Mother–infant bonding and the evolution of mammalian social relationships

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A wide variety of maternal, social and sexual bonding strategies have been described across mammalian species, including humans. Many of the neural and hormonal mechanisms that underpin the formation and maintenance of these bonds demonstrate a considerable degree of evolutionary conservation across a representative range of these species. However, there is also a considerable degree of diversity in both the way these mechanisms are activated and in the behavioural responses that result. In the majority of small-brained mammals (including rodents), the formation of a maternal or partner preference bond requires individual recognition by olfactory cues, activation of neural mechanisms concerned with social reward by these cues and gender-specific hormonal priming for behavioural output. With the evolutionary increase of neocortex seen in monkeys and apes, there has been a corresponding increase in the complexity of social relationships and bonding strategies together with a significant redundancy in hormonal priming for motivated behaviour. Olfactory recognition and olfactory inputs to areas of the brain concerned with social reward are downregulated and recognition is based on integration of multimodal sensory cues requiring an expanded neocortex, particularly the association cortex. This emancipation from olfactory and hormonal determinants of bonding has been succeeded by the increased importance of social learning that is necessitated by living in a complex social world and, especially in humans, a world that is dominated by cultural inheritance.

Keywords: maternal behaviour; pair bonding; oxytocin; endorphin; opioids; olfactory memory; prefrontal cortex; social learning

1. INTRODUCTION

A major development in the evolution of mammals was placentation, internal development of the foetus and protracted care after birth to ensure infant survival to reproductive age. The only parent guaranteed to be present at birth, that directly invests time and energy resources for *in utero* development and equipped to provide initial post-natal feeding through lactation, is the mother. Therefore, it is hardly surprising that females form their strongest social bonds with their own offspring. However, in most mammalian species, females do not show spontaneous maternal care, as the brain first requires priming with the hormones of pregnancy that are produced or regulated by the foetal placenta (Keverne 2005). The pivotal cells of the placenta are trophoblast cells, a tissue unique to mammals and intimately linked to the evolution of viviparity. The cells of this lineage are responsible for the production of steroids and hormonal peptides which not only regulate growth and development of the placenta, but also enter the maternal circulation to adapt maternal physiology, metabolism and behaviour (Heap 1994). Hence, the conceptus, via the hormones of the extraembryonic trophectoderm, capitalizes on the maternal neuroendocrine response system to ensure the synchronization of birth with maternal care and milk availability.

The social behaviour of male and female mammals also reflects these different lifestyle strategies. Reproductive success in males is generally determined by competing with other males to mate with as many females as possible. Hence, males rarely form strong social bonds and male coalitions are typically hierarchical with an emphasis on aggressive rather than affiliative behaviour. The female reproductive strategy is one of investing in the production of a relatively few offspring compared with egg-laying vertebrates, and success is determined by the quality of care and the ability to enable infant survival beyond the weaning age. Females therefore form strong social bonds with their infants and female–female relationships are also strongly affiliative, especially among matrilineal kin which often assist with infant care (Hrdy 1999). In a minority of mammals (less than 5%) ecological conditions are such that promiscuous male strategies are disadvantageous, and here males form a partner preference (bond) with females, defend them from intruders, and participate in parental care (Kleiman 1977).

The majority of mammals are small-brained (i.e. they have a high ratio of limbic to cortical structures), with the regulation of social relationships requiring individual recognition by olfactory cues. This occurs during those biologically significant life events, such as mating and parturition, which precede bond formation. The hormonal changes which accompany these events induce changes in the expression of a range of neuropeptides (e.g. β-endorphin, corticotrophin-releasing factor (CRF), oxytocin (OT) and arginine vasopressin (AVP))

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that are thought to be critically important in the mediation of maternal and other social behaviours (Keverne & Curley 2004; Curley & Keverne 2005). Gender-specific aspects of mammalian social behaviour are regulated by the steroid hormones, notably oestrogens and progestogens, which determine the expression and distribution of these receptors for neuropeptides such as endorphins, OT and AVP (Dantzer 1998; Kalamatianos *et al.* 2004). In monogamous voles, a genus which has been investigated in some detail, male monogamy is little more than a variation on this theme, with AVP and CRF receptor expression in males evolving to mirror that of OT receptor expression in females. Moreover, this activation of vasopressin receptors is triggered by the unusual combination of female–male aggression which precedes oestrus, and oestrus is in turn induced by the male's pheromones (de Kloet *et al.* 1986; Insel & Shapiro 1992; Lim *et al.* 2001, 2004; Bielsky & Young 2004; Lim & Young 2004). Thus, a common biology linked to olfaction underpins many aspects of social behaviour in small-brained mammals.

With the cortical brain expansion seen in monkeys and apes, there has been an increase in the complexity of social relationships and a decreased dependency on olfactory communication (Curley & Keverne 2005). There has also been a degree of emancipation from hormonal determinants of behaviour; maternal care occurs even in the absence of priming by pregnancy hormones, and much of Old World primate sexual activity is non-reproductive occurring outside the periods of fertility. The olfactory link to areas of the brain concerned with social reward is replaced by neocortical inputs, particularly those concerned with multimodal sensory cues, forward planning and emotional regulation (Schultz *et al.* 2000; Chiba *et al.* 2001). Moreover, the development of temporary alliances and deployment of intelligent behavioural strategies seen in primates with large brains has had a significant impact on the way social organization has evolved away from the exclusivity of contexts determined by hormones. This in turn has accelerated the importance of social learning and consequent development of cultural inheritance. The aims of this review paper are to draw together the underlying neural and hormonal mechanisms that are common to many aspects of maternal and social bonding and explore how these events have been influenced by the evolution of the mammalian brain.

2. PARENTAL BONDS IN SMALL-BRAINED MAMMALS

The majority of small-brained mammals such as rodents are altricial and produce relatively large numbers of offspring in each litter that are deaf, blind and helpless at birth, and severely deficient in motor control and temperature regulation. These offspring require considerable care by the mother, not only in nursing and suckling, but also by providing a warm nest and retrieving the offspring back into the nest when they first become mobile. In such species, maternal care may be considered as an extension of physiological homeostasis. The hormones of pregnancy, under the control of the foetal placenta, inhibit sexual behaviour,
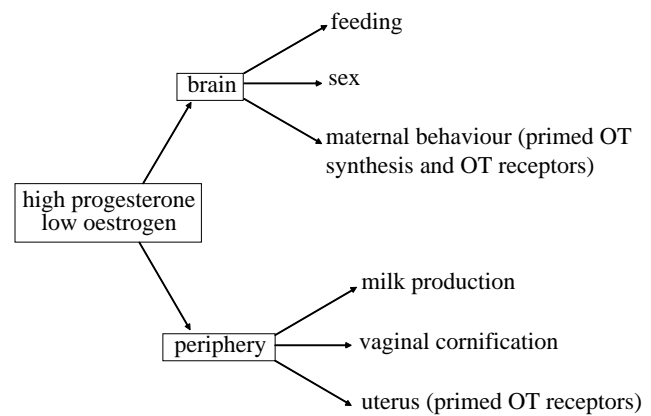
Figure 1. The importance of hormones for signalling context across and synchronizing biologically relevant events in the brain and somatic compartments.

promote feeding behaviour, develop the mammary glands and prime the brain for maternal care (figure 1), which is then triggered by parturition (Keverne 2005). Although maternal care is a function of the brain, its onset is dependent on events originating in the placenta which, in turn, are regulated by the foetal genome. Likewise, maintenance of maternal care is dependent on the presence of neonates and is synchronized with their post-natal development. Nest building stops on the day when pups can regulate their body temperature and milk production terminates when the pups decrease their suckling times, events that are related to the mother leaving the nest more frequently to prevent overheating (Leon *et al.* 1990). Hence, the onset, maintenance and termination of maternal behaviour are controlled by hormones which, in turn, are released in response to stimuli from the foetus.

OT is a neuropeptide that plays a fundamental role in maternalism, acting centrally to promote maternal care and peripherally to promote parturition and milk let-down (Keverne & Kendrick 1992; Kendrick 2000). During late pregnancy, receptors for OT are upregulated in both the brain and the uterus in response to elevated oestrogen levels. OT, synthesized in the hypothalamic neurons, is released into the brain at birth, facilitating olfactory recognition of offspring (Keverne *et al.* 1993), aiding parturition (Neumann *et al.* 1996) and stimulating the onset of maternal care (Keverne *et al.* 1993). The maintenance of maternal behaviour during lactation may also require the coordinated involvement of the OT, cholecystokinin, prolactin and dopamine (DA) systems (Mann *et al.* 1995; Grattan 2001; Champagne *et al.* 2004; Ferris *et al.* 2005).

OT release during other key life events similarly facilitates social interactions and is required for the formation of the olfactory memory that enables the social recognition of conspecifics (Dluzen *et al.* 2000; Ferguson *et al.* 2000, 2001; Winslow & Insel 2002). The formation of these relationships requires familiarity, which for kin is brought about by prolonged contact involving licking and grooming. For completely novel stimuli, such as strange males or newly born offspring, overcoming neophobia is also a necessary prelude to forming new relationships. OT release is significant in this context too, since it is noteworthy

that OT knockout mice exhibit altered levels of anxiety (Mantella *et al*. 2003; Amico *et al*. 2004) and intracerebroventricular (icv) administration of oxytocin receptor antagonists increases anxiety in female rats (Neumann *et al*. 2000).

In the context of mate recognition by the female, the formation of this familiar relationship requires sexual activity, which can only occur when the female is in oestrus. Offspring recognition immediately follows parturition, the female having completed pregnancy. Both pregnancy and oestrus provide the endocrine context for the synthesis of OT and the OT receptors (Thomas *et al*. 1996; Bale & Dorsa 1997; Young *et al*. 1997). Oestrogen acts through the oestrogen receptors ERα and ERβ; ERβ is expressed in the hypothalamic neurons that synthesize OT, whereas ERα is required for synthesis of OT receptors in the amygdala (Patisaul *et al*. 2003). Interestingly, both the ERα and the ERβ knockout mice are impaired in social recognition tests similar to mice targeted for the OT gene deletion (Choleris *et al*. 2003, 2004). Hence, in the context of oestrus and pregnancy, the female's brain undergoes radical reorganization with respect to the synthesis and activation of OT and its receptor. In particular, it is those areas of the brain associated with the social recognition that are required for olfactory preferences which underlie bond formation that are primarily affected, i.e. the olfactory bulb (OB), the amygdala (AMY) and the nucleus accumbens (NAcc; Broad *et al*. 1999; Ogawa *et al*. 1999; Choleris *et al*. 2004; Kavaliers *et al*. 2004; Young & Wang 2004).

Although the OB has no oxytocinergic terminals there is an abundance of OT receptors. This mismatch of terminals with receptors in the OB is functionally addressed by the neurohumoral release of OT into cerebrospinal fluid at parturition and mating (Yu *et al*. 1996*a*). Thus, pregnancy and parturition produce changes in sensitivity, synaptic efficacy and neural firing in the OB, changes that are part of the olfactory learning process for social familiarity (Yu *et al*. 1996*b*). Hence, OT infusions into the cerebral ventricles enhance olfactory memory for conspecifics in rats. OT infusion directly into the OB enhances maternal care and increases both the frequency and the amplitude of spontaneous excitatory post-synaptic currents of granule cells (Yu *et al*. 1996*b*) by both pre- and postsynaptic mechanisms, a process integral to olfactory recognition memory (Dluzen *et al*. 1998, 2000; Engelmann *et al*. 1998; Osako *et al*. 2001).

The amygdala has reciprocal connections with the NAcc, and both structures show enhanced levels of neural activation in rodents following exposure to biologically significant odours (Moncho-Bogani *et al*. 2005). Olfactory activation during social encounters between mother and pups induces neural activation of the amygdala (Fleming & Korsmit 1996), lesions to the amygdala eliminate aversion of pup odours in virgin rats (Fleming *et al*. 1980), and both OT and vasopressin release in the central amygdala regulates the autonomic expression of fearful or neophobic responses (Huber *et al*. 2005). The medial amygdala is also important for social recognition in mice, and infusions of OT into the medial amygdala of mice with a targeted deletion of the OT gene restores olfactory social recognition

(Ferguson *et al*. 2000, 2001). OT receptors are particularly notable in both the shell and the core of the NAcc, and lesions to these areas have shown that maternal retrieval is impaired and the rewarding experience of maternal care is not carried forward to subsequent mother–pup interactions (Lee *et al*. 1999; Numan *et al*. 2005). Moreover, if the socially relevant behaviour is experienced in the same context as biologically neutral odours, mimicking other social sensory cues in the animal's real world, a conditioned association of these second-order cues as attractive takes place and they subsequently develop behaviourally rewarding properties (Kippin *et al*. 2003)

Thus, small-brained female rodents do form bonded social relationships with their offspring and with mates, both of which are regulated by odour cues and both of which are short-lived. Male partners generally do not stay attached after mating, and owing to the close dependence of mother–offspring interaction on the maternal hormones, the mother–infant bond is restricted until weaning. Although pregnancy is a life event of considerable significance for the female (enduring for weeks as opposed to the few hours for mating), maternal care, nevertheless, gives way to other motivational priorities as hormonal secretions change. Most altricial mammals produce large litters and fail to distinguish between individual offspring. Indeed, the removal of individuals produces no obvious signs of behavioural loss, and even removing the whole litter results in the female returning to oestrus within a few days, following which mating and a further pregnancy rapidly ensue. Hence, in these rodent species, reproductive success does not require strong, enduring parental or social bonds. These relationships are transient and secondary to maximizing high 'throughput' offspring production to sustain reproductive success.

3. PRECOCIAL MAMMALS: MATERNAL BONDING

Grazing mammals, such as ungulates, live in relatively large social groups that are constantly on the move in search of food. These mammals have an alternative life history to small-brained mammals such as rodents, as it is important that their offspring should be relatively well advanced at birth in order to maintain contact with the herd. The young are born precocial, capable of maintaining their own body temperature and able to stand and walk soon after birth. Most ungulate mothers are seasonal breeders, producing synchronized births with only one or two offspring in any one year. Mothers invest heavily in producing large quantities of high quality milk to ensure the rapid maturation of their young. Because offspring are precocial and mobile, there is ample opportunity for them to extract milk from other mothers in the flock. To select against this, maternal care becomes exclusive within 1–2 h of parturition, and any strange non-related young that try to suckle are violently rejected. Initially, this selective recognition memory and selective bond is also based exclusively on olfactory cues.

Sheep provide a good example of precocial mammals and have been studied extensively in the context of maternal bonding. It is relatively easy to determine the establishment of selective bonding in sheep from the

proactive response of the mother to her own lamb (low pitch bleats, approach, suckle) which contrasts with rejection behaviour shown to strange lambs (high pitch bleats, head-butts and withdrawal from suckling approach). Moreover, any separation of the lamb from its mother following the initial bonding process produces distress calls and hyperactivity in the mother that lasts for several days (Kendrick & Keverne 1991).

The neural mechanisms that serve this selective bonding require a maternal motivational state, which is dependent on the hormones of pregnancy, and a recognition memory, which is primarily dependent on olfactory cues. The temporal profiles of oestrogen and progesterone secretion during pregnancy (Poindron & Levy 1990) and their effects on neuropeptide gene expression have much in common at the cellular and molecular level with those occurring in small-brained mammals (Broad *et al.* 1993a). Indeed, there are also many similarities across these species with regard to the neural mechanisms subserving olfactory recognition and its importance. However, there are also crucial differences, particularly in the selectivity of the recognition process and how this, in the presence of strange lambs, is able to activate rejection behaviour. In a female ewe that is highly maternal, being able to suppress maternal behaviour and then initiate a violent response to a lamb that provides many of the cues that invoke maternal care, requires a precise recognition mechanism. Although the olfactory recognition process is complex, its function serves to reject strange lambs, since anosmic ewes are fully maternal both to their own and to strange lambs (Baldwin & Shillito 1974; Levy *et al.* 1995a,b). Olfactory recognition is complex because the odour of their own lamb has more components in common with the odour of strange lambs than it has differences, but it is these differences which activate rejection in a maternally motivated mother.

As for all mammals, production of the steroid hormones during pregnancy is under the control of the foetal placenta. High levels of both progesterone and oestrogen promote synthesis of OT in both magnocellular and parvocellular neurons found in many parts of the brain that play a part in maternal behaviour (e.g. paraventricular nucleus, PVN; supraoptic nucleus, SON; bed nucleus of the stria terminalis, BNST; medial preoptic area, MPOA), with levels of OT mRNA expression in these neurons peaking at the time of birth (Broad *et al.* 1993a). Towards the end of pregnancy, oestrogen levels increase and promote the production of OT receptors in a number of brain regions that process olfactory information, in parts of the hypothalamus that mediate maternal behaviour and in the diagonal band of Broca, a region responsible for the cholinergic innervation of the OB and frontal cortex. Maternal experience further enhances increases in OT receptor expression in the paraventricular nucleus (Broad *et al.* 1993a,b, 1999). Because the paraventricular nucleus is the main source of OT release into the brain, upgrading autoreceptors on OT-containing neurons serves to promote further OT release throughout the brain. Certainly, during parturition, levels of OT in cerebrospinal fluid (CSF) increase to 400 pg ml^{-1} and reach all areas of the brain including the OB, where receptors are upregulated during pregnancy (da Costa *et al.* 1996). Since there are no OT terminals in

the OB, this humoral transport serves an important function in the context of receptor terminal mismatch (Yu *et al.* 1996a,b). The importance of parturition for the induction of maternal behaviour cannot be emphasized enough, since delivery of lambs under peridural anaesthesia blocks central OT release and inhibits maternal behaviour, while subsequent intracerebral infusions of OT restore this behaviour (Krehbiel *et al.* 1987; Levy *et al.* 1992). Moreover, induction of maternal behaviour in non-pregnant ewes can be established by hormonal priming with oestrogen and progesterone followed by vaginal stimulation, which also induces central OT release. (Keverne *et al.* 1983; Kendrick *et al.* 1988)

Precocial mammals rapidly learn to selectively recognize their own offspring within the first few hours post-partum. In sheep, this selective recognition is dependent on odour cues from the lamb mediated by the main olfactory system. Lesioning of this main olfactory system at the level of receptor neurons or at the first neural relay prevents selective recognition but notably does not impair the proactive behaviour associated with maternal care (Baldwin & Shillito 1974; Levy *et al.* 1995a,b). Electrophysiological studies of the OB have shown changes to occur in the response of mitral cells to lamb odours, while *in vivo* microdialysis studies have reported altered neurotransmitter release that is causally linked to the olfactory memory formation underlying selective recognition. These studies have further demonstrated that there are extensive plastic changes that occur in the OB as a consequence of parturition, and further changes are consequent on lamb exposure and memory formation (Kendrick *et al.* 1992, 1997; Keverne *et al.* 1993; Levy *et al.* 1995a,b).

The medial nucleus of the amygdala, in particular, is a key structure for olfactory social recognition. In sheep, OT receptors in the medial amygdala increase at parturition (Broad *et al.* 1999) and icv infusions of OT induce full maternal behaviour and bonding in nongestant ewes (Kendrick *et al.* 1987). In the sheep, reversibly inactivating various nuclei in the amygdala at the time of post-partum olfactory memory formation, by lidocaine infusions, reveals the medial nucleus to be the one required for memory formation to occur (Keller *et al.* 2004a,b). However, the medial nucleus is not required for olfactory perception *per se* or for the process of olfactory memory retrieval for lambs. Disruption of the medial amygdala by lidocaine infusions does not impair bonding and proactive behaviour to the ewe's own lamb, but it does impair the expression of rejection behaviour to strange lambs (Keller *et al.* 2004a,b). Moreover, mapping studies using the induction of immediate early gene expression (c-*fos*, *zif268*) or the neurotrophic growth factors (brain-derived nerve growth factor (BDNF) and *trk-B*) have shown that a distributed network of neuroanatomical substrates, including the anterior cingulate and medial frontal cortices, amygdala and ventral striatum are active and undergoing neurotrophic-mediated plasticity changes following lamb exposure post-partum or after artificial vagino-cervical stimulation (da Costa *et al.* 1997; Broad *et al.* 2002a,b). All of these brain regions also undergo upregulation of OT receptors towards the end of pregnancy (Broad *et al.* 1999). The medial prefrontal cortex (mPFC) is

particularly important since, in contrast to small-brained rodents, this heterogeneous region is unusually large in the sheep and is recognized from primate studies to play an important role in modulating integrative, attentional and emotional responses which allow the emancipation of behaviours from stimulus response modes and hormonal control.

4. SOCIAL AND MATERNAL BONDING IN PRIMATES

The evolutionary conserved biology which underpins mother–infant bonding in mammals raises the question as to what neural changes have occurred in the maternal behaviour of humans and certain non-human primates that enable mother–infant bonding to occur outside the context of pregnancy and parturition and in the absence of lactation. In Old World monkeys, apes and humans, the hormones of pregnancy, parturition and lactation are not necessary for maternal or alloparental care, as females of these species can be motherly towards infants even without ever being pregnant. Nevertheless, of major significance in primate and human maternal care is the endogenous opioid system. Indeed, it has been suggested that the activation of this system at parturition and during suckling promotes the positive affect arising from maternal behaviour (Franceschini *et al.* 1989; Broad *et al.* 1993*a*,*b*; Martel *et al.* 1993, 1995). Studies on naloxone treatment of post-partum rhesus monkey mothers living in social groups have addressed the importance of opioids in maternal bonding.

During the early post-partum period, a mother's social interactions are almost exclusively with her infant, and opiate receptor blockade in the mother has marked effects on the mother–infant relationship. Naloxone treatment reduces the mother's caregiving and protective behaviour shown towards her infants. During the first weeks of life when infant retrieval is normally very high, naloxone-treated mothers neglect their infants and show little retrieval even when the infant moves a distance away. As the infants approach eight weeks of age, when a bonded grooming relationship normally develops between the mother and the infant, mothers treated with naloxone fail to groom their infant. Moreover, they permit other females to groom their infants, while saline-treated control females are very possessive and protective of their infants from contact with others at this stage. The infant is not rejected from suckling, but a mother's usual possessive preoccupation with the infant declines with opioid receptor blockade. The mother is not the normal attentive caregiver, and mother–infant interactions are invariably infant-initiated (Martel *et al.* 1993, 1995; Keverne *et al.* 1997).

Primates and other mammals have in common opioid involvement in maternal care, but the consequences of opioid blockade in small-brained mammals are much greater for the biological aspects of maternal behaviour. In sheep, interference with the endogenous opioid system severely impairs maternal behaviour, including suckling, whereas monkeys neglect to show a focused preoccupation with infant care but still permit suckling (Kendrick & Keverne 1989; Martel *et al.* 1993). These differences may reflect the degree of emancipation from endocrine determinants that maternal behaviour has undergone in primates, and the increased importance of 'emotional reward' for the bonding mechanism.

If the endogenous opioid system in the monkey is positively linked to mother–infant bonding, heroin addiction, which acts at the same opioid receptor, would be predicted to have severe consequences for human maternal bonding. Women who are heroin addicted have many aspects of their social and economic life disrupted, making the data difficult to disentangle. Nevertheless, the facts are that by 1 year of age nearly 50% of children are living away from their biological mothers, and by school age only 12% remain with their biological mothers (Mayes 1995). These infants have been abandoned for adoption or are taken into the care of their grandparents and other female kin. Moreover, in a follow-up of 57 methadone-maintained mothers compared with controls matched for ethnicity, socio-economic status, infant birth weight and gestational age, opiate-addicted mothers were found to be less likely to have remained the child's primary parent. Their children were significantly more likely to have been referred to child protective care or special service agencies for neglect, abandonment or abuse (Lejeune *et al.* 1997). It is also the case that human mothers develop an attachment with their unborn foetus, but women with a history of drug abuse who were using methadone had diminished maternal–foetal attachment score when compared with normal women (Mikhail *et al.* 1995).

Integral to the bonding process in large-brained primates is the action of the endogenous opioid system on receptors which have been localized to the ventral striatum (Koob & Le Moal 1997). This area of the brain is involved in 'reward' and also requires the mesolimbic DA projection which detects rewarding stimuli and the ways in which they occur differently from prediction to enable 'updating' of the stimulus (Schultz & Dickinson 2000). In primates, the OT system may also be important in bonding, and in humans peripheral OT release is increased at birth, following female orgasm and exposure to neonatal images or sounds (McNeilly *et al.* 1983; Carmichael *et al.* 1987). The mother–infant bonding process entails obsessive grooming, especially to hands, face and genitalia, by mothers, and these are the morphological traits of infant monkeys that show the greatest changes during development. Because primates show extended post-partum care, offspring recognition requires the continual updating of any changes in these morphological features and in behavioural development. This updating of infant recognition involves visual cues and prefrontal–ventral striatal pathways which are also intimately linked to the emotional brain via the amygdala. The positive emotional responses which infants generate in females enable parental care to occur without the continual priming by pregnancy and parturition.

Human mothers also experience preoccupations and rituals in the context of maternal care, and even before the birth of their baby they are obsessive with cleaning and creating a safe environment. After birth, safety is the major concern and mothers frequently check on their baby even at times when they know the baby is fine

(Leckman *et al.* 1999). The evolution of these obsessive psychological and behavioural states can be seen as a developmental extension of the preoccupations which all primates show for their infants. Thus, it is notable that areas of the human brain which, using magnetic resonance imaging, have been shown to be responsive to babies crying include the brain's reward structures (mesolimbic DA from the ventral tegmental area (VTA), ventral striatum and amygdala). These same regions of the brain are also active in the context of romantic love (Bartels & Zeki 2004).

The evolutionary progression away from hormonal-centric determinants of maternal behaviour to emotional, reward-fulfilling activation probably involves dopaminergic and opioidergic activity in the ventral striatum. The enhanced role of this circuitry for regulating behaviour in humans may also provide vulnerability to various forms of psychopathology such as obsessive compulsive disorder (OCD) and substance abuse. Mild forms of addictive behaviour (gambling, video games, internet use, and consumption of caffeine and chocolate) are such indicators of this neurological predisposition for obsessive behaviour seen in humans (Greenberg *et al.* 1999). *In vivo* neuro-imaging studies identify the orbital frontal cortex, head of the caudate, and closely associated ventral striatum and anterior cingulate as being involved in OCD (Rauch 2000), while acquired OCD occurs later in life in patients with striatal lesions (Chacko *et al.* 2000). There is also evidence that CSF levels of the neuropeptide, OT are elevated in OCD, and this peptide also plays a fundamental role in many obsessive aspects of maternalism (Leckman *et al.* 1994). Therefore, not surprisingly, OCD is more common in women. The influence of gonadal hormones on periodicity of OCD (Weiss *et al.* 1995) and the post-partum exacerbation of OCD symptoms in women suggest that the course of this disorder may be influenced by the hormones of pregnancy (Williams & Koran 1997; Labad *et al.* 2005). Hence, there are components of human behaviour that occur in the post-partum maternal period which are influenced by hormones, but interestingly they relate to areas of the brain concerned with reward and not with the direct execution of maternal behaviour *per se.*

5. A DECLINING ROLE FOR OLFACTORY SYSTEMS IN SOCIAL REWARD FOR PARENTING

Olfaction is the most important sensory modality coordinating social behaviour of small-brained mammals, with this information being processed via both the main and the accessory olfactory systems. The accessory system contains the vomeronasal organ (VNO) enclosed in a cartilaginous capsule on the medial surface of the nasal septum, from which neurons convey non-volatile odour (pheromones) signals directly to the brain's hypothalamic and limbic systems (Keverne 1999). Through this chemosensory system, pheromone signals are able to change endocrine states (e.g. advance the onset of oestrus) and regulate parental and sexual behaviour (Brennan & Keverne 2004). The chemosensory receptors of this system are divided into two distinct families (V1r, V2r) and are coded for by approximately 300 genes, while

the functional importance of this chemosensory system in regulating the social behaviour of rodents can be observed from transgenic mice studies. Male mice that have one subfamily cluster (12% of the 137 gene V1r gene family) selectively excised have motivational behavioural defects, including reduced sexual interest (Del Punta *et al.* 2002). Transgenic male mice that have a mutation in the *Trp2c* cation channel gene, the selective pheromone transduction channel in mice, also exhibit motivational behaviour impairments, including a failure of nursing mothers to engage maternal aggression to intruders when they are suckling their young (Leypold *et al.* 2002). Males with this mutation fail to show sexual preferences for females and readily mate with other males (Stowers *et al.* 2002). Moreover, mice selectively lacking heterotrimeric G-proteins of the Gq family (transduction proteins) in vomeronasal receptors do not display any maternal behaviour despite having normal levels of OT and prolactin, and exhibiting normal lactation. Using c-*fos* immunohisto-chemistry to investigate pup-induced neuronal activation in post-partum females reveals a significant reduction in activity in those areas of the brain concerned with motivated behaviour, including MPOA, BNST and lateral septum, in post-partum females (Wettschureck *et al.* 2004). The pheromone to which the mother rat's VNO responds is dodecyl propionate, which originates in the pup's preputial gland and stimulates licking of the anogenital region (Brouette-Lahlou *et al.* 1999). This licking is an important component of rat maternal behaviours and is thought to be involved in maternal bonding and promotes pup survival.

The main olfactory system has the capacity to respond to a vast array of odours, many of which have no intrinsic social significance, but can acquire this social significance through association when activated in contexts that are rewarding and biologically significant (Kippin *et al.* 2003). Thus, in the context of parturition, odours that convey individual or group identity become important recognition signatures which give added social value to these individuals. The main olfactory system of small-brained mammals (rodents) has over 1200 olfactory receptor genes, the largest mammalian gene family (Zhang & Firestein 2002), and incredible sensitivity brought about by a 1000 : 1 convergence of each receptor neuron at the first relay (Hellman & Chess 2002). Biological odours are rarely simple and the spatial and temporal patterns that can be generated at this first relay have the coding capacity to distinguish individuals in the social group. This is a very significant function for odour in species like rodents which are nocturnal, live underground and have poorly developed vision.

A question of some importance is how does the brain confer significance to non-significant odours? One way is to associate this odour with other sensory cues that signify biologically significant contexts, usually con-texts associated with motivational reward (feeding, sexual activity, birth and aggression; Kippin *et al.* 2003). For visually impaired nocturnal rodent species, it is the two olfactory sensory systems that work in harmony to sustain this association (figure 2). The limited repertoire of vomeronasal receptors that
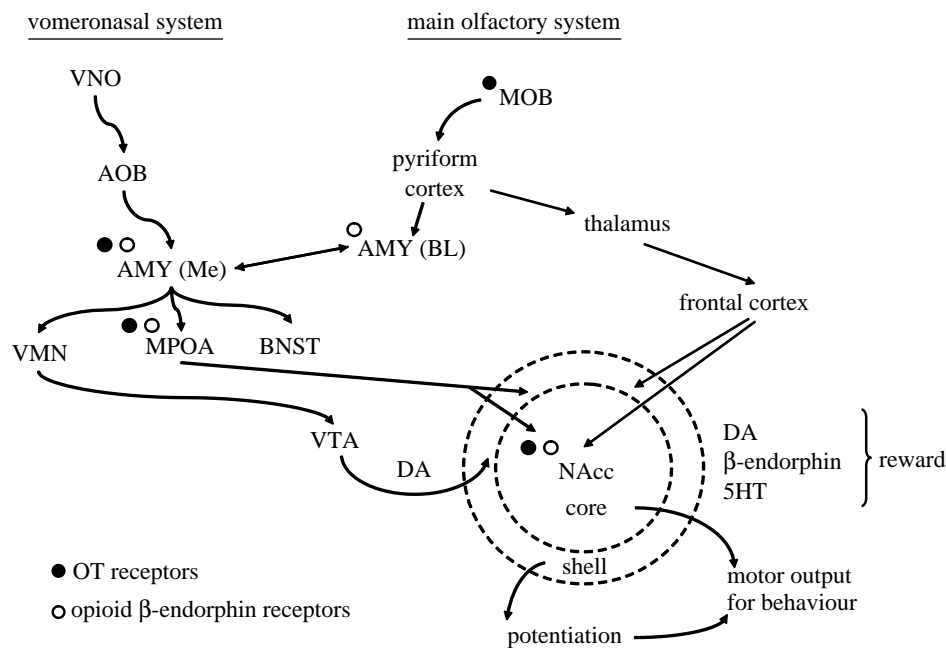
Figure 2. Convergence of main and accessory olfactory systems for distinguishing and appropriately engaging behaviour through the NAcc/ventral striatal 'reward' system. The hormones of pregnancy upregulate oxytocin receptors (filled circle) and opioid (open circle) receptors which provide the 'maternal' context. AMY (BL), basolateral amygdala; AMY (Me), medial amygdala; 5HT, 5-hydroxytryptamine; VMN, ventromedial nucleus.

respond to social pheromones (sex, aggression, feeding and parenting) have a direct projection to those parts of the brain that promote and are integral to primary motivated behaviour. This projection is via the medial amygdala to the various hypothalamic nuclei that regulate these behaviours. These same neural pathways that transduce pheromone signals also access the brain's 'reward' circuitry via the amygdala to the shell of the NAcc (Moncho-Bogani *et al.* 2005). The main olfactory projections also relay in the amygdala via the main OB and pyriform cortex, the pyriform cortex also making connections with the frontal cortex via the medial–dorsal nucleus of the thalamus (figure 2). Major outputs from the rodent frontal cortex then project to the NAcc. Hence, these dual chemosensory pathways converge at the amygdala and NAcc, a part of the brain concerned with reward and capable of providing the incentive salience of reward related cues which access the NAcc via the frontal cortex. Interestingly, unlike lesions to the main olfactory system, lesions of the vomeronasal system do not prevent rodents from distinguishing biologically salient differences in odour; however, they do prevent them from employing the salience of these cues to demonstrate a preference (Pankevich *et al.* 2004).

What might be the function of this olfactory relay via the frontal cortex in small brained rodents? Generally speaking, biological odours, including those of amniotic fluid and pups, are complex and composed of a multitude of components. Oscillations across cortical structures (usually in the low frequency range of 7–11 Hz) are known to be important for the synchronization of populations of neurons that simultaneously process these components. In this context, the frontal cortex electroencephalogram has been recorded in rats in various reproductive states. During periods of lactation, nest bedding odours from pups invoke

increased electric activity at 8–11 Hz frequency in the mPFC when compared with virgin females (12–21 Hz) provided with the same odour (Hernandez-Gonsalez *et al.* 2005). This lower frequency activity is common to other regions of the brain processing olfactory information and may provide the synchronized frequency for 'binding' of neurons that respond to odour (Keverne 1995*a*,*b*). This synchronizing of activity across a population of olfactory neurons along the pathway to reward processing nuclei and motor generating regions of the brain provides the gestalt for recognition-to-action, the context of which is provided by the hormones of pregnancy and parturition.

Evolutionary changes in olfactory processing across mammals are clearly illustrated from comparative genetic analysis of the *Trp2c* gene; a gene which is central to regulating pheromone-induced motivational behaviour in rodents (Liman & Innan 2003; Zhang & Webb 2003). This gene encodes a cation channel that enables vomeronasal neurons to generate action potentials, but has become a non-functional pseudogene in primates, as indeed have genes that code for vomeronasal receptors (Grus *et al.* 2005; Young *et al.* 2005). Furthermore, while it appears that ancestral primates were able to process olfactory information via the vomeronasal system, this ability became vestigial *ca* 23 Myr ago in the ancestor of modern day New World and Old World monkeys and apes (Zhang & Webb 2003). Hence, Old World primates, including the rhesus monkey (*Macaca mullata*), gorilla (*Gorilla gorilla*), chimpanzee (*Pan troglodytes*) and orang-utan (*Pongo pygmaeus*), exhibit a decreased reliance on olfactory information, particularly via the vomeronasal pheromonal system, for the regulation of social behaviour. Good evidence for degenerate function of the main olfactory system comes from comparative phylogenetic analysis of the genes that encode olfactory
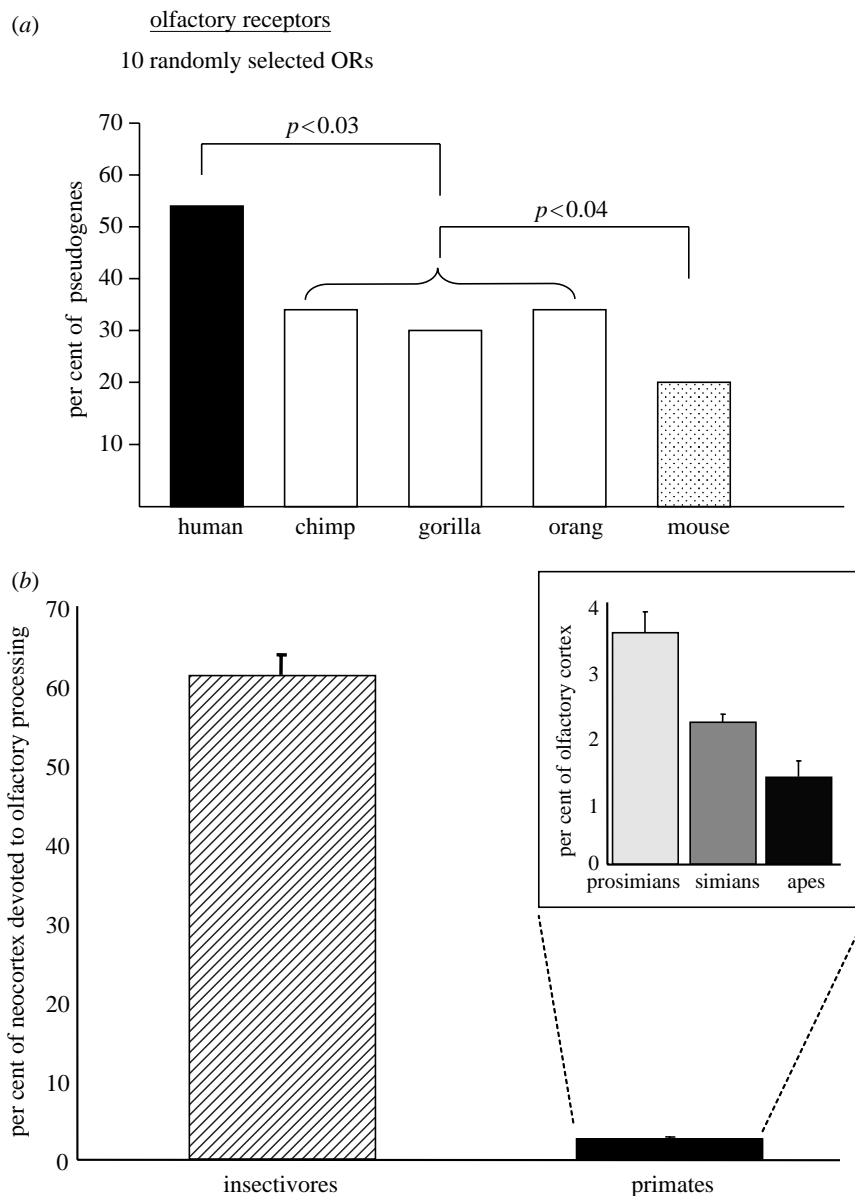
Figure 3. (*a*) A substantial number of olfactory receptors are coded for by non-functional pseudogenes which increase in number with the enhanced development of the neocortex. (*b*) Congruent with this reduction in olfactory receptors, there is a reduction in the proportion of cortex given over to processing olfactory information. This decreases from insectivores through primates.

receptors (Gilad *et al.* 2003, 2004; Whinnett & Mundy 2003; figure 3*a*). These studies estimate from sequence disruptions that more than 30% of olfactory receptor genes are non-functional pseudogenes in non-human primates, rising to more than 60% in the human genome. Coupled with these genetic changes, there has also been a dramatic reduction in the size of the olfactory cortex, from 65% of total cortex in insectiv-orous mammals to less than 5% in Old World primates (figure 3*b*; Frahm *et al.* 1982; Stephan *et al.* 1982).

This decline in olfactory processing has clearly been driven by the need of large-brained mammals to gather their social information from visual cues, as they evolved from nocturnal to a diurnal lifestyle. Arguably, the most significant visual change in Old World primates was the evolution of trichromacy (Surridge *et al.* 2003), which occurred at approximately the same time as the pseudogenization of the Old World primate chemo-sensory genome (Gilad *et al.* 2004; Webb *et al.* 2004), allowing individuals to interpret social information such

as colourful sexual adornments. In primates, post-partum maternal care also extended mother–infant bonding beyond the period of suckling, thereby increas-ing selection for visual recognition of offspring when infant mobility required facial recognition at a distance.

Congruent with these selective pressures, the primate visual cortex has also become especially enlarged, comprising up to 50% of the total neocortex (Barton 1998). Visual association areas have, likewise, become increasingly complex, with several regions devoted to the differential processing of specialist visual information such as facial expression (Perrett *et al.* 1992). Indicative of this shift in the regulation of social behaviours from reliance on olfactory information in small-brained rodents, to dependence on visual infor-mation in primates, is the negative correlation found between the size of an area of the brain central to relaying visual information (the lateral geniculate nucleus) and the size of the OB, which relays chemosensory information (Barton 1998).

6. FRONTAL CORTEX ENHANCED ROLE IN SOCIAL REWARD FOR PARENTING

The frontal cortex is a part of the brain which has shown progressive enlargement throughout mammalian evolution. In small-brained rodents, the mPFC matures around day 13–15 post-partum (Diergaarde *et al.* 2005) while in the human, this development continues late into adolescence (years 17–21; Sowell *et al.* 2001). In the rat, this area of the cortex mainly receives a strong olfactory input via the mediodorsal thalamic nucleus, and lesions to this system decrease the frequency with which the mother protects her pups by attacking intruders who threaten to cannibalize her infants (Ferreira *et al.* 1987). Unlike males, females rarely initiate aggression to others unless they are nursing offspring. The mPFC synchronizes this response to odour cues via the release of CRF from the BNST and PVN where the majority of CRF neurons are found (Spencer *et al.* 2005). A second major output from mPFC is to the ventral striatum (NAcc), an area of the brain concerned with reward. Hence, in the context of emotionally rewarding behaviours associated with maternal care, olfactory signals relayed in the mPFC are endowed with incentive salience. The reward value provided by the NAcc requires a biological context signalled by the hormonal state of the female and activated by the release of opioids and DA in the NAcc. It is well established that oestrogen increases synthesis of preproenkephalin (PPE) in the NAcc (LeSaux & Di Paolo 2005), while the dopaminergic projections from the mesolimbic neurons of the midbrain are also immunoreactive for oestrogen receptors (Creutz & Kritzer 2004).

In sheep that have already given birth, exposure to lamb odours provokes intense c-*fos* activity in the mPFC as well as in the pyriform and cortical amygdala, all relays for main olfactory inputs known to be important in lamb recognition and selective bonding. However, in sheep, reversible inactivation of the medial frontal cortex (medial limbic area) using tetracaine infusions is not required for the performance of proactive maternal behaviour or for own lamb recognition. However, it is required to enable the ewe to execute an aggressive motor action in response to the odours of strange lambs. This reversible inactivation does not interfere with other forms of motor activity related to maternal care including emotionally generated rejection vocalizations, walking, approaching, licking and suckling lambs and or feeding (Broad *et al.* 2002*a*,*b*). Rejection behaviour directed at strange lambs is associated with increases in c-*fos* mRNA expression in the large output cells of layer V of the mPFC (which project to the ventral striatum). This suggests that in order to execute the aggressive motor response underlying rejection, novel and anxiety provoking olfactory information needs to be routed by the projections from the cells in this layer to the striatum (Lidow *et al.* 1998). Aggressive responses to the odours of strange lambs are also associated with increased levels of DA, 5-hydroxytryptamine (5-HT), glutamate and γ-aminobutyric acid (GABA) in this cortical region, increases that did not occur in the absence of rejection behaviour (Broad *et al.* 2002*a*). It

seems likely that the primary action of the local anaesthetic under these circumstances is to cause a shutdown of neuronal activity in the mPFC which promotes local large increases in inhibitory transmitter concentrations (notably GABA and 5-HT). Tetracaine has effects similar to localized cooling on inhibiting membrane conductance (Luzzati *et al.* 1999) and therefore it is probable that behavioural and neurochemical actions observed with tetracaine infusions result from inhibition of these mPFC neurons disabling their communication with the ventral striatum.

Medial frontal cortex infusions of tetracaine, which prevent overt motor rejection of strange lambs, resemble the type of behaviour seen in ewes failing to form an olfactory recognition memory. However, following the withdrawal of tetracaine, maternal selectivity returns, showing the olfactory recognition memory to be intact. Inactivating this discrete part of the mPFC during the critical period for lamb recognition memory did not, therefore, interfere with memory formation of the lamb. Moreover, inactivating the mPFC does not prevent memory retrieval for generating emotional vocal responses, but prevents the ewe downloading the information necessary for initiating an aggressive motor response via the striatum (Broad *et al.* 2002*a*,*b*).

Olfactory recognition in multiparous sheep is usually established by 2 h post-partum (Kendrick *et al.* 1992). The data demonstrating the effects of inactivating the frontal cortex for 4 h are consistent with some of the human and rat data which demonstrate that some medial areas of the frontal cortex have little or no influence on mnemonic encoding, but have a greater influence on the suppression of learned strategies in response to changes in behavioural contingencies. This executive function is believed to facilitate the matching of an appropriate behavioural strategy to rapid changes in task requirements (Bechara *et al.* 1994, 1996, 2000; Ragozzino *et al.* 1999*a*,*b*). All female mammals in immediate post-partum period are extremely maternal, and preoccupied with their offspring to the extent that they show no interest in food or sexual activity. What is unusual in sheep is that lambs which have many physical features in common, apart from their odour, can be selectively rejected by aggressive head butts by a highly maternal ewe. This one sensory feature, odour cues, is sufficient to switch a maternal ewe from proactive acceptance behaviour to aggressive rejection. Such a response has much in common with the post-partum aggression of rodents initiated by the odour of strange intruders.

These studies interestingly reveal how different parts of the brain, in the biological context of parturition, respond to odour cues that confer recognition integral to selective bonding. The recognition component in this bonding process requires the medial amygdala for bonding to occur (Keller *et al.* 2004*b*), but is not necessary for retrieval of the recognition memory required to reject strange lambs, while the mPFC is necessary for selective rejection but not required for recognition memory of own lamb (Broad *et al.* 2002*a*,*b*; Keller *et al.* 2004*a*,*b*). Neither of these areas, when inactivated, impairs maternal behaviour, but they do impair the selective nature of the bond. The question
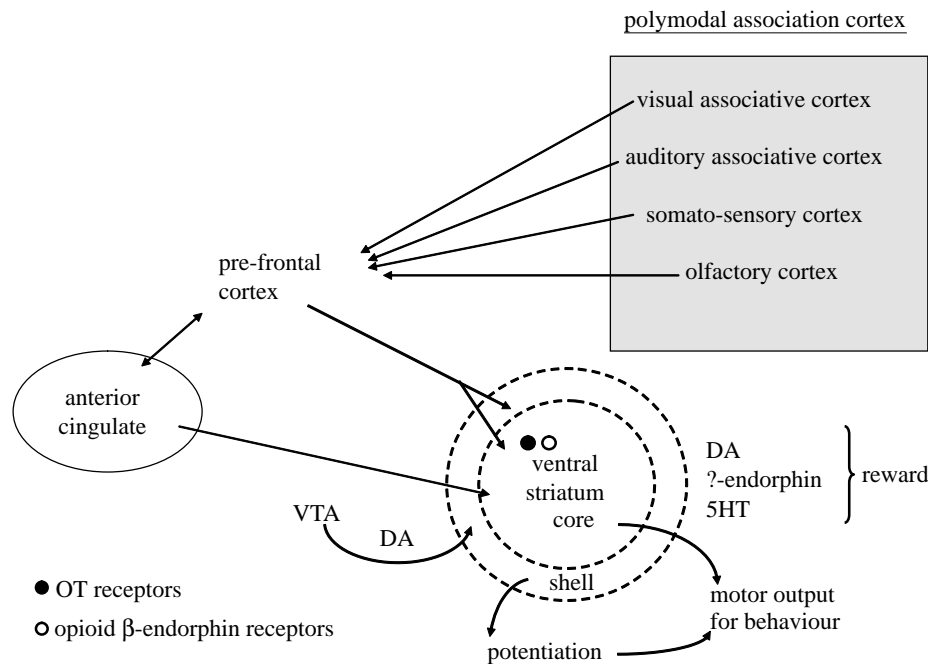
Figure 4. Redundancy in the olfactory systems together with increases in the volume of the prefrontal cortex provide for complex polymodal cues to address the ventral striatal 'reward' system. Emotionally arousing cues (infant distress cries, infant faces and infant suckling) signal release of DA in the ventral striatum both within and beyond the context signalled by the hormones of pregnancy.

arises, therefore, as to which regions of the brain are required to sustain proactive maternal care and the positive aspects of the bond.

In addition to increasing OT synthesis and OT receptor synthesis in the brain, the hormones of pregnancy also induce pro-opiomelanocortin (POMC) and PPE synthesis in the hypothalamus of sheep (Broad *et al.* 1993*a,b*) and the release of opioids into CSF at parturition (Wardlaw & Frantz 1983). Moreover, an opioid agonist or CRF given icv is effective in enhancing proactive maternal care (low pitch bleats, licking) towards lambs as well as reducing rejection behaviour (head butts, high pitch bleats) in the context of vaginal–cervical stimulation (Keverne & Kendrick 1991), while the opiate receptor blocker, naltrexone, blocks the induction of proactive behaviour that signifies positive bonding (Kendrick & Keverne 1989). These potentiating effects of exogenous opiates together with OT on acceptance behaviour and bonding in ewes are probably subserved by opioid receptors in the ventral striatum, an area of the brain that increases c-*fos* mRNA expression in ewes on exposure to own lambs (da Costa *et al.* 1997).

Infant primates, both human and non-human, are highly susceptible to social perturbations in maternal care. While the mother's brain has been 'maternalized' by the hormones of pregnancy generated by the foetal extra-embryonic placenta, the infant's developing brain requires social stimulation from a mother committed to providing the emotional rewards of suckling, huddling and grooming. It is clear that the process of infant socialization benefits from this close relationship and, because this occurs during early brain development, mother–infant separations are likely to have long-term consequences (Hinde *et al.* 1978). Indeed, extreme consequences for social relationships and maternal bonding when adult occur if infants are separated from

mother and reared with peers (Suomi & Harlow 1975; Kraemer *et al.* 1991). Nursery reared rhesus monkeys deprived of a maternal upbringing demonstrate reduced OT secretion and social behaviours, but show increased aggressive and stereotypical behaviours. Increased stereotypical behaviours are often classically associated with the disruption of frontal cortical function and often result from an inability to suppress inappropriate behavioural responses (Winslow *et al.* 2003). Squirrel monkeys, 4 years after experiencing separations from their mother early during development, generate differences in emotional behaviour, stress physiology and development of the brain, notably in the mPFC. Behaviour tests have subsequently shown these monkeys to be impaired in reward-related memory tasks (Lyons & Schatzberg 2003). Electrophysiological recordings from normal adult monkeys have shown that the mPFC mediates the achievement of goals (Matsumoto & Tanaka 2004). The precise involvement of the prefrontal cortex in reward-related behaviour has also been examined in humans using imaging techniques (figure 4). Interestingly, the detection of unfavourable outcomes, response conflict and decision uncertainty elicit overlapping clusters of activation foci in the mPFC (Ridderinkhof *et al.* 2004). Choosing between actions associated with uncertain rewards and punishments in humans is mediated by neural circuitry involving frontal cortex, anterior cingulate and striatum (Rogers *et al.* 2004). Showing alternating videos of the own child versus that of a stranger to mothers provoked the greatest signal contrasts in the mPFC and orbito-frontal cortex. These distinctions required face recognition and emotional processing which correlated with activation in the visual cortex, temporal pole and amygdala (Ranote *et al.* 2004).

The extent to which social cognition, the ability to perceive inferences about psychological aspects of

other people, relies on distinct frontal cortical areas is supported by recent human neuro-imaging research. Medial regions of the frontal cortex appear to contribute to the recognition of different emotions (Hornak *et al.* 1996; Shamay-Tsoory *et al.* 2005) and to the task of forming a 'person impression'. This area is activated specifically when subjects are asked to form an impression of a person but not when they are asked to form an impression of an inanimate object, suggesting that this region specifically indexes social cognition (Mitchell *et al.* 2005).

7. DISCUSSION

The word bonding is a loosely used descriptive term to signify an especially meaningful relationship between two or more individuals. In all mammalian species, this relationship primarily involves mother and infant. The evolution of viviparity and the birth of live offspring as opposed to egg production have required consolidation of the mother's *in utero* investment, resulting in extended post-natal care. This in turn has required offspring recognition. Common to all bonding relationships are hormonal mechanisms, brain reward mechanisms and sensory recognition (Curley & Keverne 2005). However, the way in which these mechanisms are deployed and their relative importance are dependent on the species and in particular on the evolution of the brain.

The precise nature of bonding needs to be examined in the context of its biology. Hence, in monogamous species, this terminology embraces father–infant, mother–father as well as mother–infant, while in large-brained primates it extends beyond the mother–infant to include social cohort, usually of kin related through the matriline. In looking for common mechanisms that sustain bonding and cross-species boundaries, it is important to take into account the evolutionary expansion of the brain. Thus, although recognition is common to all bonded relationships, in nocturnal small-brained altricial mammals this is primarily dependent on olfaction. This recognition is not for individual pups, but for the litter as a whole since the pups are immobile and unlikely to cross-foster. The interbirth interval is relatively short and the elements of the olfactory recognition memory are carried forward to subsequent births and result in reduced cannibalism. In precocial ungulates that are seasonal breeders and produce a single offspring at yearly intervals, recognition is unique to each offspring. Here offspring are mobile within hours of birth and are likely to attempt cross-fostering; therefore mothers need to be selective in their bonding to ensure only their own offspring receives milk. Within weeks of birth, multiple sensory cues, including auditory and visual are used for offspring recognition, which in comparison with nocturnal rodents involves increased deployment of PFC.

With enhanced brain evolution, trichromatic vision in primates has been the dominant sensory system for infant recognition. The olfactory system is deconstructed at the genetic level with total redundancy of the vomeronasal genome and substantial silencing of main olfactory receptor genes. In the context of

mother–infant bonding, the steroid hormones of pregnancy are virtually redundant in that maternal care can and does occur without pregnancy and parturition, and in humans infant-bonded relationships extend to sister, fathers, aunts and grandparents. The hormones of pregnancy do, however, prime the mesolimbic DA projection to the NAcc as well as upregulation of receptors for OT and opioids in the ventral striatum/NAcc. This undoubtedly predisposes the brain reward system to forming mother–infant bonds at birth. However, adoption of infants and alloparenting by related kin is clearly successful outside the context of neuroendocrine priming. At the cellular level, it is well established that steroid (progesterone and oestrogen) signalling converges with DA transmission through recruitment and phosphorylation of co-regulators (steroid receptor coactivator 1; Mani 2003). Hence, in the mouse with a genetically modified non-functional progesterone receptor, DA agonists are still able to facilitate hormone-dependent behaviour. Such redundancy and hence emancipation from hormonal determinants of bonding enables extended parental and alloparental care to continue long after weaning. Indeed, they are lifetime occupations for many primate species, a development that has, in turn, impacted significantly on brain evolution. Brain growth is energetically costly, and postponing the greater part of this to the post-partum period has not only conserved the energetic demands on mother, but also has enabled brain growth to expand the cranial capacity way beyond the dimensions of the pelvic floor and birth canal. Moreover, postponing most of cortical brain growth to the post-partum period has also ensured that the brain develops in a social environment which promotes social skills as well as provides experience in alloparenting. Even more significant is the provision of an attachment figure, usually that of the mother, which provides the secure base from which to explore and develop other social relationships.

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