OPINION

The neurobiology of attachment

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It is difficult to think of any behavioural process that is more intrinsically important to us than attachment. Feeding, sleeping and locomotion are all necessary for survival, but humans are, as Baruch Spinoza famously noted, "a social animal" and it is our social attachments that we live for. Over the past decade, studies in a range of vertebrates, including humans, have begun to address the neural basis of attachment at a molecular, cellular and systems level. This review describes some of the important insights from this work.

Social attachment is not only intrinsically important, it is intrinsically difficult to study. One of the early pioneers in this area, Harry Harlow, described the different behavioural processes that are involved in the formation of parent–infant, filial and pair (male–female) bonds[1]. Each of these involves multi-sensory processing (predominantly olfactory in rodents and visual in primates) and complex motor responses (for example, proximity seeking, nurturing responses and defensive behaviours). Attachment also requires several cognitive processes that link sensory inputs to motor outputs, including attention, memory, social recognition, and, perhaps most characteristically, motivation. In non-human animals, this motivational aspect of attachment can be assessed as proximity seeking, a social preference or a separation response. In humans, the ultimate form of this motivation is what we experience as 'love'. Recent studies have begun to reveal neural mechanisms for social recognition, nurturing behaviour and, most importantly, the development of specific social preferences.

Model systems

To study the neural basis of attachment, we need model systems with three features. First, we need to be able to observe a clear onset of the behaviour to identify factors that initiate or inhibit the formation of attachment bonds. Second, attachment behaviour must be, by definition, selective and enduring. Selectivity distinguishes attachment from generalized social interaction. Duration distinguishes a bond from a transient preference. And finally, we need to be able to measure and manipulate these behaviours. Studies of social affiliation and attachment have spanned gene targeting in *Caenorhabditis elegans*[2] to psychodynamic approaches in humans[3]. In mammals, elegant studies of non-human primates, particularly of monogamous species including the New World callitrichids who show biparental care[4] and the Old World titi monkey in which pair bonds are expressed by tail twining[5], have described the behavioural features of social attachment. There is, as yet, no indication of neural systems that are involved in pair bond formation in these species. With the exception of pharmacological studies in maternal monkeys[6] and recent human imaging studies[7,8], investigations of neural systems that are important for attachment have so far used non-primate mammals. Investigations of the molecular and cellular mechanisms that underlie these behaviours have focused on: first, infant attachment to a parent; second, maternal behaviour in species with selective care of their young; and last, partner preference formation in species with long-term, selective bonds.

Infant–mother attachment

The study of neural mechanisms that underlie infant attachment has progressed furthest in species with precocial offspring. Within a discrete developmental window, the newly hatched chick shows visual imprinting, an enduring selectivity for following the mother (or a mother-like object) that can be quantified with great accuracy. Imprinting in the chick is not a single process but consists of at least three largely independent processes that are relevant to all other forms of attachment. First, there is the approach response, which is associated with increased arousal and inhibition of avoidance. This is followed by the acquisition or learning stage when chicks form a long-term memory for the imprinted stimulus, a stimulus that is partially pre-specified[9]. Finally, marking the end of the sensitive period for learning, there is a reversal of the approach–avoidance bias as chicks begin to avoid new objects while continuing to follow the familiar imprinted object.

A region within the intermediate medial part of the hyperstriatum ventrale (IMHV) of the chick brain is critical for acquisition and early consolidation of the memory of an imprinted visual stimulus[10]. A related region, the mediorostral neostriatum[11], responds selectively to imprinted auditory stimuli[12,13]. The learning phase of imprinting in the chick, whether it is visual or auditory, involves early and persistent enhancement of presynaptic release of amino acids, as well as changes in postsynaptic ultrastructure within specific cortical regions[10]. It is not clear how, or if, these changes differ from other forms of visual or auditory learning in chicks or which systems modulate the approach–avoidance changes that are necessary for imprinting.

The study of infant attachment in mammals has not identified a specific neural circuit or predominant neurochemical system. In rat pups, a great number of neurochemical systems increase or decrease the number of ultrasonic distress calls[14], but the response to separation might be neurochemically distinct from the process of attachment. We know

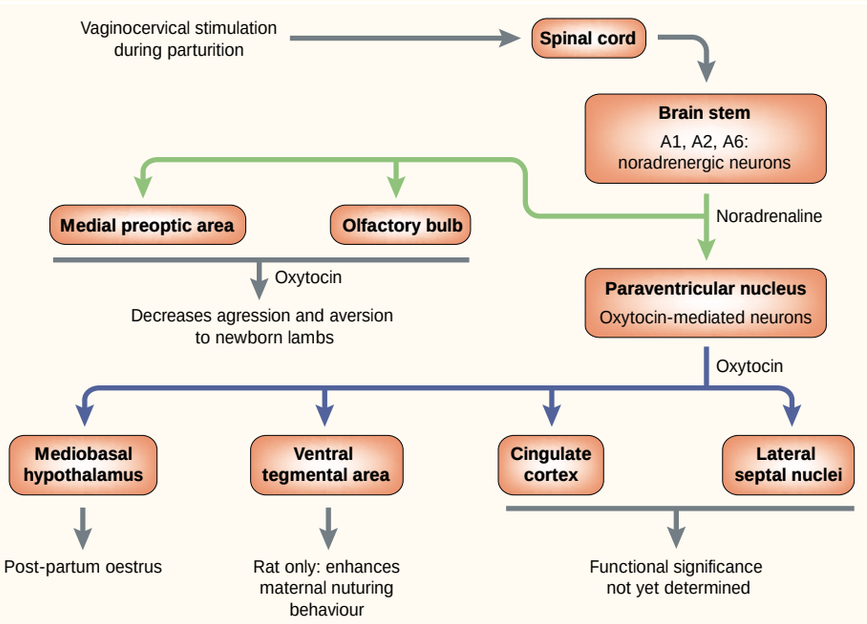

Figure 1| **Oxytocin and maternal behaviour in the sheep brain.** Within 2 hours of parturition the ewe develops a selective, permanent bond to her lamb. One neurobiological model for this process[43] posits that afferent stimulation through the spinal cord from vaginocervical dilation during parturition increases the activity of noradrenaline cells in the brainstem (A1, A2 and A6), which project to the paraventricular nucleus (PVN) in the hypothalamus, as well as to the olfactory bulb. Stimulation of oxytocin cells in the PVN facilitates maternal behaviour through coordinated effects on several regions in which oxytocin increases GABA (γ-aminobutyric acid) and noradrenaline release. Oxytocin in the olfactory bulb and medial preoptic area reduces aggressive or aversive responses to newborn lambs. Oxytocin in the mediobasal hypothalamus inhibits post-partum oestrus. On the basis of data from rats, oxytocin in the ventral tegmental area might facilitate the onset of maternal nurturing behaviours, although this has yet to be shown in the sheep brain. Projections to the lateral septum and cingulate cortex have not yet been studied for their functional significance. (Figure modified from REF. 43 © (1997) with permission from Elsevier Science, and includes release data based on microdialysis studies and behaviour data based on retrodialysis of oxytocin into regions noted.)

more about how infants learn to identify their mothers. Unlike imprinting in chicks, maternal recognition is largely an olfactory process in rat pups, involving noradrenaline-mediated pathways for olfactory learning[15]. The neuropeptide oxytocin has a curious effect on olfactory learning in rat pups. Pups can be rapidly conditioned to stimuli that are associated with maternal odours or maternal care[16]. Oxytocin facilitates learning in pups when the association is to social cues, such as the mother, but it fails to alter learning that is associated with non-social stimuli[17]. Conversely, an oxytocin antagonist delays this form of conditioning, indicating that this neuropeptide might be important for forming associations that are specifically related to the mother[17]. In contrast to the studies of imprinting in chicks, so far there are no comparable reports that identify a specific cortical region for attachment in the neonatal mammalian brain. Although social experience is critical for the normal development of the brain and behaviour in mammals, we know remarkably little about how social attachment, as opposed to general environmental enrichment[18], modifies the developing brain.

Mother–infant attachment

Mammalian maternal behaviour is extremely diverse[19]. At one extreme are the minimally maternal eutherian species such as tree shrews and rabbits that spend only a few minutes each day in contact with their young. At the other extreme are species, including many primates, that seem 'promiscuously parental', showing maternal behaviour throughout the life cycle. Between, there are many species for whom maternal care is restricted to the post-partum period, providing a clear onset and offset, with an opportunity for the study of neural mechanisms of this behaviour.

Maternal motivation — the rat. The Norway rat is a species in which females either actively avoid or attack pups until just before delivery, at which time they begin to build a nest, retrieve and defend young, and develop a species-typical arched back posture for nursing[20]. Many of the same neuroendocrine factors that are associated with pregnancy, parturition and lactation are also critical in this transition from avoidance to nurturing behaviour. Indeed, the changes in oestrogen and progesterone that accompany gestation and delivery are sufficient for inducing maternal behaviour in virgin females[21]. However, we still know relatively little about where or how these gonadal steroids affect neuronal activity to facilitate maternal behaviour.

Although there is no defined nucleus or circuit for motherhood in the rat brain, lesion studies, patterns of immediate-early gene expression and pharmacological manipulations have all implicated the medial preoptic area (MPOA), the overlying bed nucleus of the stria terminalis (BNST) and selected projection sites, including the lateral habenula and the ventral tegmental area (VTA)[20,22,23]. The abundant literature on the MPOA has still not defined how this structure changes with the onset of maternal behaviour, but there is considerable evidence from lesion studies that the MPOA is particularly critical for the integration of perioral sensory cues that permit nest building and retrieval of pups[24].

Neuropeptides, such as prolactin and oxytocin, which are involved in lactation, have been implicated as central neuroendocrine mediators of rat maternal care. In rats, prolactin administration facilitates maternal behaviour in a steroid-primed non-pregnant rat and treatments that decrease prolactin levels inhibit maternal care[25]. A mouse with a prolactin receptor null mutation shows impaired maternal retrieval and nest building[26]. Oxytocin, a uniquely mammalian neuropeptide, also facilitates the onset of maternal behaviour[27], but is not required once maternal behaviour is established[28]. These results have indicated that oxytocin might be important for the transition from avoidance to approach of the young. The facilitation of maternal behaviour by oxytocin might be mediated either through the VTA, the MPOA or from within the olfactory bulb, as injections of a selective oxytocin antagonist into each of these sites can block the onset of maternal care[29,30].

It is important to realize that in rats, as in many mammals, the onset of maternal behaviour involves overcoming a natural avoidance of neonates and, specifically neonate odours. Thus, in rat females, the initiation of maternal care is facilitated by lesions that reduce olfactory processing[31]. Oxytocin that is released centrally at parturition[32] seems to decrease the firing rate of mitral and granule

cells in the bulb[33], thereby decreasing olfactory processing and facilitating approach behaviour. This might be a critical step for the initial acceptance of pups (in addition to the effects of the peptide on maternal motivation) and it might be mediated through the VTA. The onset of maternal care in the rat requires at least two potentially neurobiologically independent events: first, inhibition of the avoidance/attack response to pup odours; and second, subsequent initiation of nurturing responses to pups.

Selective maternal care — sheep. A post-partum rat is virtually a maternal machine, caring for any pups placed in her nest. Rat maternal care may be intense, reflecting 'attachment' to a generic pup, but it is not selective. Sheep, which are highly selective, have proven more rigorous models of attachment, because the post-partum ewe rejects any lamb that is not her own. In addition to overcoming avoidance and initiating nurturing behaviour as observed with rats, the ewe must learn who is her lamb. Being a herd animal and seasonal breeder, she must learn this individual recognition quickly and accurately.

As with rats, gonadal steroids are important for priming the onset of maternal behaviour in sheep. But, in contrast to rats, prolactin does not seem critical for sheep maternal behaviour[34]. Much of our understanding of the onset and selectivity of maternal care in sheep has been based on the curious observation that vaginocervical stimulation (VCS) can induce almost immediate maternal behaviour in a steroid-primed non-pregnant ewe[35]. Furthermore, VCS will induce acceptance of an alien lamb even two to three days after she has bonded with her own lamb[36]. Epidural anaesthesia blocks these effects of VCS, indicating that central feedback might be essential[34].

How does the process of birth or VCS induce acceptance of a lamb? VCS and birth are both potent stimuli for release of the neuropeptide oxytocin within the central nervous system (CNS)[37] and, as with rats, oxytocin seems to be important for the onset of maternal care. Oxytocin can facilitate acceptance of an alien lamb, even in a non-pregnant ewe within 30 seconds of intra-cerebral ventricular (icv) injection[38,39]. In post-partum females in which maternal behaviour has been prevented by epidural anaesthesia, icv administration of oxytocin can induce a maternal response[40]. Although the location of the effects of oxytocin is not entirely clear, oxytocin mRNA and oxytocin receptor mRNA are increased regionally in the sheep brain post-partum[41,42]. A series of site-specific injection studies by Kendrick and colleagues point to a distributed network of effects with some regions that are important for selectivity and others that are related to nurturance[43] (FIG. 1). Injections of oxytocin into the MPOA or olfactory bulb reduce rejection of an alien lamb, much as described in rats, but these injections in sheep are not sufficient for inducing nurturing behaviour. Injections near the oxytocin synthesizing cells of the paraventricular nucleus of the hypothalamus (PVN) induce the entire complement of sheep maternal behaviours, possibly because autoreceptors on these cells mediate a short positive-feedback loop to increase oxytocin cell firing and coordinate oxytocin release in several terminal fields[44].

> "… recent studies with chicks, rats, sheep, voles and now humans have begun to reveal some important candidates for the neurobiology of social attachment".

Although considerable data might indicate the importance of oxytocin release in the CNS for the initiation of maternal care, the effects of oxytocin interact with experience, as they are more evident in females with a history of parental care. Oxytocin can induce lamb acceptance in an inexperienced ewe in which peridural anaesthesia blocks maternal behaviour[40], but oxytocin release (in the olfactory bulb) is reduced during parturition and virtually absent after VCS in inexperienced ewes compared with experienced females[43,45]. After development of a bond, even within a few hours, VCS can stimulate oxytocin release and induce maternal acceptance for the rest of the ewe's life. This permanent effect of experience on a neurochemical and behavioural response to a simple sensory input is reminiscent of imprinting in chicks. But how does experience result in a permanent reorganization of the response to lambs? And how does this acceptance become selective, such that a single lamb is accepted but all others are rejected? An answer to this latter question requires an investigation of olfactory learning.

Olfactory learning. In contrast to declarative memory or various types of hippocampal learning that have been studied in rats and monkeys[46], the form of permanent 'imprinting' that occurs in sheep seems to involve primarily a reorganization of the olfactory bulb[47]. Early in the post-partum period, the mother's selective bond with her lamb can be shown by two marked physiological changes in addition to her behaviour. Recordings in the mitral cell layer of the bulb during the first weeks post-partum reveal a 60% increase in the number of cells that respond preferentially to lamb odours, compared with those made during late pregnancy[47]. Of this group of cells, ~30% respond specifically to the ewe's own lamb and not to other lambs[47]. In addition to this physiological correlate of selectivity, within 24 hours of parturition, the ewe's own lamb odour elicits a robust increase in extracellular concentrations of glutamate and GABA (γ-aminobutyric acid) within the olfactory bulb[47]. This effect seems to be selective, as neither glutamate nor GABA is released in response to

Box 1 | Mechanisms for olfactory learning

Mitral cells contain glutamate and are closely regulated by inhibitory synapses with granule cells and periglomerular cells. According to the model developed by Kendrick and co-workers, during vaginocervical stimulation (VCS) or birth, increased noradrenaline-mediated stimulation leads to decreased release of GABA (γ-aminobutyric acid) from granule cells, disinhibiting mitral cells[47]. With incoming olfactory signals from the lamb in the presence of this disinhibited state, mitral cells increase their release of glutamate, which activates ionotropic autoreceptors and provides a short loop positive feedback on mitral cell activation. This model is consistent with the results of *in vivo* microdiaysis experiments: extracellular concentrations of both glutamate and GABA within the bulb increase in response to lamb odours, with the ratio favouring glutamate. With concurrent granule cell and mitral cell activation, there is an increase in nitric oxide (NO) generation[48]. Mitral cells (but not granule cells) have the guanylyl cyclase subunits that are necessary for generation of cyclic GMP. The increase in cGMP in mitral cells facilitates the release of glutamate. Blockade of either neuronal nitric-oxide synthase or guanylyl cyclase activity blocks the increase in glutamate and GABA release and also prevents formation of the memory of the ewe's own lamb[48]. The same treatments have no effect 24 hours post-partum, after the ewe has learned her lamb's odour.

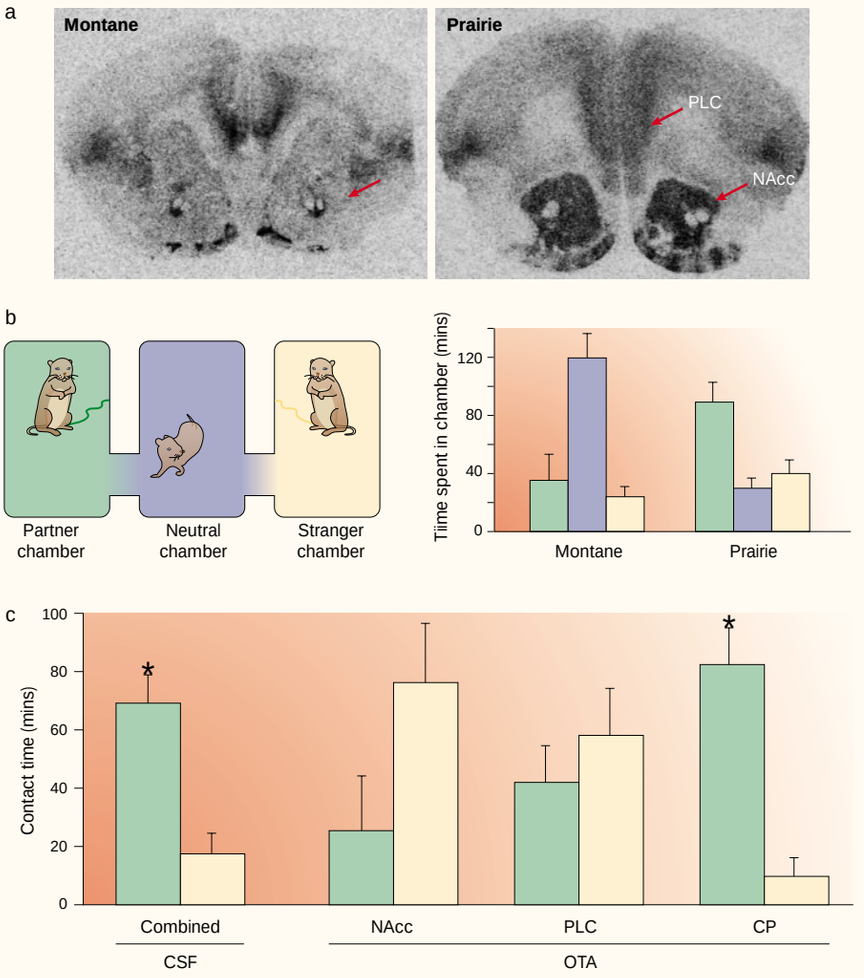

Figure 2 | **Oxytocin and social attachment in the monogamous prairie vole female. a** | Prairie and montane voles have different distributions of oxytocin receptors in the brain, particularly in the nucleus accumbens (NAcc) and the prelimbic cortex (PLC; arrow). **b** | In the laboratory, pair bonding is assayed using a partner-preference test. After mating or cohabitation with a 'partner,' the experimental vole is place in a three-chambered arena in which the partner is tethered in one chamber (green) and an equivalent non-familiar vole or 'stranger' is tethered in another chamber (yellow). The experimental animal has free access to both chambers. After mating, female prairie voles spend more time in the partner's chamber (green bar) than in the neutral or stranger's chamber (yellow bar), indicating a partner preference. By contrast, mated montane voles show no preference for either the partner or the stranger, indicating the absence of a mating-induced social attachment. **c** | Partner preference formation is blocked in the mating female prairie vole by infusions of oxytocin receptor antagonist (OTA) into the NAcc as well as the PLC, whereas cerebrospinal fluid (CSF) into either area or OTA infused into the caudate putamen (CP) had no effect on partner preference formation. OTA had no effect on mating. (Panel **c** modified from REF. 65).

lamb odours before birth or in response to unfamiliar lambs post-partum. These changes are reminiscent of the enhancement of amino-acid release that is observed after imprinting in chicks.

How does this reorganization of the olfactory bulb take place? We know that, as is the case for olfactory learning in rat pups, afferent projections from noradrenaline cells in the brainstem are critical. We also know that the signals from the lamb are largely volatile and act through the main olfactory bulb[34]. The main event seems to be at the granule cell–mitral cell synapses in the bulb (BOX 1). The ewe learns the identity of her lamb through a nitric-oxide-dependent process that occurs within a few hours of birth, resulting in an increase in the ratio of excitatory to inhibitory tone in the granule cell–mitral cell synapses in the olfactory bulb[48]. But this process might not be unique to the post-partum ewe, as analogous changes have now been observed with olfactory conditioning in mice[49]. In sheep, these changes seem to be under the influence of gonadal steroids[50], but it is otherwise not yet clear how the process in sheep is distinct from olfactory learning that does not involve an enduring, selective attachment to the young. Specifically, we do not know how, in sheep, the 'imprinting' of the lamb's odour permanently opens a sensory gate that signals acceptance to the ewe, whereas rejection remains her response to all other lambs. The permanent experience-dependent changes in the post-partum ewe offer an excellent opportunity for identifying the cellular mechanisms for long-term memory in either the olfactory bulb or the higher order stages of olfactory processing.

Studies in sheep might not only yield important clues for the cellular mechanisms of long-term memory, they might also hold great promise for revealing the neural mechanisms of attachment. The key will be to link the process of olfactory learning to the motivation for maternal care. Somehow the process of birth (or VCS) leads to willingness to interact with a lamb and then within a few hours, a permanent change in the behavioural, physiological and neurochemical responses to this and no other lamb. The investigation of molecular and cellular changes in the ewe's brain during this initial period of interaction with the lamb, like the process of imprinting in the chick, should reveal critical clues to the neurobiology of attachment.

Adult–adult pair bond formation

About 5% of mammals are monogamous and biparental[51,52]. With the development of quantitative, operational definitions of various behavioural aspects of pair bonding, the voles (microtine rodents) have proven to be excellent model species for molecular and cellular studies of complex social behaviours[53]. Two North American species have been compared extensively for neural differences: prairie voles that are monogamous and montane voles that fail to form social bonds.

Oxytocin and vasopressin. As oxytocin has been implicated in maternal behaviour in rats and sheep, it seems plausible that oxytocin or its close relative vasopressin might also be involved in adult–adult attachment. Prairie voles normally form pair bonds after mating[53]. As copulation (or VCS) releases oxytocin and vasopressin[54], one possibility is that these neuropeptides are involved in the process of pair bond formation after mating. Indeed, all of the major behavioural aspects of monogamy can be facilitated in the prairie

vole by central injections of either oxytocin or vasopressin, even in voles that do not have the opportunity to mate[55,56] (FIG. 2). Conversely, these behaviours are inhibited by either oxytocin or vasopressin antagonists given to prairie voles just before mating[56,57]. The antagonists do not alter mating behaviour *per se*, but seem to prevent the partner preference that normally occurs with mating in prairie voles (FIGS 2,3). Thus, in monogamous prairie voles, oxytocin and vasopressin seem to be necessary and sufficient for pair bond formation. Neither peptide has notable effects on social behaviour in the non-monogamous montane voles[58,59].

Are these pharmacological responses to oxytocin or vasopressin relevant to the behavioural differences between the vole species? Although there are no evident species differences in the expression of these neuropeptides[60], there are regional differences in the receptors for both peptides, assessed by either receptor binding[61,62] or receptor mRNA[59,63]. In the monogamous prairie vole, in which oxytocin and vasopressin facilitate partner preference formation, receptors are expressed at high levels in the nucleus accumbens and related regions (for example, oxytocin receptors in the prelimbic cortex and vasopressin receptors in the ventral pallidum) that are associated with reinforcement and conditioning (FIGS 2,3). Montane voles have few detectable receptors for either oxytocin or vasopressin in these regions, but have high levels of receptor binding for both neuropeptides in the lateral septum. In the prairie vole, blockade of oxytocin receptors in the nucleus accumbens inhibits partner preference formation[64] (FIG. 2) and viral vector-induced overexpression of the vasopressin V1a receptor in the ventral pallidum facilitates partner preference formation[65], suggesting that receptors in these regions might be critical for pair bond formation. Indeed, vasopressin receptors in the ventral pallidum are present not only in prairie voles but also in monogamous mice and primates, whereas they are absent in this region in related rodent and primate species that do not form pair bonds[66].

A simple model posits the release of oxytocin and vasopressin with mating leading to the activation of reinforcement circuits in monogamous species that form pair bonds. In non-monogamous species, oxytocin and vasopressin activate unrelated circuits without the conditioned response that is essential for attachment. Interestingly, there is an increase in oxytocin receptors in montane voles post-partum, associated with the onset of nurturing behaviour towards pups[61]. Recent studies have described the role of the nucleus accumbens and specifically D2 dopamine receptors in this region for partner preference formation in prairie voles[67,68]. D2 agonists facilitate and D2 antagonists inhibit partner preference formation, whether given systemically or directly into the nucleus accumbens. It seems likely that the neuropeptides (or mating) might be activating a mesolimbic circuit implicated in the reinforcing effects of psychostimulants. It is not yet clear, however, how the neuropeptides interact with dopamine or, at the systems level, how either neuropeptides or dopamine influence partner preference formation. On the basis of studies in rats, Everitt and colleagues have recently suggested that the effects of dopamine on reinforcement might be mediated by increasing the gain on glutamate-containing afferents to the nucleus accumbens[69]. It seems likely that the neurobiology of partner preference formation in monogamous species will resemble the neurobiology of other forms of conditioning, such as place-preference formation in non-monogamous species. However, in monogamous species there might be a selective predisposition to condition to social stimuli, in part, due to the role of oxytocin or vasopressin neurotransmission.

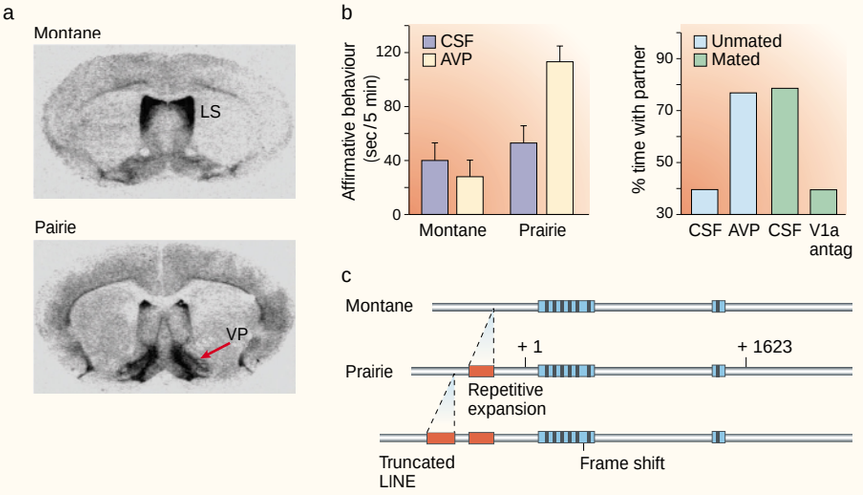

Figure 3 | **Vasopressin V1a receptor and attachment in prairie vole male. a** | Montane and prairie voles have different distributions of V1a receptor binding, with prairie voles having relatively high densities of receptors in the ventral pallidum (VP). (LS, lateral septum.) **b** | The species differences in receptor distribution are probably responsible for the species differences in the behavioural effects of arginine vasopressin (AVP) and perhaps in the formation of social attachments. In a test of nonspecific affiliative behaviour, intracerebroventricular AVP infusions increase social interest in the male prairie vole but not in the montane vole. Furthermore, AVP stimulates the formation of a partner preference in the absence of mating and V1a receptor antagonists prevent partner preference formation after extensive mating bouts. (CSF, cerebrospinal fluid.) **c** | These species differences in receptor distribution might be the result of species differences in gene structure. The prairie vole V1a receptor gene has been duplicated with one copy being downstream of a retrotransposon element (LINE) and it also has a frameshift mutation in the coding region. Both copies have a large complex repetitive expansion (red) just over 700 bp from the transcription start site. Either the gene duplication or the promoter expansion could contribute to the evolution of the expression pattern. (Figure modified with permission from REF. 70 © (1999) Macmillan Magazines Ltd.)

One additional aspect of the vole research has investigated the molecular mechanism for the species differences in the neuroanatomical distribution of receptors, potentially a molecular basis for monogamy. The coding regions for both the oxytocin and vasopressin (V1a) receptors are essentially identical between monogamous and non-monogamous voles. However, there are marked species differences in the 5′ flanking region of the vasopressin V1a receptor gene with an ~460 bp microsatellite insertion into the prairie vole receptor gene that is not evident in the montane vole V1a receptor gene[70] (FIG. 3). As promoter sequences or related *cis* regulatory regions might be important determinants of tissue-specific gene expression, these microsatellites could contribute to the species differences in V1a receptor expression. In a transgenic mouse with 2.2 kb of the 5′ flanking region (including the microsatellite) along with the coding region and 2.4 kb of the 3′ flanking region of the prairie vole V1a receptor, the V1a receptor was expressed in a prairie vole-like pattern within the CNS[70]. Supporting the importance of receptor location for function, this transgenic mouse responded to arginine vasopressin (AVP) with increased affiliation, similar to the

Box 2 | Of human bonding

Are animal studies of attachment relevant to human love? In the human brain, oxytocin receptors are concentrated in several dopamine-rich regions, especially the substantia nigra and globus pallidus, as well as the preoptic area[90]. Whereas this pattern is consistent with a monogamous brain, the receptors are not found in the ventral striatum or ventral pallidum, areas in which either oxytocin or vasopressin V1a receptors are abundant in monogamous voles and monkeys[91]. There is no evidence, at this time, that these pathways are involved in human attachment.

A recent functional magnetic resonance imaging (fMRI) study of adults looking at pictures of their partners, as opposed to close non-romantic friends, found bilateral activation in the anterior cingulate (Brodmann's area 24), medial insula (Brodmann's area 14) as well as caudate and putamen[7]. The pattern of cortical activation was distinct from previous studies of face recognition, visual attention, sexual arousal or other emotional states, but resembled preliminary results from an fMRI study of new mothers listening to infant cries[8]. Both studies of human attachment show marked overlap between the pattern of activation when looking or hearing a loved one and a previous report of activation during cocaine-induced euphoria[92]. It seems likely that pathways that mediate the hedonic properties of psychostimulants evolved as neural systems for social attachment.

prairie vole response to AVP. In contrast to these results with transgenic mice and prairie voles, AVP did not increase affiliation in wild-type mice without the prairie vole V1a receptor[70]. These results are consistent with the hypothesis that the species differences in promoter sequence are responsible for the species differences in receptor distribution, but they do not rule out other factors, such as environmental influences that would be different between the species.

Neuropeptides. The studies with voles provide a model by which changes in gene structure could alter regional receptor expression with profound effects on the functional response to endogenous or exogenous ligands. Oxytocin and vasopressin are interesting candidates because they could link the neuroendocrine response to copulation with the behavioural consequence of partner preference formation and ultimately pair bonding. In sheep, several studies have begun to define how the ewe recognizes her lamb[71]. In voles, this has not been studied to the same extent. Although pheromones are important for reproductive function in prairie voles[72] , we know very little about how the prairie vole learns the identity of its partner.

Furthermore, it remains unclear whether oxytocin and vasopressin primarily increase the preference for the partner because they confer reinforcing properties onto the mate or whether they simply facilitate recall. Oxytocin has been implicated in the reinforcing effects of psychostimulants (cocaine)[73], but we know of no evidence that either oxytocin or vasopressin is, by itself, reinforcing. Conversely, there is considerable evidence that implicates both oxytocin and vasopressin in social recognition or social memory. Oxytocin knockout mice, capable of full maternal behaviour, show a profound social amnesia without other evident cognitive deficits[74]. In contrast to the sheep studies of olfactory memory described above, in these knockout mice a social stimulus elicits normal amounts of Fos activation in the olfactory bulb, but fails to activate the medial amygdala and its projection sites, the bed nucleus of the stria terminalis and the MPOA. In the mouse brain, the medial nucleus of the amygdala is enriched with oxytocin receptors and in the knockout mouse, injections of oxytocin into this region (but not into the olfactory bulb) restores social recognition[75]. Therefore, it remains possible that the absence of partner preferences in prairie voles treated with oxytocin and vasopressin antagonists results from an inability to recognize the partner, not from an absence of pair bonding. Wang *et al.*[67] have shown that D2 dopamine receptor blockade given just before a preference test does not interfere with recognition of the partner but, given just after mating, a D2 dopamine antagonist inhibits consolidation of the memory for the mate. Analagous studies have yet to be done with oxytocin or AVP in prairie voles.

Unifying principles

What do the studies of infant, maternal and adult attachment have in common? Although the data, so far, have been obtained in different species, the neurobiological tasks in each form of attachment are the same: first, approach the parent, infant or partner; second, learn the identity of this individual; and third, invest in this individual while rejecting all other individuals. These tasks might be accomplished by different mechanisms at different life stages, contingent on developmental and gonadal status. However, a working hypothesis is that not only the tasks but the neural mechanisms of attachment behaviour have been largely conserved. In a general sense, neuropeptides that are modulators of fast neurotransmitters, have discrete CNS distributions, and that are regulated by highly plastic receptors seem especially suited as mediators of attachment.

Approach behaviour requires overcoming a natural avoidance of offspring or strangers along with the initiation of pro-social, proximity-seeking behaviours. Paradoxically, olfactory lesions seem to facilitate the initiation of maternal acceptance in rats and sheep, presumably by permitting females to overcome a natural aversion to offspring odours. We know less about the neuroanatomical circuit for releasing pro-social behaviours, but affiliative behaviours in rodents and primates are facilitated by opiates[76,77] and oxytocin[78,79]. Receptors for oxytocin are increased in the hypothalamus and bed nucleus of the stria terminalis by the physiological changes in oestrogen and progesterone that occur at the end of gestation[80], providing a mechanism by which pathways for affiliation can be entrained to parturition.

For species that form selective bonds, learning must be rapid but enduring, analogous to single-trial learning. In chick imprinting, this process is associated with enhanced release of glutamate in select cortical regions. In the case of maternal behaviour in sheep, selectivity is associated with enhanced excitatory amino-acid release in the olfactory bulb (although also see REF. 81), secondary to cyclic GMP generation within mitral cells. In prairie voles, the circuitry for selectivity is not known, but on the basis of studies with knockout mice, the medial amygdala might be critical for individual recognition. It is not yet clear how this process in any of these species that form selective bonds differs from the plasticity in other regions of the CNS that are associated with other forms of learning.

Finally, the process of investing in a single attachment partner probably involves the same pathways that are required for other forms of motivation. Oxytocin has emerged as one candidate from studies in rats, sheep and monogamous voles, but we do not understand fully how this neuropeptide, released during nursing and copulation, fits into a systems model for motivation (FIG. 1). Oxytocin is, at most, one element in a cascade. Endogenous opioids have been shown to influence affiliative and maternal behaviours in sheep[82] and primates[83], possibly by stimulating oxytocin release[84] or possibly by an independent effect on reinforcement. Oxytocin modulates release of monoamines, acetylcholine and GABA[43]. The available data

might indicate an important link with mesolimbic dopamine pathways as oxytocin effects on rat maternal care might be mediated through the VTA[85] and several studies have shown that mesolimbic dopamine pathways influence motivational aspects of maternal behaviour[86–88]. As noted above, only monogamous voles that pair bond after mating have receptors for oxytocin in the nucleus accumbens and vasopressin in the ventral pallidum. But, there are still unanswered questions concerning whether these neuropeptides are specific for social stimuli or how they interact with other forms of reinforcement that are mediated through mesolimbic pathways. The connection between attachment and addiction has been suggested phenomenologically and might provide important clues for future research[89].

Summary

Attachment behaviour is both biologically important and technically difficult to study. The behaviour is complex and there are changes in several cognitive and affective variables to consider. Nevertheless, recent studies with chicks, rats, sheep, voles and now humans (BOX 2) have begun to reveal some important candidates for the neurobiology of social attachment. The neuropeptides oxytocin and vasopressin have yielded a model that links molecular, cellular and systems approaches. Dopamine pathways in the forebrain, especially the nucleus accumbens and ventral pallidum, seem to be important for certain aspects of partner preference formation. It seems likely that for attachment to occur, these neuropeptides must link social stimuli to dopamine pathways associated with reinforcement. It is also possible that neural mechanisms that we associate with drug abuse and addiction might have evolved for social recognition, reward and euphoria — critical elements in the process of attachment. In the very near future, we can hope that discoveries of the molecular and cellular mechanisms of addiction might be applied to the neurobiology of attachment, providing a new understanding of one of our most complex and intriguing emotions.

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1. Harlow, H. & Suomi, S. The nature of love — Simplified. *Amer. Psychol.* **25**, 161–168 (1970).
2. de Bono, M. & Bargmann, C. Natural variation in a neuropeptide Y receptor homolog modifies social behavior and food response in *C. elegans*. *Cell* **94**, 679–689 (1998).
3. Bowlby, J. *Attachment and Loss: Attachment* 2nd edn Vol. 1 (Basic Books, New York, 1982).
4. Snowdon, C. in *Contemporary Issues in Comparative Psychology* (ed. Dewsbury, D.) 225–251 (Sinauer, Sunderland, Massachusetts, 1990).
5. Mendoza, S. & Mason, W. Contrasting responses to intruders and involuntary separation by monogamous and polygynous New World monkeys. *Physiol. Behav.* **38**, 795–801 (1986).
6. Martel, F. L., Nevison, C. M., Rayment, F. D., Simpson, M. J. & Keverne, E. B. Opioid receptor blockade reduces maternal affect and social grooming in rhesus monkeys. *Psychoneuroendocrinology* **18**, 307–321 (1993).
7. Bartels, A. & Zeki, S. The neural basis of romantic love. *NeuroReport* **11**, 3829–3834 (2000).
8. Lorberbaum, J. *et al.* Feasibility of using fMRI to study mothers responding to infant cries. *Depression and Anxiety* **10**, 99–104 (1999).
9. Bolhuis, J. & Honey, R. Imprinting, learning and development: from behaviour to brain and back. *Trends Neurosci.* **21**, 306–311 (1998).
10. Horn, G. Visual imprinting and the neural mechanisms of recognition memory. *Trends Neurosci.* **21**, 300–305 (1998).
11. Metzger, M., Jiang, S. & Braun, K. Organization of the dorsalcaudal neostriatal complex: a retrograde and anterograde tracing study in the domestic chick with special emphasis on pathways relevant to imprinting. *J. Comp. Neurol.* **395**, 380–404 (1998).
12. Bredenkotter, M. & Braun, K. Changes of neuronal responsiveness in the mediorostral neostriatum/hyperstriatum after auditory filial imprinting in the domestic chick. *Neuroscience* **76**, 355–365 (1997).
13. Gruss, M. & Braun, K. Stimulus evoked increase of glutamate in the mediorostral neostriatum/hyperstriatum ventrale of domestic chicks after filial imprinting: an *in vivo* microdialysis study. *J. Neurochem.* **66**, 1167–1173 (1996).
14. Winslow, J. T. & Insel, T. R. The infant rat separation paradigm: A novel test for novel anxiolytics. *Trends Pharmacol. Sci.* **12**, 402–404 (1991).
15. Sullivan, R. & Wilson, D. The locus ceruleus, norepinephrine, and memory in newborns. *Br. Res. Bull.* **35**, 467–472 (1994).
16. Johnson, B. & Leon, M. Spatial distribution of [14C]2-deoxyglucose uptake in the glomerular layer of the rat olfactory bulb following early odor preference learning. *J. Comp. Neurol.* **376**, 557–566 (1996).
17. Nelson, E. & Panksepp, J. Oxytocin and infant-mother bonding in rats. *Behav. Neurosci.* **110**, 583–592 (1996).
18. van Praag, H., Kemperman, G. & Gage, F. Neural consequences of environmental enrichment. *Nature Rev. Neurosci.* **1**, 191–198 (2000).
19. Rosenblatt, J. S. & Siegel, H. I. in *Parental Care in Mammals* (eds Gubernick, D. J. & Klopfer, P. H.) 1–76 (Plenum, New York, 1981).
20. Numan, M. in *The Physiology of Reproduction* (eds Knobil, E. & Neill, J.) 221–302 (Raven, New York, 1994).
21. Bridges, R. S. A quantitative analysis of the roles of dosage, sequence, and duration of estradiol and progesterone exposure in the regulation of maternal behavior in the rat. *Endocrinology* **114**, 930–940 (1984).
22. Corodimas, K. P., Rosenblatt, J. S. & Morrell, J. I.The habenular complex mediates hormonal stimulation of maternal behavior in rats. *Behav. Neurosci.* **106**, 853–865 (1992).
23. Numan, M. & Sheehan, T. P. Neuroanatomical circuitry for mammalian maternal behavior. *Ann. NY Acad. Sci.* **807**, 101–125 (1997).
24. Numan, M., Corodimas, K. P., Numan, M. J., Factor, E. M. & Piers, W. D. Axon-sparing lesions of the preoptic area and substantia innominata disrupt maternal behavior in rats. *Behav. Neurosci.* **102**, 381–395 (1988).
25. Bridges, R. S. & Ronsheim, P. M. Prolactin (PRL) regulation of maternal behavior in rats: Bromocriptine treatment delays and PRL promotes the rapid onset of behavior. *Endocrinology* **126**, 837–848 (1990).
26. Lucas, B., Ormandy, C., Binart, N., Bridges, R. & Kelly, P. Null mutation of the prolactin receptor gene produces a defect in maternal behavior. *Endocrinology* **139**, 4102–4107 (1998).
27. Pedersen, C. A., Ascher, J. A., Monroe, Y. L. & Prange, A. J. Jr Oxytocin induces maternal behaviour in virgin female rats. *Science* **216**, 648–649 (1982).
28. Insel, T. R. in *Mammalian Parenting, Biochemical, Neurobiological, and Behavioral Determinants* (eds Krasnegor, N. & Bridges, R.) 260–280 (Oxford Univ. Press, New York, 1990).
29. Pedersen, C. A., Caldwell, J. O., Walker, C., Ayers, G. & Mason, G. A. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav. Neurosci.* **108**, 1163–1171 (1994).
30. Yu, G.-Z., Kaba, H., Okutani, F., Takahashi, S. & Higuchi, T. The olfactory bulb: A critical site of action for oxytocin in the induction of maternal behaviour in the rat. *Neuroscience* **72**, 1083–1088 (1996).
31. Fleming, A. S. & Rosenblatt, J. S. Olfactory regulation of maternal behavior in rats: II. Effects of peripherally induced anosmia and lesions of the lateral olfactory tract in pup-induced virgins. *J. Comp. Physiol. Psychol.* **86**, 233–246 (1974).
32. Landgraf, R., Neumann, I., Russell, J. & Pittman, Q. Push-pull perfusion and microdialysis studies of central oxytocin and vasopressin release in freely moving rats during pregnancy, parturition, and lactation. *NY Acad. Sci.* **652**, 326–339 (1992).
33. Yu, G. -Z. *et al.* The action of oxytocin originating in the hypothalamic paraventricular nucleus on the mitral and granule cells in the rat main olfactory bulb. *Neuroscience* **72**, 1073–1082 (1996).
34. Levy, F., Kendrick, K., Keverne, E., Porter, R. & Romeyer, A. in *Advances in Study of Behavior* (eds Rosenblatt, J. & Snowdon, C.) 385–422 (Academic, San Diego, 1996).
35. Keverne, E. B., Levy, F., Poindron, P. & Lindsay, D. R. Vaginal stimulation: An important determinant of maternal bonding in sheep. *Science* **219**, 81–83 (1983).
36. Kendrick, K. M., Levy, F. & Keverne, E. B. Importance of vaginocervical stimulation for the formation of maternal bonding in primiparous and multiparous parturient ewes. *Physiol. Behav.* **50**, 595–600 (1991).
37. Kendrick, K. M., Keverne, E. B., Chapman, C. & Baldwin, B. A. Microdialysis measurement of oxytocin, aspartate, GABA and glutamate release from the olfactory bulb of sheep during vaginocervical stimulation. *Brain Res.* **442**, 171–177 (1988).
38. Kendrick, K. M., Keverne, E. B. & Baldwin, B. A. Intracerebroventricular oxytocin stimulates maternal behaviour in the sheep. *Neuroendocrinology* **46**, 56–61 (1987).
39. Keverne, E. & Kendrick, K. Oxytocin facilitation of maternal behavior in sheep. *Ann. NY Acad. Sci.* **652**, 83–101 (1992).
40. Levy, F., Kendrick, K., Keverne, E., Piketty, V. & Poindron, P. Intracerebral oxytocin is important for the onset of maternal behavior in inexperienced ewes delivered under peridural anesthesia. *Behav. Neurosci.* **106**, 427–432 (1992).
41. Broad, K., Kendrick, K., Sirinathsinghji, D. & Keverne, E. Changes in oxytocin immunoreactivity and mRNA expression in the sheep brain during pregnancy, parturition and lactation and in response to oestrogen and progesterone. *J. Neuroendocrinol.* **5**, 435–444 (1993).
42. Broad, K. *et al.* Previous maternal experience potentiates the effect of parturition on oxytocin receptor mRNA expression in the paraventricular nucleus. *Eur. J. Neurosci.* **11**, 3725–3737 (1999).
43. Kendrick, K. *et al.* Neural control of maternal behaviour and olfactory recognition of offspring. *Brain Res. Bull.* **44**, 383–395 (1997).
44. Da Costa, A. P. C., Guevara-Guzman, R. G., Ohkura, S., Goode, J. A. & Kendrick, K. M. The role of oxytocin release in the paraventricular nucleus in the control of maternal behaviour in the sheep. *J. Neuroendocrinol.* **8**, 163–177 (1996).
45. Levy, F., Kendrick, K. M., Goode, J. A., Guevara-Guzman, R. & Keverne, E. B. Oxytocin and vasopressin release in the olfactory bulb of parturient ewes: changes with maternal experience and effects on acetylcholine, γ-aminobutyric acid, glutamate and noradrenaline release. *Brain Res.* **669**, 197–206 (1995).
46. Eichenbaum, H. A cortical–hippocampal system for declarative memory. *Nature Rev. Neurosci.* **1**, 41–50 (2000).
47. Kendrick, K., Levy, F. & Keverne, E. Changes in the sensory processing of olfactory signals induced by birth in sheep. *Science* **256**, 833–836 (1997).
48. Kendrick, K. *et al.* Formation of olfactory memories mediated by nitric oxide. *Nature* **388**, 670–674 (1997).
49. Brennnan, P., Schellinck, H., De La Riva, C., Kendrick, K. & Keverne, E. Changes in neurotransmitter release in the main olfactory bulb following an olfactory conditioning procedure. *Neuroscience* **87**, 583–590 (1998).
50. Guevara-Guzman, R., Barrera-Mera, B., De La Riva, C. & Kendrick, K. Release of classical neurotransmitters and nitric oxide in the rat olfactory bulb, evoked by vaginocervical stimulation and potassium, varies with the oestrus cycle. *Eur. J. Neurosci.* **12**, 80–88 (2000).
51. Kleiman, D. G. Monogamy in mammals. *Q. Rev. Biol.* **52**, 39–69 (1977).
52. Dewsbury, D. A. in *American Zoology Nebraska Symposium on Motivation* (ed. Leger, D. W.) 1–50 (Nebraska Univ. Press, Lincoln, Nebraska, 1988).

53. Carter, C., DeVries, A. & Getz, L. Physiological substrates of mammalian monogamy: The prairie vole model. *Neurosci. Biobehav. Rev.* **19**, 303–314 (1995).
54. Witt, D. M. Oxytocin and rodent sociosexual responses: from behavior to gene expression. *Neurosci. Biobehav. Rev.* **19**, 315–324 (1995).
55. Williams, J., Insel, T., Harbaugh, C. & Carter, C. Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (*Microtus ochrogaster*). *J. Neuroendocrinol.* **6**, 247–250 (1994).
56. Winslow, J. T., Hastings, N., Carter, C. S., Harbaugh, C. R. & Insel, T. R. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature* **365**, 545–548 (1993).
57. Insel, T. R. & Hulihan, T. J. A gender specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. *Behav. Neurosci.* **109**, 782–789 (1995).
58. Winslow, J. T., Shapiro, L. E., Carter, C. S. & Insel, T. R. Oxytocin and complex social behaviors: species comparisons. *Psychopharmacol. Bull.* **29**, 409–414 (1993).
59. Young, L. J., Winslow, J. T., Nilsen, R. & Insel, T. R. Species differences in V1a receptor gene expression in monogamous and nonmonogamous voles: Behavioral consequences. *Behav. Neurosci.* **111**, 599–605 (1997).
60. Wang, Z. X., Zhou, L., Hulihan, T. J. & Insel, T. R. Immunoreactivity of central vasopressin and oxytocin pathways in microtine rodents: A quantitative comparative study. *J. Comp. Neurol.* **366**, 726–737 (1996).
61. Insel, T. R. & Shapiro, L. E. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proc. Natl Acad. Sci. USA* **89**, 5981–5985 (1992).
62. Insel, T. R., Wang, Z. & Ferris, C. F. Patterns of brain vasopressin receptor distribution associated with social organization in microtine rodents. *J. Neurosci.* **14**, 5381–5392 (1994).
63. Young, L. J., Huot, B., Nilsen, R., Wang, Z. & Insel, T. R. Species differences in central oxytocin receptor gene expression: Comparative analysis of promoter sequences. *J. Neuroendocrinol.* **8**, 777–783 (1996).
64. Young, L. J., Gingrich, B. & Insel, T. R. Molecular and cellular mechanisms of monogamy. *Horm. Behav*. (in the press).
65. Sharer, C. *et al.* Manipulation of vasopressin receptor expression in adult brain using an AAV viral vector. *Soc. Neurosci. Annu. Meeting* **30**, 373.11 (2000).
66. Young, L. J. Oxytocin and vasopressin receptors and species-typical social behaviors. *Horm. Behav.* **36**, 212–221 (1999).
67. Wang, Z. *et al.* Dopamine D2 receptor-mediated regulation of partner preferences in female prairie voles: A mechanism for pair bonding. *Behav. Neurosci.* **113**, 602–611 (1999).
68. Gingrich, B., Liu, Y., Cascio, C., Wang, Z. & Insel, T. R. Dopamine D2 receptors in the nucleus accumbens are important for social attachment in female prairie voles. *Behav. Neurosci.* **114**, 173–183 (2000).
69. Everitt, B. *et al.* Associative process in addiction and reward. *Ann. NY Acad Sci.* **877**, 412–438 (1998).
70. Young, L., Nilsen, R., Waymire, K., MacGregor, G. & Insel, T. Increased affiliative response to vasopressin in mice expressing the V1a receptor from a monogamous vole. *Nature* **400**, 766–768 (1999).
71. Levy, F., Kendrick, K. M., Keverne, E. B., Porter, R. H. & Romeyer, A. in *Parental Care: Evolution, Mechanisms, and Adaptive Significance* (eds Rosenblatt, J. S. & Snowdon, C. T.) 385–416 (Academic, San Diego, 1996).
72. Carter, C. S., Witt, D. M., Schneider, J., Harris, L. & Volkening, D. Male stimuli are necessary for female sexual behavior and uterine growth in prairie voles (*Microtus ochrogaster*). *Horm. Behav.* **21**, 74–82 (1987).
73. Kovacs, G. L. & Telegdy, G. in *Oxytocin: Clinical and Laboratory Studies* (eds Amico, J. & Robinson, A. G.) 359–371 (Elsevier, New York, 1985).
74. Ferguson, J., Young, L., Hearn, E., Insel, T. & Winslow, J. Social amnesia in mice lacking the oxytocin gene. *Nature Genet.* **25**, 284–288 (2000).
75. Ferguson, J., Aldag, J., Winslow, J., Insel, T. R. & Young, L. J. Neural activation in the socially amnestic mouse. *Soc. Neurosci. Annu. Meeting* **30**, 373.8 (2000).
76. Herman, B. H. & Panksepp, J. Effects of morphine and naloxone on separation distress and approach attachment: Evidence for opiate mediation of social affect. *Pharmacol. Biochem. Behav.* **9**, 213–220 (1978).
77. Martel, F. L., Nevison, C. M., Simpson, M. J. & Keverne, E. B. Effects of opioid receptor blockade on the social behavior of rhesus monkeys living in large family groups. *Dev. Psychobiol.* **28**, 71–84 (1995).
78. Insel, T. R. Oxytocin: a neuropeptide for affiliation — evidence from behavioral, receptor autoradiographic, and comparative studies. *Psychoneuroendocrinology* **17**, 3–33 (1992).
79. Holman, S. D. & Goy, R. W. in *Motherhood in Human and Non-Human Primates* (eds Pryce, C. R. & Martin, R. D.) 87–93 (Karger, Basel, 1994).
80. Insel, T. R. Regional changes in brain oxytocin receptor post-partum: Time-course and relationship to maternal behavior. *J. Neuroendocrinol.* **2**, 539–545 (1990).
81. Ferreira, G. *et al.* Learning of olfactory cues is not necessary for early lamb recognition by the mother. *Phys. Behav.* **69**, 405–412 (2000).
82. Kendrick, K. Oxytocin, motherhood, and bonding. *Exp. Physiol.* **85**, S111–S124 (2000).
83. Keverne, E. B., Martensz, N. & Tuite, B. B-endorphin concentrations in CSF of monkeys are influenced by grooming relationships. *Psychoneuroendocrinology* **14**, 155–161 (1989).
84. Bicknell, R. J. & Leng, G. Endogenous opiates regulate oxytocin but not vasopressin secretion from the neurohypophysis. *Nature* **298**, 161–162 (1982).
85. Pedersen, C. A., Caldwell, J. D., Walker, C., Ayers, G. & Mason, G. A. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic area. *Behav. Neurosci.* **108**, 1163–1171 (1994).
86. Giordano, A., Johnson, A. & Rosenblatt, J. Haloperidol-induced disruption of retrieval behavior and reversal with apomorphine in lactating rats. *Physiol. Behav.* **48**, 211–214 (1990).
87. Hansen, S., Harthon, C., Wallin, E., Lofberg, l. & Svensson, K. Mesotelencephalic dopamine system and and reproductive behavior in the female rat: Effects of ventral tegmental 6-OHDA lesions on maternal and sexual responsiveness. *Behav. Neurosci.* **105**, 588–598 (1991).
88. Keer, S. & Stern, J. Dopamine receptor blockade in the nucleus accumbens inhibits maternal retrieval and licking, but enhances nursing behavior in lactating rats. *Physiol. Behav.* **67**, 659–669 (1999).
89. Panksepp, J. *Affective Neuroscience* (Oxford Univ. Press, New York, 1998).
90. Loup, F., Tribollet, E., Dubois-Dauphin, M. & Dreifuss, J. J. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Res.* **555**, 220–232 (1991).
91. Wang, Z. *et al.* Vasopressin in the forebrain of common marmosets (*Callithrix jacchus*): Studies with *in situ* hybridization, immunocytochemistry and receptor autoradiography. *Brain Res.* **768**, 147–156 (1997).
92. Breiter, H. *et al.* Acute effects of cocaine on human brain activity and emotion. *Neuron* **19**, 591–611 (1997).

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OPINION

The genetics of *g* in human and mouse

Robert Plomin

The *g* factor refers to the substantial overlap that exists between individual differences in diverse cognitive processes in humans. In this article, I argue that a mouse model of *g* could provide a powerful analytic tool for exploring cognitive processes that are linked functionally by genes.

Despite its name, analysis of variance — the most widely used statistical tool in biomedical science — is actually an analysis of mean effects in which individual differences are literally called the error term. This error term, the very standard deviation, is the topic of this essay. Instead of treating differences between individuals as error or noise, and averaging individual data across groups as commonly occurs, I believe that the analysis of the individual differences themselves might provide new insight into how the brain works. The analysis of means and variances represent different perspectives. Neither perspective is right or wrong, just more or less useful for a particular purpose. Means lead us into thinking about universal or at least species-wide phenomena, whereas variances lead towards inter-individual differences within species — variations on species themes. Given the importance of individual differences for human cognitive abilities and disabilities it is surprising that textbooks in cognitive neuroscience seldom mention individual differences[1,2].

The very standard deviation

Because the species-universal and the individual-variability perspectives ask different questions they can arrive at different answers. In most species-universal research, the researcher manipulates something — creates lesions, administers drugs or sets specific tasks — and examines the average effect of the manipulation on the study population. By contrast, rather than creating variance through manipulations, the individual-variability perspective focuses on the naturally occurring differences between individuals that would be considered noise in a species-universal approach. Research on individual differences is therefore correlational; it investigates factors that do have an effect in the world outside the laboratory. One of these factors is genetic background. Indeed, although 99.9% of the human DNA is identical for all human beings, the 0.1% that differs — three million base pairs — is ultimately responsible for the ubiquitous genetic influence found for all individual traits, including cognitive abilities and disabilities[3].