly, lidocaine injections into CoA and MeA of parturient ewes have been found to disrupt the development of maternal selectivity without interfering with ongoing maternal motivation (Keller et al., 2004). Lidocaine-treated ewes showed maternal behavior toward their own and alien lambs, while control females only cared for their own lamb. Since OTRs are located in MeA of sheep (Broad et al., 1999), and since OT action in MeA influences the formation of olfactory memories involved in individual recognition in rodents (Ferguson et al., 2001; Gur et al., 2014), an interesting hypothesis is that interactions between OT, MeA/CoA, and BMA during an initial maternal experience participate in switching a parturient ewe from responding to a general lamb stimulus to responding to the specific olfactory characteristics of a familiar lamb. As a result, a specific lamb stimulus may ultimately acquire the ability to activate VP attraction mechanisms, replacing the ability of a general lamb stimulus to do so. If olfactory bulb, CoA, MeA, and OT interactions and plasticity mechanisms are disrupted, BMA input to VP may allow the mother to form an enduring attraction to a general lamb stimulus (as described for rats). Another possibility is that plasticity processes within CoA/MeA may result in specific lamb stimuli acquiring the ability to directly activate MPOA output pathways (see Numan, 2015). It would certainly be interesting to determine whether OT antagonism within the olfactory bulbs and/or amygdala would block selective recognition in ewes without interfering with ongoing maternal behavior, resulting in a nonselective recognition mechanism.

Summary and Conclusions: Comparisons Between Rats and Sheep

At this point, it is interesting to emphasize the potentially diverse roles that OT plays in mother-infant bonding. Activation of the PVN in parturient mammals causes the release of

OT into several different brain regions (Numan et al., 2006), and OT appears to exert a variety of functional effects at these sites. OT release into MPOA, VTA, and NA boosts maternal motivation and attraction to young at parturition. OT release into NA, in conjunction with DA, appears to promote the synaptic plasticity within the NA-VP circuit so that maternal attraction to young persists throughout the postpartum period in the absence of continued pregnancy hormone stimulation. Finally, in those species, such as sheep, that form selective attachments to particular young, OT action on the olfactory bulbs and MeA/CoA may participate in the neural plasticity mechanisms that regulate the development of selective recognition, with this process limiting the types of stimuli that gain access to NA-VP reward and attraction circuits.

The research we have described for sheep has focused on the mechanisms underlying the development of the selective recognition process, while the research we have described for rats has focused on the mechanisms that may be responsible for the development an enduring attraction between a mother and her young. Future research on sheep might examine how a persistent attraction is formed between a ewe and her lamb, using the rodent research as a guide. Explorations of the role of MPOA interactions with the mesolimbic DA system, and amygdala input to VP, in the development of the maternal bond in sheep should be illuminating. It would also be interesting to determine whether OT and DA interact in NAs to influence maternal bond formation in sheep.

In comparing sheep with rats, the types of stimuli that either directly or indirectly activate VP attraction mechanisms may determine whether a mother forms a selective or a nonselective long-term attraction to young. Under natural conditions in sheep, neural plasticity mechanisms within the olfactory bulbs and amygdala limit the types of infant stimuli that are hypothesized to activate VP attraction mechanisms; only the specific olfactory signature of the lamb that the ewe was exposed to at birth acquires to ability to persistently activate the attraction mechanism. In contrast, for rats, a generic pup stimulus, presumably composed of general olfactory, gustatory, auditory, and tactile properties, acquires the ability to persistently activate the attraction system. Significantly, however, the processes through which generic pup stimuli are shifted from promoting avoidance in virgins to promoting approach in parturient females is part of the nonselective recognition process that occurs in parturient rats, and there is some indirect evidence that such a shift may be promoted by OT action on the amygdala (and olfactory bulbs). Although we have not described this nonselective recognition process in detail, a more detailed discussion of this issue can be found in Numan (2015; 2012) and Numan and Insel (2003).

In conclusion, the recognition process and the persistent attraction process are the result of neural plasticity mechanisms that occur in two interacting neural systems, one regulating the types of infant stimuli that acquire a positive valence and the other regulating the relay of those stimuli to maternal attraction/motivational mechanisms and the strengthening of that neural connection. These processes will be elaborated in Fig. 5, which provides a model of pair bond formation, a model that might be quite similar to what occurs during sheep maternal bonding to their lambs.

Maternal Behavior in Mice and Allomaternal Behavior

Feral virgin female house mice act like virgin female laboratory rats when first exposed to pups: they ignore or attack pups; the hormonal and other physiological events associated with the end of pregnancy stimulate the immediate onset of maternal behavior in feral parturient mice (Numan & Insel, 2003). In contrast, as a result of the inbreeding and selective breeding used to create laboratory strains of mice, virgin female laboratory mice typically show spontaneous maternal behavior, retrieving and adopting a nursing posture over pups within minutes after the pups are placed in the female's home cage (Numan, 2015; Numan & Insel, 2003). Therefore, the onset of maternal behavior in laboratory mice is relatively emancipated from the control of pregnancy hormones. However, the hormonal events of pregnancy do boost maternal motivation, which results in primiparous postpartum mice being more likely than virgin females to enter a novel (fear-inducing) environment in order to retrieve displaced pups back to their home cages (Numan & Insel, 2003). Importantly, after four days of pup exposure, virgin female laboratory mice are also more willing to retrieve pups from a novel environment back to their home cages (Stolzenberg & Rissman, 2011). Therefore, maternal experience can influence the future maternal behavior of laboratory mice. It would be interesting to perform the following maternal memory-like experiment on lab mice: allow one group of primiparous mice 1 hr of maternal experience with pups in the home cage and then remove the pups. For the other group of postpartum mice, remove the pups as soon as they are born. Ten days later, test the degree to which these females are willing to retrieve foster pups from a novel T-maze back to their home cages. It is predicted that the brief 1 hr maternal experience will increase the tendency of females to retrieve pups from the novel environment.

MPOA neural activity is essential for maternal motivation in virgin and postpartum laboratory mice (Akther et al., 2014; Tsuneoka et al., 2013; Wu et al., 2014), as is the OTR, since mutant female mice with a knockout mutation of the OTR show deficits in the onset of maternal behavior (Rich et al., 2014; Takayanagi et al., 2005). There is also evidence that the MPOA may promote BMA/BLA input to VP in the regulation of maternal behavior in mice (Akther et al., 2014; Okabe et al., 2013; also see Lee & Brown, 2007), and that OT may act at the level of NA to influence such behavior (Akther et al., 2013; Jin et al., 2007; cf. Dolen et al., 2013). Therefore, given that maternal experience influences the future maternal behavior of mice, it is likely that some of the neural plasticity changes proposed for rats also occur in mice.

Allomaternal behavior, where adult virgin females care for conspecific pups, occurs naturally in some mammalian species (Numan & Insel, 2003). In prairie voles, about 50% of virgins are spontaneously maternal (Olazabal & Young, 2006a; cf. Lonstein & De Vries, 1999). Note that the remaining 50% of virgins are not maternal, and that when an OTR antagonist is injected into NAs, 0% of virgin female prairie voles are spontaneously maternal (Olazabal & Young, 2006a). Interestingly, using systemic injections of a nonselective DA receptor antagonist, Lonstein (2002) has provided evidence that DA neural systems promote maternal motivation in postpartum prairie voles. Therefore, since 100% of primiparous female prairie voles are naturally maternal at parturition (Hayes & De Vries, 2007), the combined experimental results suggest that the physiological events of pregnancy

termination, coupled with OT, and perhaps DA, action on NA, promote full maternal motivation (cf. Ross et al., 2009b). Surprisingly, the involvement of the MPOA in vole maternal behavior has not been directly examined. In order to distinguish maternal motivation from maternal memory and the formation of a persistent maternal bond in prairie voles, it would be interesting to determine whether 100% of primiparous females that receive a brief maternal experience at parturition would subsequently respond maternally to foster pups that are presented to them 10 or more days later, after the influences of pregnancy hormones have waned. As in rats, perhaps DA and OT action on NA would contribute to the formation of such a long-lasting mother-infant bond.

Insights from allomaternal behavior in non-human mammals are clearly relevant to humans. Hrdy (2009) has proposed that allomaternal behavior was essential for infant survival during early human evolution in hunter-gatherer type societies, and therefore favored by natural selection. The evolution of brain mechanisms that promote allomaternal behavior may explain why maternal behavior is relatively emancipated from endocrine control in women, allowing for the adoption of infants and perfectly normal maternal behavior. As in mice, however, the hormonal and neuropeptide (OT) events associated with parturition boost maternal motivation and mother-infant bonding in women (Numan & Insel, 2003; Rilling, 2013), and the maternal motivation of nulliparous women who adopt infants may also improve with experience, suggesting that neural plasticity mechanisms similar to those involved in rodent maternal memory may also occur in the human maternal brain (cf. Scanlan et al., 2006).

Partner Preferences and the Pair Bond

Socially monogamous prairie voles (*Microtus ochrogaster*) have provided a wonderful opportunity to explore the neural mechanisms of social attachment between adults in a mating pair, and this research has revealed remarkable parallels between the neural mechanisms of mother-infant bonding and pair bonding (Johnson & Young, 2015; McGraw & Young, 2010; Ross & Young, 2009; Young & Wang, 2004). In fact, it is highly plausible that the neural mechanisms present in virtually all mammalian species to promote maternal motivation and mother-infant bonding have been modified by natural selection to establish the capacity to develop a selective bond with a mate during the evolution of monogamous mating strategies. The formation of a pair bond in prairie voles in the laboratory is assessed by using the partner preference test (Williams et al., 1994). In this test, after a period of cohabitation, during which experimental manipulations can occur, the partner of the experimental subject is tethered to one chamber of a 3-chambered testing arena, restricting its movement to that chamber. A novel opposite sex “stranger” is tethered to the opposite chamber, and the experimental subject is placed in the center chamber and is free to associate with either stimulus animal. A partner preference, which is considered to be a proxy for a pair bond, is typically defined as the experimental animals spending twice as much time in contact or close proximity with partner compared to with the stranger. Mating facilitates the development of a partner preference in both male and female prairie voles. However, longer exposures to an opposite sex partner without mating can also result in a partner preference, perhaps analogous to the onset of maternal care in virgin female rats following repeated exposure to pups. We will focus our attention in this review on mating-

induced partner preference formation as the neurochemical processes underlying mating-induced partner preferences are best understood and share a number of features with the onset of maternal care following parturition and with the establishment of maternal memory.

As is the case for maternal responsiveness, once the partner preference has been established, it endures in the absence of further partner stimulation. Following the establishment of a partner preference, the pair can be separated for two weeks and still display a partner preference when they are reunited (Insel & Hulihan, 1995). Thus the partner preference is thought to involve neural plasticity resulting in selective neural responsiveness to the unique social stimuli of the partner (e.g. olfactory signature) much like that proposed to give rise to maternal selectivity in sheep. An apparent difference between maternal behavior and pair bonding is that both male and female prairie voles develop partner preferences following mating. Although there may be subtle differences in the regulation of partner preference formation between the sexes, common neural pathways are engaged during pair bonding in males and females. However, in those species where paternal behavior occurs, the brain mechanisms for paternal behavior match those regulating maternal behavior (Dulac et al., 2014; Numan, 2015; Wu et al., 2014). Therefore, it is highly likely that there is also significant overlap between the mechanisms of paternal-infant bonding and male pair bonding to a female partner.

Brain Mechanisms of Pair Bonding

As mentioned above, the proposed neural circuitry of maternal motivation, maternal recognition processes, and maternal memory outlined here and elsewhere (Numan, 2015) has been influenced by our understanding of the neural mechanisms underlying pair bonding. The opposite is true as well. While the roles of OT, vasopressin, and DA in the NAs and VP in regulating pair bonding have been well documented (Young et al., 2011; Young & Wang, 2004), the precise neural mechanisms by which these molecules lead to the formation of a selective social preference for the partner has yet to be determined, and is the subject of speculation. However, one thing is clear. There are many remarkable parallels between maternal bond formation and pair bond formation. Here we will present the findings from experimental manipulations and then propose a neural network model highlighting the parallels with the regulation of maternal behavior. We will show that pair bond formation represents an amalgam of the sheep and rat maternal literature: the mechanisms regulating the selective recognition of one's mating partner map on to the selective recognition mechanisms that develop in maternal sheep, and the mechanisms regulating a mate's persistent attraction to his/her mating partner map on to the persistent attraction of a rat mother to her pups (maternal memory).

Oxytocin, Nucleus Accumbens, and the Mesolimbic Reward System

With the knowledge that OT plays a role in maternal bonding, Sue Carter and colleagues hypothesized that OT may also play a role in the development of the pair bond. This hypothesis was first tested in females and similar results were later found in males (Cho et al., 1999; Williams et al., 1994). In the initial study, virgin female prairie voles were given central (intracerebroventricular) infusions of OT or vehicle and cohabitated with a male for 6 hr without mating. Vehicle control females failed to display a partner preference.

However, those females receiving OT displayed robust partner preferences and this effect was blocked with co-administration of an OT antagonist. Centrally infused OT antagonist also prevented mating-induced partner preferences in females, suggesting that the endogenous OT system plays a role in partner preference formation (Insel & Hulihan, 1995). The vast majority of studies examining the role of OT on partner preference formation have been performed in female prairie voles because of the incorrect assumption that OT does not play a role in male partner preference formation based on the results of early seminal studies (Insel & Hulihan, 1995; Winslow et al., 1993). However, we now know that the endogenous OT system plays an important role in both males and females (A.C Keebaugh, Z.R. Johnson and L.J. Young, unpublished data), but our discussion here will be restricted to studies in female prairie voles that have been published.

Clues to the neuroanatomical site of OT action in the formation of partner preferences came from comparative analysis of OTR distribution in prairie voles compared to vole species that do not form pair bonds. Prairie voles had higher densities of OTR in the mPFC, NA and lateral amygdala than nonmonogamous montane and meadow voles (Fig. 4; Insel & Shapiro, 1992). Indeed, OTR is virtually absent in the NA of nonmonogamous vole species. This robust species difference in OTR density in the mesolimbic reward pathway led to speculation that these receptor populations may be involved in mating-induced partner preference formation. Indeed, infusion of an OT antagonist into the NA or mPFC, but not into the adjacent caudate-putamen, prevents mating-induced partner preferences in female prairie voles (Young et al., 2001). As already noted, similar infusions of OT antagonists into the NA also disrupt allomaternal care in female prairie voles (Olazabal & Young, 2006a) and maternal memory formation in rats (D'Cunha et al., 2011), consistent with the notion of parallel processes being involved in both behaviors. The effects of such infusions on paternal behavior in voles would be interesting to explore.

There is significant individual variation in the density of OTR in the NA of prairie voles (Young, 1999). Female prairie voles with higher density of OTR in the NA are more likely to display spontaneous allomaternal behavior toward novel pups. However, the regulation of allomaternal behavior and partner preference formation by the OT system can be dissociated to some degree. For example, increasing OTR expression in the NA of female prairie voles in adulthood using viral vector gene transfer accelerates partner preference formation but does not increase allomaternal nurturing (Ross et al., 2009b). In contrast, increasing OTR expression by infusing the viral vector at weaning (21 days of age) accelerates partner preference formation and allomaternal nurturing when the subject becomes an adult (Keebaugh & Young, 2011). Similarly, suppressing OTR expression in the NA using viral vector mediated RNA interference beginning at weaning inhibits both partner preference formation and alloparental behavior (Keebaugh et al., 2015). This suggests that OTR signaling in the NA may have an organizational role in developing the neural pathways involved in spontaneous allomaternal behavior that is not necessary for enhancing partner preference formation. Nevertheless, OT action on NA is involved in both behaviors.

In mothers, OT is released in the brain during parturition and nursing due to vaginocervical and suckling stimulation, respectively. What is the stimulus leading to OT release within the mesolimbic dopamine system of prairie voles during sexual interactions? This question was

addressed by placing an *in vivo* microdialysis probe into the NA of female prairie voles in order to monitor OT release during social interactions and mating with a male. Peak extracellular OT concentrations were detected in females during mating bouts (Ross et al., 2009a). Thus, while vaginocervical stimulation during delivery stimulates OT release in the parturient mother, similar stimulation during mating induces OT release in the NA to facilitate the formation of partner preferences in females. Although not examined in male prairie voles, mating has also been shown to stimulate central OT release in male rats (Waldherr & Neumann, 2007). As we shall see, OT does not act alone, but rather interacts with DA in the NA to facilitate partner preference formation.

Vasopressin and the Ventral Pallidum

Early research in male prairie voles suggested that arginine vasopressin (AVP, which is structurally similar to OT), but not OT, regulated the development of partner preferences following mating (Winslow et al., 1993). However, there is evidence that blocking OTR in the NA (and mPFC) prevents partner preference formation in males just as it does in females (A.C Keebaugh, Z.R. Johnson and L.J. Young, unpublished data). However, in addition to activation of the OTR system, males require AVP activation of V1a receptors (V1aR) for both the formation and the expression of mating-induced partner preferences (Donaldson et al., 2010; Winslow et al., 1993). Significantly, there is also evidence that central AVP systems may be important for pair bonding in female prairie voles (Cho et al., 1999).

As was the case for OTR, comparison of the distribution of the V1aR in the brains of prairie voles and nonmonogamous montane and meadow voles revealed robust species differences in expression patterns (Fig. 4; Young & Wang, 2004). Of particular interest, prairie voles have a higher density of V1aR binding in the VP compared to meadow and montane voles, although differences are also found in the amygdala and thalamus. To identify which of these regions is responsible for AVP-dependent partner preference formation, a selective V1aR antagonist was infused into each site in virgin male prairie voles prior to cohabitation and mating. Blocking V1aR in the VP, but not the amygdala or thalamus, prevented partner preference formation (Lim and Young, 2004). It is likely that the species differences in V1aR expression in the VP may be partly responsible for the species differences in the ability to form a partner preference. When V1aR is over-expressed in the VP of male meadow voles to resemble the expression pattern of prairie voles, the meadow vole males develop partner preferences (Lim et al., 2004). Furthermore, reducing V1aR density in the VP of prairie voles using viral vector mediated RNA interference inhibited mating induced partner preferences in male prairie voles (Barrett et al., 2013). A separate study found that blocking V1aR in the lateral septum (LS) also prevented mating-induced partner preferences in male prairie voles (Liu et al., 2001). Furthermore, genetic variation in the 5' flanking region of the V1aR gene (*avpr1a*) is associated with variation in V1aR density in the LS and the probability of forming a partner preference following a brief cohabitation with a female (Hammock & Young, 2005). Interestingly, AVP signaling in the LS has also been shown to play a role in paternal behavior in prairie vole males (Wang et al., 1994), providing another intriguing example of parallels between parental nurturing and pair bonding.

Given the importance of the NA-VP circuit for pair bond formation in voles, with OT action on OTRs in NA being important in both males and females, and for AVP action on V1aR in VP being essential for the development of male partner preferences, it would be interesting to determine whether AVP acts on the VP of female voles to influence their pair bonding. In drawing parallels between maternal bond formation in rats and pair bonding in voles, it would also be interesting to examine whether AVP action on VP influences maternal memory.

In other rodents, AVP has been implicated in both social recognition and territorial behavior and aggression (Albers, 2012; Bielsky et al., 2005). This has led to speculation that pair bonding in male prairie voles may have developed, in part, by modifying neural systems typically involved in territorial behaviors (Young & Alexander, 2012). In this context, it is interesting to note that pair bonding in male prairie voles involves not only a selective preference to associate with the partner that requires both OT and AVP signaling in the NA-VP circuitry, but also a robust induction in selective aggressive behavior (mate guarding) towards unfamiliar male and female voles that is regulated in part by V1aR signaling in the anterior hypothalamus (Gobrogge et al., 2007; Gobrogge et al., 2009). The fact that AVP acts at different neural sites in male prairie voles to promote pair bond formation (VP) and mate guarding (anterior hypothalamus) shows that the bonding system and the aggression system are at least partly independent. Relevant to our discussion of parallels between the maternal system and the pair bonding system, there has been growing evidence that AVP also plays a role in vigilance and protective maternal aggression toward male intruders in rat dams (Bosch, 2013; Bosch & Neumann, 2012).

Dopamine, the Nucleus Accumbens and Partner Preference Formation and Maintenance

The discovery that OTR and V1aR signaling in the NA and VP, respectively, is necessary for partner preference formation strongly suggested that DA may also be involved in pair bonding. Indeed DA signaling is critical for partner preference formation in both sexes. Peripheral administration of a non-selective DA antagonist prevented mating-induced partner preference formation following a 24 hr cohabitation period, while administration of apomorphine, a non-selective agonist facilitated partner preferences following a 6 hr cohabitation in the absence of mating (Aragona et al., 2003; Wang et al., 1999). Female prairie voles have a 50% increase in extracellular DA in the NA relative to baseline during mating, while males that mate are reported to have a 33% increase in DA turnover in the NA compared to males that do not mate (Aragona et al., 2003; Gingrich et al., 2000). DA acting on D2 receptors, but not D1 receptors, is necessary for partner preference formation since a selective D2 receptor antagonist prevents mating-induced partner preferences while selective D1 antagonists do not (Young et al., 2011). The neuroanatomical localization of D2-dependent partner preference formation was further explored using site-specific infusions of selective DA receptor antagonists or agonists into the NA. Microinjections of the D2 antagonist, eticlopride, into the NA, but not the mPFC, prevented mating-induced partner preferences in female prairie voles (Gingrich et al., 2000). Likewise, microinfusion of the D2 agonist, quinpirole, into the NAs, but not the NAc, facilitated partner preferences in male prairie vole in the absence of mating (Aragona et al., 2006).

In female prairie voles, simultaneous activation of D2 and OTR in the NA is required for partner preference formation. Infusion of a D2 antagonist into the NA prevented OT-induced partner preferences, while infusion of an OTR antagonist prevented D2 agonist-induced partner preferences (Liu & Wang, 2003). Thus neither OT nor DA is sufficient to develop a social attachment with a partner, but rather the simultaneous activation of both receptors is absolutely required for the development of a pair bond.

D1 and D2 DA receptors actually have opposing actions in the regulation of partner preference formation in male prairie voles. A selective D1 agonist prevents D2 agonist-dependent partner preference formation as well as mating-induced partner preference formation (Aragona et al., 2006). It has been proposed that the D1 receptor may play an important role in the maintenance of the pair bond in male prairie voles. Male prairie voles experience a reorganization in their NA DA receptor systems, such that during the first 2 weeks after the pair bond is formed, the density of D1 receptor increases substantially. Consequently, while in virgin males, mating induced DA release may result in higher D2 signaling in the NA relative to D1 signaling, once the bond is formed, D1 signaling becomes more prominent and therefore acts to prevent subsequent pair bonds with novel partners. Indeed, D1 antagonists significantly reduce the expression of selective aggression in pair bonded males (Aragona et al., 2006).

In comparing the roles of DA action in NA in pair bond formation in voles and maternal memory in rats, note that DA action on D1 and D2 receptors in NA promotes maternal memory. Unlike pair bonding in voles, DA action on D1 receptors does not act to depress maternal bonding. It would be interesting to determine whether in voles D1 receptors are only located on MSNs, while in rats, D1 receptors are also located presynaptically on incoming amygdala afferents to NA, as hypothesized in the model shown in Fig. 3.

The Amygdala, the Transmission of Social Information, and the Development of Selective Recognition

The role of the BMA/BLA in partner preference formation has yet to be explored, but given their roles in maternal motivation and their role in transmitting multimodal social information to the NA and VP, these nuclei may play a significant role in pair bond formation. There is one study that provides indirect evidence for this proposal (Kirkpartick, Carter, Newman, & Insel, 1994). Male prairie voles were paired with an ovariectomized female for 2 days, allowing the males to become familiar with the female's stimulus characteristics. Subsequently, the males received either large neuron-specific lesions of the amygdala that included MeA, CoA, and BMA, or sham lesions. Males were then placed in a two-compartment cage, with one compartment containing the familiar female, while the other compartment was empty. When given a choice, control males spent most of their time in physical contact with the familiar female, and this time was significantly greater than that exhibited by the amygdala-lesioned males. Although this test is not partner preference test, it is a social attraction test. Perhaps, as described for sheep, the BMA relays general sensory qualities to NA-VP circuits that mediate social attraction, while MeA and CoA relay specific olfactory stimuli to these attraction mechanisms.

In the rat mother, the hormones of pregnancy termination prime the MPOA/vBST to maximally respond to OT release that is triggered by vaginocervical stimulation during parturition so that, in response to sensory input from the pups, MPOA/vBST projections stimulate the VTA to release DA in the NA. In prairie voles, one hypothesis is that sex steroids prime the MPOA to generate sexual motivation, and it is mating itself that stimulates the release of dopamine from VTA projection into the NA. Alternatively, it has been proposed that MPOA projections to VTA are involved not only in maternal motivation, but also in male and female sexual motivation (Stolzenberg & Numan, 2011). Therefore, it should not be excluded that the MPOA participates in the release of DA into NA during mating in prairie voles. During mating, OT and D2 receptors are being simultaneously activated in the NAs, perhaps suppressing the inhibition of the VP. In males there is also V1aR activation in the VP. The release of the VP from inhibition is proposed to lead to appetitive affiliative responses to the partner. Yet, for a selective bond to be formed, neural encoding representing the identity of the partner must also be transmitted to the NA and/or VP according to our hypothesis. Olfactory social information representing the partner's identity is transmitted through olfactory amygdala nuclei (e.g. MeA, CoA), which then relay that neural encoding either directly or via the BMA/BLA to the NA and VP. Studies in mice demonstrate that both OTR and V1aR signaling are required for individual recognition (Bielsky et al., 2005; Ferguson et al., 2001). Most importantly, OT signaling in the MeA is critical for the formation of a social memory. OT knockout mice have social amnesia after a social encounter, and microinfusion of OT into MeA restores social recognition ability (Ferguson et al., 2001). We hypothesize that the convergence of the simultaneous activation of OTR/V1aR and D2 receptor in the NA-VP circuit combined with OTR activation in MeA allows the neural signature of the social cues from the partner to be transmitted from the MeA/BMA/BLA to the NA-VP, resulting in synaptic plasticity within this amygdala to NA-VP circuitry. This plasticity leads to enhanced mesolimbic reward system activation by the neural olfactory signature of the partner even in the absence of further OT and DA stimulation, perhaps caused by a heightened stimulation of VP output by the partner's stimuli.

In comparing the development of selective recognition mechanisms for pair bonding in voles and maternal bonding in sheep, it is interesting to speculate that OT release into the brain caused by the vaginocervical stimulation or other mating stimuli in voles and with vaginocervical stimulation associated with parturition in ewes acts on both the olfactory bulbs and MeA/CoA to restrict that nature of the olfactory stimuli relayed to the VP so that selective recognition for one's mate or lamb develops. As mentioned for sheep, experimental research should be aimed at determining whether antagonism of OTRs in the amygdala, and perhaps olfactory bulbs, is actually capable of blocking the development of selective recognition in prairie voles.

A Hypothetical Neural Model for Pair Bonding in Voles

This research and analysis strongly supports the view that the neural networks involved in sexual motivation, processing of social cues, and bonding in prairie voles overlap in significant ways with the models proposed for maternal motivation and mother-infant bonding (Figs. 2 and 3). Fig. 5 presents a hypothetical model of pair bond formation in

prairie voles that highlights these similarities. The model proposes that during mating, both VTA-DA input to NAs and PVN-OT input to the NAs and to the olfactory bulbs and amygdala are stimulated. In addition, olfactory and other stimuli from the mating partner activate amygdala glutamatergic input to NA-VP and AVP input, proposed to arise from MeA (Lim & Young, 2004), to VP. The mechanisms of pair bond formation are proposed to involve a two-step plasticity process: an individual recognition stage and a persistent attraction phase. OT action at the level of the amygdala, and perhaps also at the level of the olfactory bulbs, is shown as promoting selective social recognition and memory by strengthening synapses in the amygdala (outlined with a dashed circle) that then allow olfactory and other stimuli from the mating partner to activate amygdala input to NA-VP. For the development of a persistent attraction to one's mating partner, DA action on D2 receptors and OT action on OTRs in NA (shown as D2-OTR heteromers) are proposed to depress the activity of NA GABAergic MSN input to VP, resulting in a disinhibition of VP. The disinhibited VP is now strongly activated by the partner-induced glutamate and AVP input that it receives from the amygdala, and these synapses are strengthened (outlined with dashed circles). Once mating is completed, and a mate is given a partner preference test, the specific olfactory and other stimulus characteristics of the partner, but not of a stranger, are now capable of strongly activating VP over long periods of time, creating an enduring and selective social bond. As described in the maternal section, mechanisms similar to these may underlie selective mother-infant bonding in sheep.

This detailed model is supported by much research, but it clearly contains many hypothetical elements that are in need of future research support. As some examples: (a) On which neurons within NAs are OTRs located? More specifically, are D2-OTR heteromers present on MSNs in the NAs of prairie voles and are they necessary for bond formation? (b) Is MeA the source of AVP input to VP, and is AVP input to VP only important for pair bonding in males, or is it also important for females? (c) Is the output of VP necessary for pair bond formation and maintenance? For example, would inactivation of VP prevent bond formation or disrupt its maintenance? (d) Do OT and DA act to depress NA and activate VP during a mating bout in prairie voles as has been hypothesized for the maternal system? (e) Is OT action on MeA involved in the development of selective recognition?

Comparative Analysis of the Neural Regulation of Maternal-Infant Bonding and Pair Bonding

In comparing Fig. 3 with Fig. 5, note the crucial similarities in the mechanisms proposed to regulate mother-infant bonding and pair bonding. Activation of the mesolimbic DA and oxytocinergic systems is involved in both bonding processes. Further, DA and OT action on NA is proposed to depress NA input to VP. This depression allows amygdala input to VP, which relays either general or specific social stimuli to VP, to be strengthened, allowing for the development of a persistent attraction to those particular social stimuli. Also, although not shown in Fig. 3, which represents a model for maternal memory in rats, OT action in the olfactory bulbs and/or amygdala may promote the development of selective recognition in maternal sheep and in pair-bonded voles (see Fig. 5).

While there are remarkable similarities in the neural systems involved in maternal behavior and pair bonding, there are some notable differences that may be informative for understanding the uniqueness of each behavior. D2 facilitates and D1 inhibits pair bonding, while it is clear that D1 enhances maternal responsiveness and that DA action on both D1 and D2 receptors in NAs contributes to maternal memory formation. This difference may be related to differences in the NA-VP circuitry that regulates each kind of bonding. Perhaps presynaptic D1 receptors are present in the rat NAs (Fig. 3) but not in the vole NAs (Fig. 5).

Another apparent difference is in the role of the MPOA. In rat dams, the MPOA orchestrates the activity of the VTA and PVN to release DA and OT into the NA in response to pup stimuli, while in prairie voles, it is hypothesized that sensory input (e.g. vaginocervical stimulation in females) during mating is stimulating release of these neuromodulators. However, it should be noted that no experimental manipulations have investigated a role for the MPOA in partner preference formation and maintenance, and this structure is likely involved in regulating the motivation to engage in sexual activity (see Stolzenberg & Numan, 2011) that leads to the pair bond. Further, since mating stimuli activate the MPOA in male and female rodents (Lim & Young, 2004; Pfaus et al., 2006), it is certainly possible that the MPOA activates VTA and PVN in prairie voles, in this way further enhancing DA and OT release into NAs. Since neural inactivation of the MPOA disrupts the established mother-infant bond in rats and sheep, it would be interesting to determine whether such inactivation would disrupt an established pair bond in male and female prairie voles. With respect to pair bond formation in female prairie voles, since MPOA inactivation in rodents does *not* disrupt lordosis (a consummatory female sexual response which allows the male to have a successful intromission and which provides the female with vaginocervical stimulation), an interesting question is whether such inactivation would disrupt pair bond formation in females.

There are undoubtedly other important differences in the regulation of mother-infant bonding and pair bonding, although a basic neural scaffold may be common to both behaviors. Maternal nurturing is evolutionarily very ancient and present in all mammalian species, and under heavy selection pressure to be maintained. By contrast, pair bonding is rare in mammals and has evolved multiple times independently, and we can only speculate that in each species where it exists common pathways with maternal bonding are present in general form, but that specific neural differences between species are likely to exist as well, with such differences contributing to variations in the strengths of the particular social bonds that actually form (cf. Dolen et al., 2013).

Future Directions

Since the pioneering studies of Jay Rosenblatt and his colleagues, we have learned a great deal about the hormonal and neural regulation of maternal behavior, which has guided, and has been guided by, our understanding of the underlying neural mechanisms of pair bonding. However, there are areas where our models presented in this review are built upon informed speculation, and there are many gaps in our understanding of precisely how the various neurochemicals modulate connectivity between regions within the circuit. As already noted, we do not know whether OTRs are localized on neurons expressing D1 or D2 receptors, or

both. Sensitive molecular techniques such as *in situ* hybridization and single-cell transcriptomics will likely help us test our models and better understand the interaction of these receptors. We do not understand how OT or AVP is affecting the neural activity of the NA and VP, respectively. Nor do we completely understand the role of the MPOA in driving neural changes in NA and VP, particularly in prairie voles. Simultaneous electrophysiological recordings in multiple brain regions (e.g. PFC, BMA/BLA, MeA, MPOA, NA, VP) in free moving animals following exposure to pups or mating partners, combined with pharmacological manipulations would allow us a better understanding of the mechanisms through which OT, DA, AVP and their receptors modulate the communication across these brain regions.

Finally, optogenetics is a powerful tool for dissecting out the role of subpopulations of neurons in a selected brain region in the regulation of behavior. A recent report used optogenetics to identify the role of MPOA galanin-containing neurons in the transition to paternal responsiveness in male mice (Wu et al., 2014). Optogenetics and electrophysiology could be a powerful combination to detect patterns of neural communication associated with parenting or pair bonding behavior and then to demonstrate causality by mimicking that communication experimentally with laser stimulation.

Broader Implications

The neural models outlined in this chapter are derived predominantly from laboratory studies in rats, sheep, and voles. Are these findings relevant to our own species? Clearly we have become somewhat emancipated from the strict regulation of parental behavior and pair bonding by hormones and neurochemistry. However, there is growing evidence that OT and many of the neural systems outlined in this chapter are engaged in both parental behavior and other social relationships in humans (Numan, 2015; Rilling, 2013; Rilling & Young, 2014; Scheele et al., 2013; Strathearn et al., 2009; Walum et al., 2012; Walum et al., 2008). Indeed, a case has been made that MPOA interactions with the OT and mesolimbic DA systems are involved in mother-infant bonds in humans (Numan, 2015), although more research needs to focus on the septal-MPOA-hypothalamic regions (cf. Moll et al., 2012). With respect to the involvement of OT neural systems in human parents, intranasal OT leads to increased parental synchrony and engagement with the child, which in turn increases salivary OT in the child (Weisman et al., 2012). Intranasal OT also decreases aversive responses from infant stimuli (e.g. crying) and increases activation of reward systems (Rilling, 2013). With respect to pair bonding, intranasal OT given to men in romantic relationships causes the men to rate their partner, but not other females, as being more attractive than after placebo, and results in a heightened BOLD response in the NA specifically when viewing images of the partner (Scheele et al., 2013).

Since maternal behavior can be viewed as the most primordial caregiving system in mammals, that system has likely provided the rudimentary neural foundation for the broader types of prosocial bonds and aid-giving responses that form in human societies, even beyond those involved in monogamous pair bonds. Indeed OT and many of the other neural systems described in this review have been implicated in a wide range of human social cognition, emotion, and behavior, including empathy, trust, cooperation, and altruism, that may well

have evolutionary roots in their roles in regulating maternal responsiveness. In other words, the neural systems regulating maternal responsiveness may not only serve as a foundation for pair bonds, but also for other strong social bonds that form in human societies, where cooperation and altruism play such important roles in fostering social cohesion. In humans, neocortical brain regions, cognitive factors, and emotional feeling states are clearly important for mother-infant bonding and for other types of social relationships (Numan, 2015; Parsons et al., 2013; Rilling, 2013), but such mechanisms likely interact with some form of the primarily subcortical mechanisms regulating parental responsiveness and pair bonding that were described in this review. Such an interaction may allow thinking and feeling to be translated into prosocial aid-giving behavioral responses. As an example, the anterior insular cortex (AI) is a prominent part of the neural circuitry underlying empathic feeling states in humans (Craig, 2009; Engen & Singer, 2013), and AI has direct and indirect neural connections with the amygdala, PFC, NA, and hypothalamus. Such projections may allow empathic emotions to promote aid-giving responses not only to one's offspring or spouse, but also to other individuals in one's larger social group (for reviews, see Brown et al., 2012; Numan, 2015).

Understanding the neurobiology of mother-infant bonding and pair bonding may also have important clinical implications for improving social functioning in psychiatric disorders. Common features of maternal behavior and pair bond formation include the neural processing of social information by the amygdala and PFC, and the transmission of that social information to the mesolimbic DA pathway to lead to directed prosocial responses to another individual. Both processes involve neurotransmission at OTR, V1aR and DA receptors within the neural network presented in this chapter. There is increasing evidence that activating the OT system in human subjects increases the salience of social stimuli and the reinforcing value of those stimuli, as it does in a rat dam (Young, 2015). These properties could be incredibly useful for improving social functioning in psychiatric disorders such as autism spectrum disorder [ASD] (Penagarikano et al., 2015; Modi et al., 2015; Modi & Young, 2012). There is already promising evidence that intranasal OT can improve some aspects of social functioning in ASD (Andari et al., 2010; Young & Barrett, 2015).

Therefore, the transformations that occur in the maternal brain of rats and sheep, and neural mechanisms that lead to the intense and enduring maternal motivation to nurture and protect offspring, are a powerful model for understanding many aspects of social relationships in our own species, with implications for human parenting, romantic partnerships, as well as healthy functioning in a complex social environment.

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Highlights

- Mother-infant bonding is typical of all mammals but monogamy with pair bonding is rare.
- Remarkable similarities exist in the neural mechanisms of mother-infant bonding and pair bonding.
- Dopamine and oxytocin action on the nucleus accumbens-ventral pallidum circuit is involved.
- The maternal neural circuitry may have provided the foundation for other types of strong social bonds in mammals.

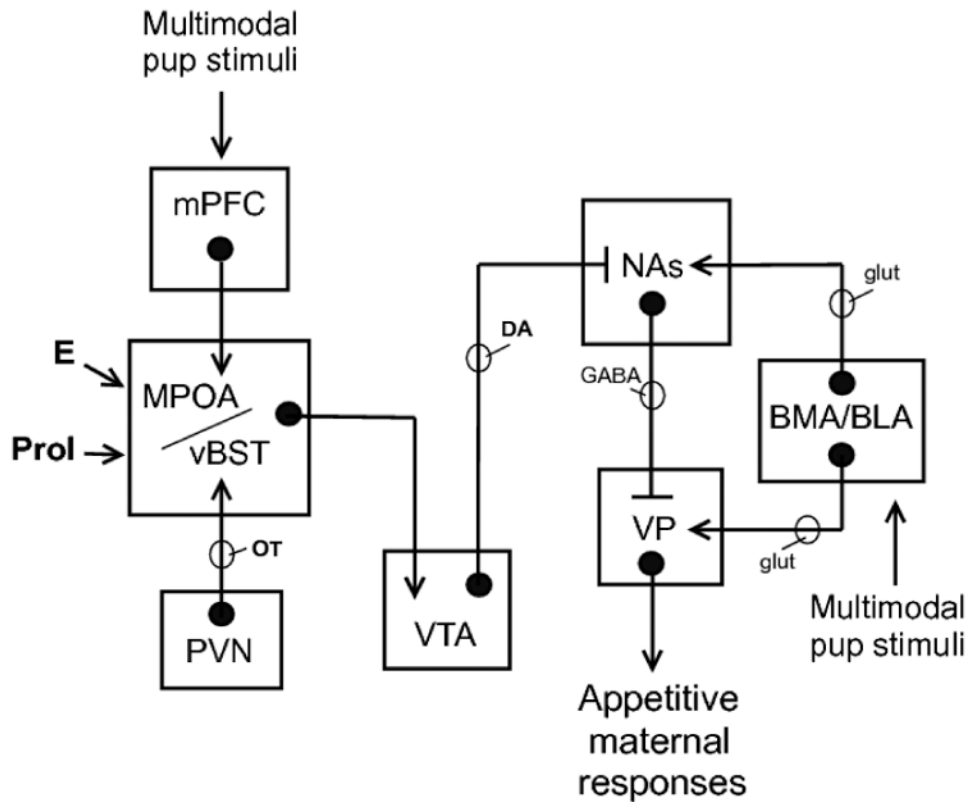


Figure 1.

A neural model showing how an hormonally primed medial preoptic area and adjoining ventral bed nucleus of the stria terminalis (MPOA/vBST) might influence maternal motivation by interacting with the mesolimbic dopamine (DA) system. Pregnancy hormones (estradiol = E; prolactin = prol) act on MPOA/vBST, rendering such neurons responsive to oxytocin (OT) (derived from the paraventricular hypothalamic nucleus: PVN) and to multimodal pup stimuli derived from the medial prefrontal cortex (mPFC). The activated MPOA/vBST efferents project to and stimulate ventral tegmental area (VTA) DA input to nucleus accumbens shell (NAs). DA action on NAs depresses the responsiveness of NAs to afferent glutamatergic (glut) inputs from the basomedial and basolateral amygdala (BMA/BLA). These latter regions are shown as relaying pup-related sensory inputs to both NAs and ventral pallidum (VP). Depression of NA responsiveness releases the VP from GABAergic inhibition derived from NAs, which opens a gate that allows VP to fully respond to BMA/BLA inputs. A fully active VP is proposed to be necessary for the occurrence of appetitive maternal responses. Axons ending in an arrow indicate excitation and those ending in a bar indicate inhibition. *Modified from Figure 6 in Numan and Stolzenberg (2009) with permission from Elsevier.*

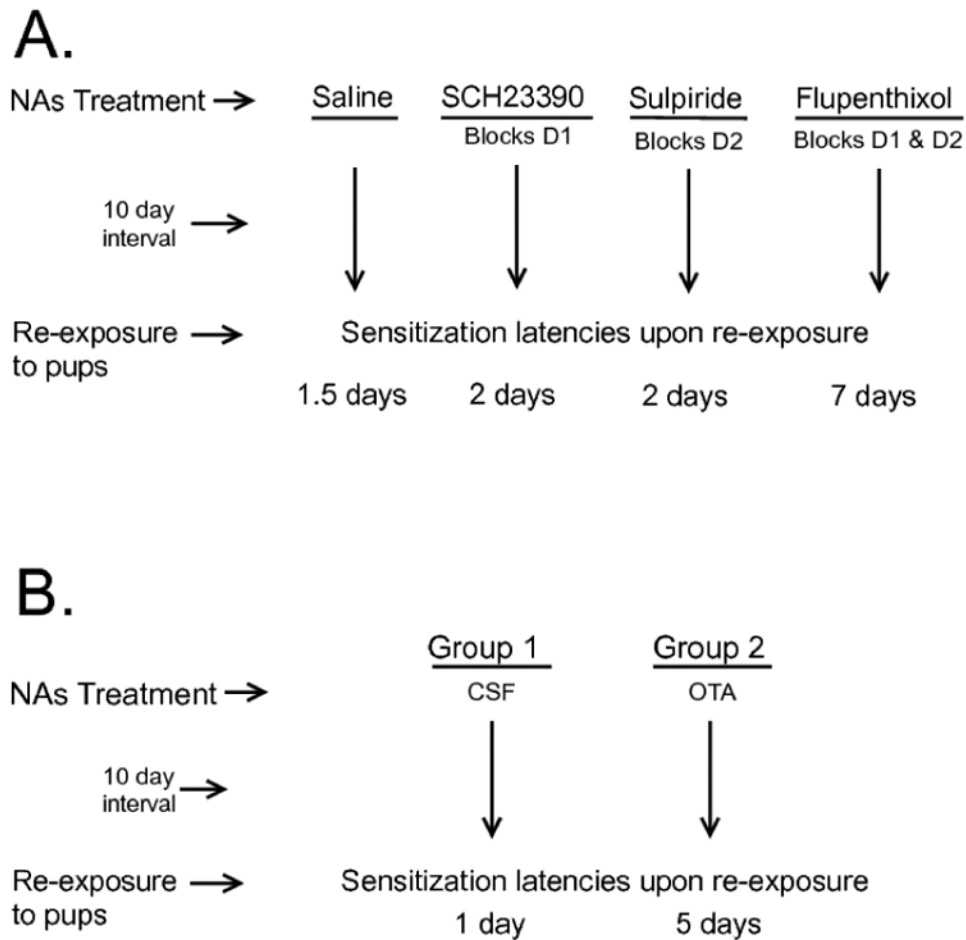


Figure 2.

Dopamine action on D1 and D2 receptors (**A**), and oxytocin action on oxytocin receptors (**B**), in the nucleus accumbens shell (NAs) are involved in the establishment of maternal memory in rats. Primiparous rats are allowed one hour of postpartum experience with their young, after which the pups are removed. Immediately thereafter, various neurochemicals are microinjected into NAs in different groups of rats. Ten days later, the rats are re-exposed to pups and sensitization latencies are measured. As shown in **A**, blockade of both D1 and D2 receptors in NAs with flupenthixol disrupts maternal memory formation (Parada et al., 2008). As shown in **B**, injection of an oxytocin receptor antagonist (OTA) into NAs also blocks maternal memory formation (D’Cunha et al., 2011). Other abbreviations: CSF = artificial cerebrospinal fluid. In comparing these findings with the development of pair bonds in prairie voles, as shown in Fig. 5, a crucial similarity is that DA action on D2 receptors and OT action on OT receptors within NA are involved in both types of bond formation. *Reproduced from Figure 5.16 in Numan (2015) with permission from Elsevier.*

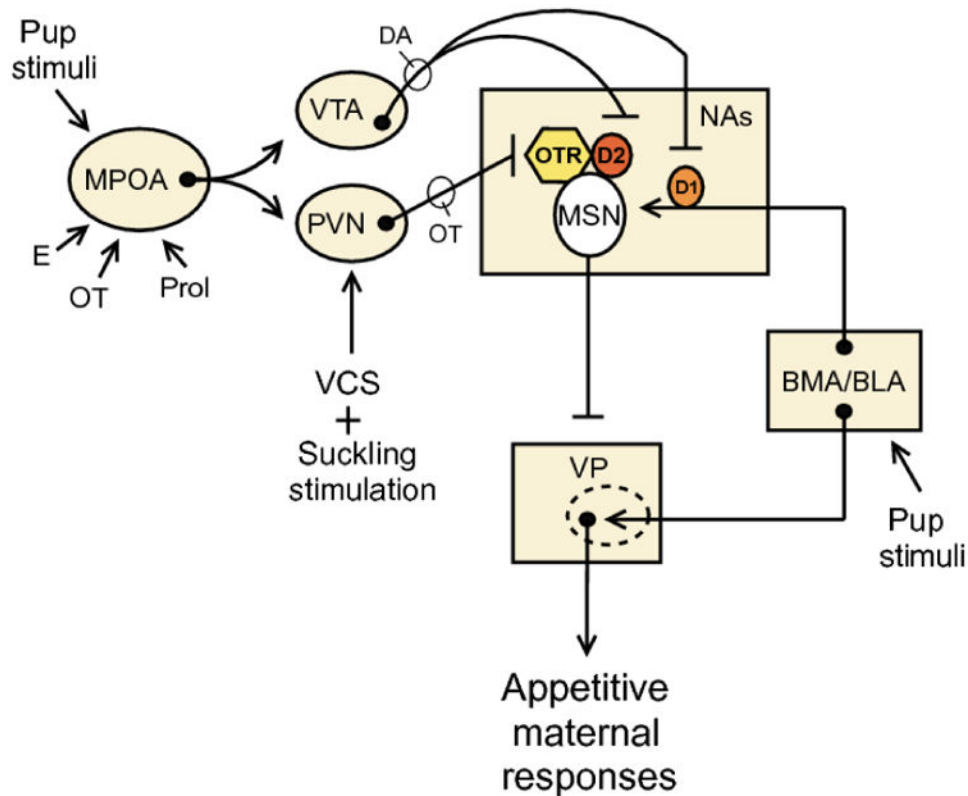


Figure 3.

A neural model for maternal memory formation in rats. The model describes how oxytocin (OT) and dopamine (DA) action on the nucleus accumbens shell (NAs), driven in part by medial preoptic area (MPOA) activity during an initial maternal experience, might promote synaptic strengthening (dashed circle) across synapses between the basomedial/basolateral amygdala (BMA/BLA) and the ventral pallidum (VP). This synaptic strengthening is proposed to be important for maternal memory formation. An important underlying assumption of the model is that strong depression of NAs medium spiny neuron (MSN) inhibition of VP allows the VP to be super-excited by BMA/BLA glutamatergic inputs, which then strengthens the BMA/BLA-to-VP synapse. The MPOA is shown as activating DA and OT release into NAs. OT release into NAs is also activated by the vaginocervical stimulation (VCS) and suckling stimulation that occurs in parturient rats. The paraventricular hypothalamic nucleus (PVN) is shown as the source of OT input to NAs. DA action on presynaptic D1 receptors depresses BMA/BLA excitation of MSNs. DA action of D2 receptors directly depresses MSNs that project to VP. D2 dopamine receptors may form heteromers with oxytocin receptors (OTR) on MSNs, and OT action at such OTRs appears to act as a neuromodulator, enhancing the inhibitory effects of DA at the associated D2 receptor. These combined effects should result in a profound depression of neural activity between NAs and VP. Axons ending in a bar have inhibitory effects, and those ending in an arrow are excitatory. Other abbreviations: E = estradiol; Prol = prolactin; VTA = ventral tegmental area. *Modified from Figure 5.17 in Numan (2015) with permission from Elsevier.*

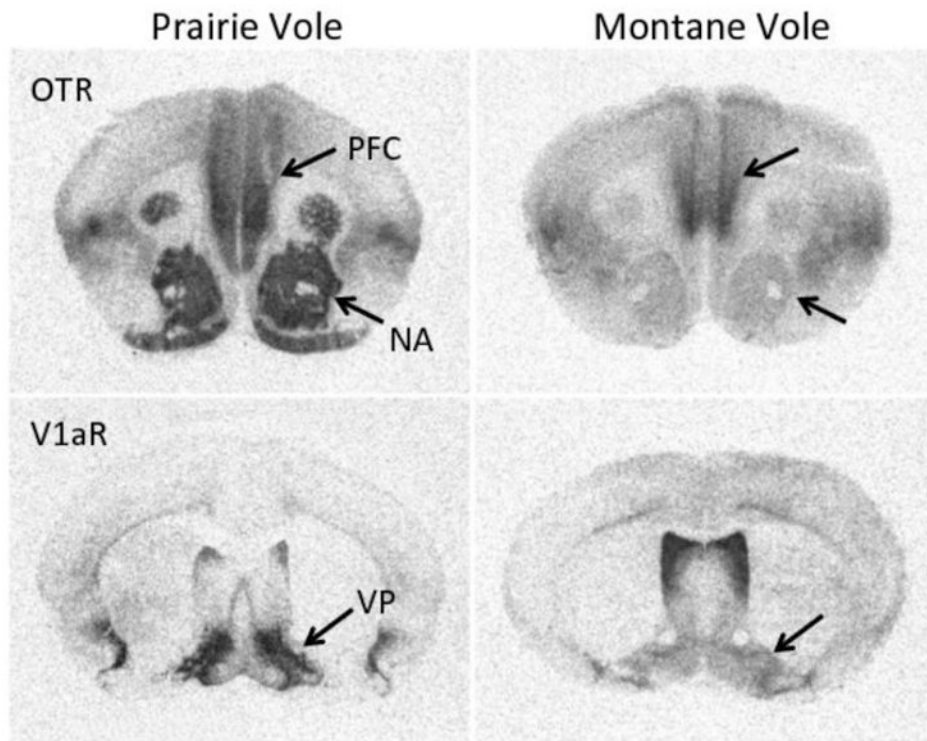


Figure 4. Receptor autoradiograms illustrating species differences in oxytocin receptor (OTR, top row) and vasopressin V1a receptor (V1aR, bottom row) densities in the nucleus accumbens (NA) and ventral pallidum (VP) of monogamous prairie voles (left panels) and nonmonogamous montane voles (right panels). These species differences in distribution of receptors in the NA-VP circuit are thought to mediate species differences in the ability to form pair bonds in voles. While the role of OTR in the NA has been most extensively studied in female bonding, and the role of V1aR in the VP has been most extensively studied in male bonding, there are no sex differences in receptor density in either brain region. *Modified from Young and Wang (2004).*

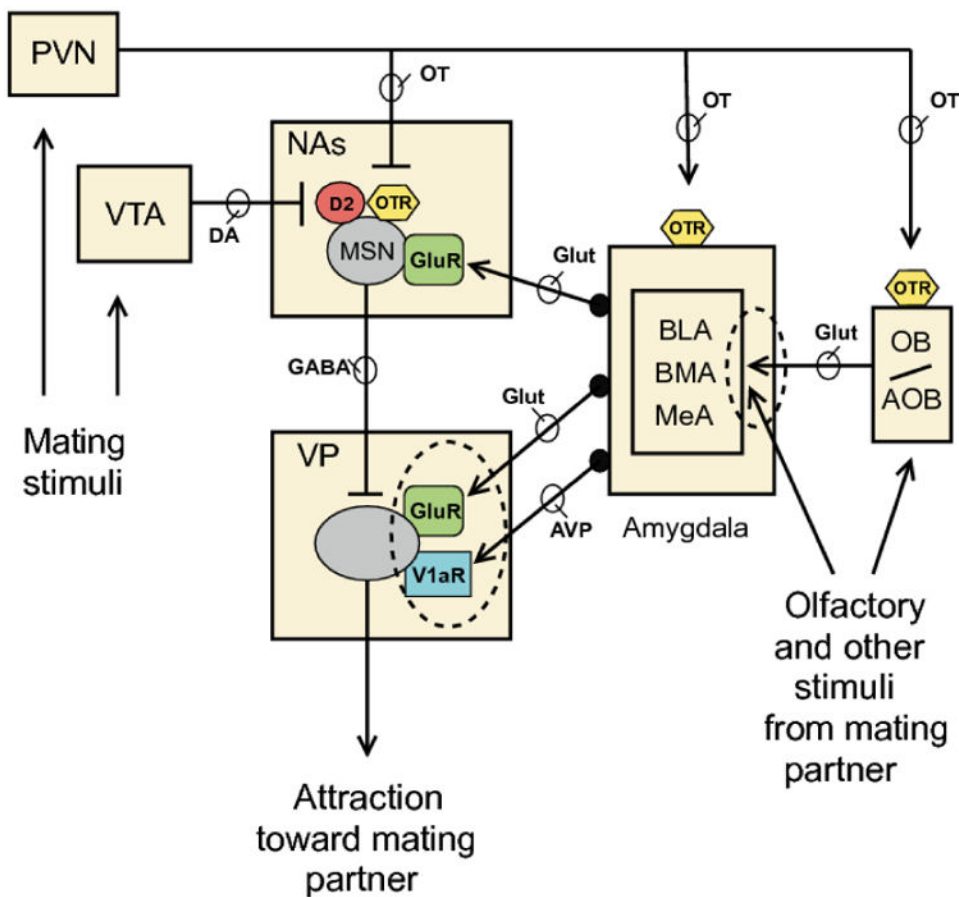


Figure 5. A hypothetical neural model of pair bond formation in prairie voles. The model proposes that during a mating bout both ventral tegmental area (VTA) dopamine (DA) input to nucleus accumbens shell (NAs) and paraventricular hypothalamic (PVN) oxytocin (OT) input to the NAs and to the olfactory bulbs and amygdala are stimulated. In addition, olfactory and other stimuli from the mating partner activate amygdala glutamatergic (Glut) input to nucleus accumbens-ventral pallidum circuit (NA-VP) and arginine vasopressin (AVP) input, proposed to arise from the medial amygdala (MeA: Lim & Young, 2004), to VP. The mechanisms of pair bond formation involve a two-step process: an individual recognition stage and a persistent attraction phase. OT action on oxytocin receptors (OTR) at the level of the olfactory bulbs and amygdala is shown as promoting social memory by strengthening synapses in the amygdala (outlined with a dashed circle) that then allow olfactory and other stimuli from the mating partner to strongly activate amygdala input to NA-VP. For the development of a persistent attraction to one's mating partner, DA action on D2 receptors and OT action on OTRs in NA (shown as D2-OTR heteromers) are proposed to depress the activity of NA GABAergic medium spiny neuron (MSN) input to VP, resulting in a disinhibition of VP. The disinhibited VP is now strongly activated by the partner-induced glutamate and AVP input that it receives from the amygdala, and these synapses are strengthened (outlined with a dashed circle). Once mating is completed, and a mate is given a partner preference test, the olfactory and other stimulus characteristics of the

partner, but not those of a stranger, are now capable of strongly activating VP over long periods of time, creating an enduring and selective social bond. In fact, stranger-related stimuli activate AVP release into anterior hypothalamus (not shown) leading to aggression and rejection. Mechanisms similar to these may be involved in maternal bonding *and* selectivity in sheep. Note that although OT typically has excitatory effects in neurons (Terenzi & Ingram, 2005), when it acts at sites composed of D2-OTR heteromers, it functions to potentiate the inhibitory effects of DA at the D2 receptor. In order to simplify the diagram and show its similarities with Fig. 3, the presence of D1 receptors on NA MSNs is not shown although, as indicated in the text, DA action at this site suppresses pair bond formation. Perhaps OT not only suppresses the output of MSNs with D2 receptors, but also those with D1 receptors (see Numan, 2015). Other abbreviations: AOB = accessory olfactory bulb; BLA = basolateral amygdala; BMA = basomedial amygdala; GluR = glutamate receptor; OB = olfactory bulb; V1aR = vasopressin V1a receptor. *Modified from Figures 6.2 and 6.3 in Numan (2015) with permission from Elsevier.*