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Sexual Behaviour as Adaptation: Relating Brain, Endocrine System and the Social Environment

Sexual Behaviour as Adaptation

The function of sexual behaviour may be thought of as one form of homeostasis, and the behaviour itself as a form of adaptation or response to a perceived or actual deficit. This may seem odd at first sight, since, as Beach once memorably remarked, no-one has yet died for lack of sex. But I want to argue that the neural control of sexual behaviour has all the hallmarks of an adaptive response, though there are some distinctions to be made between this form of behaviour and others, more classically concerned with adaptation. The proposition is that the neural mechanisms for sexual behaviour are closely related to (and, perhaps, have evolved from) those concerned with adaptive responses (ie reactions to defined demands from the physical and/or social environment). The neural systems involved in sexual behaviour thus have many of the features of those concerned with adaptive responses, though there are, of course, important specific differences. But sexuality (as part of reproduction) is a homeostatic mechanism in the sense that it operates (at a distal level) to regulate population numbers and distribution, and at a proximal level to play an important role in social organisation and individual behaviour.

I will develop this argument by, first, setting out what I believe to be the general neural basis of an adaptive response. Then I will try to show that we can analyse such a response in terms of its neural control, and that there are distinct elements of this control. In particular, I will emphasise the distinct roles played by peripheral steroid hormones, by central aminergic systems, and by distributed neural networks that use peptides as their transmitter. I will attempt to show how these systems together enable an animal (including man) to mount an effective and co-ordinated response to a defined homeostatic challenge. Then I will apply these ideas to the neural control of sexual behaviour, to determine how far they apply to this, rather different, behaviour and the biological and social context in which it occurs.

Sexual Behaviour as Information Processing

Before a more detailed presentation of the argument that sexual behaviour is part of an adaptive response, it is important to recognise that much of the debate about

the neuropsychology of sexuality over the past decades has been in quite a different direction. Sexual behaviour is usually studied, in the laboratory, under specific and stringent conditions. Typically, a male of the species being studied (usually a rat) is placed together with a female in an arena, from which neither can escape, and in which there is no access to any other category of stimulus, or (in most cases) any constraint – from other animals, for example – on the interaction between the oppositely-sexed pair. Variations on this scheme include having one animal perform an operant response to obtain access to the other, or imposing some sort of learned (conditioned) response prior to access. The objective of such experiments is to reveal the neuroendocrine processes that underlie the propensity of either the male or the female to engage in sexual behaviour under these conditions (Baum, 1992).

These approaches have, in their own terms, proved highly informative. They have enabled, for example, distinct psychological mechanisms to be distinguished during the process of sexual encounters. These include the classic separation of sexual 'arousal' (the process whereby an animal is sexually engaged by the stimuli emitted by another) from 'consummatory' responses, the stereotyped and species-typical pattern of behaviour that represents successful copulation (Beach, 1942). Subsequent work has been directed towards defining the roles of various neural and endocrine mechanisms in these separable phases of sexual behaviour. For example, the effects of castration and hormone replacement in the male and female have been much studied, as have those of lesions in regional brain areas, such as either the hypothalamus or amygdala. The evidence from such studies has given rise to an information-processing view of sexual behaviour, in which the objective is to define how and why an animal classifies a given set of stimuli as 'sexual' (as opposed to other categories, such as 'edible' or 'attackable'), and how this information is translated into sexual arousal and then sexual performance (review by Herbert, 1996). Experience of interaction under a given set of circumstances will, of course, also have its effect on later behaviour (a kind of social learning) and this, too has been the subject of neurobiological enquiry.

Whilst I will refer to the results of these experiments when they are relevant to the present context, it is important to recognise that, valuable as they are, most of these experiments leave out some significant aspects of sexuality. First, there is little attention to the social context in which sexual behaviour takes place, and which is a major controlling factor in its expression, though studies on captive and free-living primates have emphasised their relevance (eg Herbert, 1981; Dixson, 1998). Secondly, sexual behaviour is often studied in arbitrary isolation from other behaviours, a contrast to the realities of the biological world. This means that the processes that determine why and how an animal prioritises behaviour are often ignored. Finally, although it has been recognised for years that the occurrence and distribution of sexual behaviour (and reproduction) is the cornerstone of successful competition, since this will determine which genes, for example, are promulgated, there is little consideration of the competitive aspect of sexuality in discussions of its neural control. In short, the information-processing view of sexual behaviour, whilst valuable and informative, is limited.

Adaptation and the Hypothalamus

All discussions of the neural basis of adaptive responses naturally begin with the hypothalamus. The hypothalamus, termed the 'head ganglion of the autonomic nervous system' by Sherrington is, in fact, much more than this. The hypothalamus contains two sets of neural structures: those that enable it to detect deviations from some acceptable homeostatic mean, and those that enable the organism to respond to these deviations in such as way as to mitigate them. Thus the hypothalamus has distinct areas that are sensitive to blood levels of sodium and glucose, to blood pressure and to core temperature, amongst others. In each case this information is brought to the hypothalamus either directly, as in the case of sodium or glucose, for which there are hypothalamic sensors, or indirectly, as for blood pressure, for which there are afferent pathways that impinge on the hypothalamus after traversing the brainstem (Schulkin, 1999).

The hypothalamus, either directly or indirectly, monitors the state of the internal environment. In some cases, the peripheral signal is not only a change in the target substance but part of a sequence of events. For example, reduced blood sodium not only activates the hypothalamus by acting directly on it, but also causes the release of peripheral signals (in this case, angiotensin II and/or mineralocorticoids such as aldosterone) that also can activate central neural structures (in the hypothalamus and elsewhere) (Fitzsimons, 1998). The hypothalamus can also sense alterations in levels of peripheral steroids of physiological importance, such as corticoids or testosterone, and adjust pituitary responses accordingly. The essential features of this homeostatic system is that the hypothalamus has access directly to signals that indicate deficit or excess (that is, deviations from acceptable homeostatic limits). It also is responsive to secondary signals, derived from peripheral physiological reactions to primary needs or deficiencies. These signals of deficit thus arrive at the hypothalamus either from the blood, or from afferent neural pathways that provide homeostatic information.

Thus process can be illustrated by a short description of the hypothalamic response to water loss or hypovolaemia, classic deficiency states. Lack of water results in a rise in extracellular osmolality, and consequent intracellular dehydration. (Fitzsimons, 1992, 1998). There is still debate over how this is detected: the classic view is that there exist osmoreceptors in the hypothalamus (probably in the anterior region of the third ventricle), and these signal the deficient state. Thirst can also be stimulated by other mechanisms, including hypovolaemia (which can also be a consequence of persistent shortage of water, or of more acute events such as haemorrhage); this also calls for fluid replacement to correct the deficit.

Hypovolaemia is detected by pressure receptors in the vascular system, and this information is carried to the brain by afferent pathways, but also to the kidney. This enables an endocrine signal: angiotensin II, an octapeptide, is activated in the blood by renin released from the kidney. Angiotensin II acts directly on the brain, probably through circum-ventricular organs (such as the sub-fornical organ) which are permeable to blood-borne peptides. But angiotensin II is also released centrally by hypovolaemic stimuli, and both central and peripheral angiotensin II are powerful dipsogens. Angiotensin also has other effects: for example, it releases vasopressin, and

activates heart-rate and peripheral vasoconstriction; the point here is that a single chemical stimulus, acting in the hypothalamus, is able to set in train a co-ordinated series of behavioural, endocrine and autonomic mechanisms that, together, operate to restore the deficiency state (Herbert, 1993).

The expression of the immediate-early genes such as c-fos, which are activated when neurons are stimulated, reveals a distributed, but localised network of neurons in the brain responsive to angiotensin II; these include the anterior region of the third ventricle (behavioural responses), the paraventricular nucleus (vasopressin and other endocrine actions) the central nucleus of the amygdala and the brain stem areas concerned with autonomic activation (Herbert et al, 1992). These results show that: there are neural systems in the basal forebrain directly sensitive to deficiency states; there are also peripherally-derived endocrine signals, responsive to deficits, and these signals are also detected by receptors in the basal forebrain; there may be common chemical signalling mechanisms in the central and peripheral compartments that, together, activate a sequence of co-ordinated responses that act to reduce, correct or (even) prevent the deficiency state; these are represented by a distributed, but specific, array of neural elements that, it is presumed, are responsible for the observed adaptation to the deficit state. How far is this applicable to the neural control of sexual behaviour?

The Hypothalamus and Sexual Behaviour

There is no doubt that the hypothalamus also plays a central role in sexual behaviour, though the exact nature of that role is still discussed. The traditional experimental approach of lesioning the hypothalamus shows that this procedure disrupts sexual behaviour. Damaging the preoptic area/anterior hypothalamus bilaterally reduces or abolishes copulation in males of many species, including rats, goats and monkeys (Heimer and Larsson, 1966; Hart, 1986; Slimp et al, 1978). Damage rather more posteriorly, in the ventromedial hypothalamus, is more effective in females (the distinction is actually between the pattern of behaviour, rather than the sex of the recipient) (Pfaus, 1995). The hypothalamus also contains receptors for gonadal steroid hormones, and local infusions or implants of these hormones show that they act within the hypothalamus both to facilitate sexual behaviour and to regulate the activity of the anterior pituitary, and hence levels of gonadal hormones (Schulkin, 1999). Both lesions and infusions into the hypothalamus of substances that inhibit sexual behaviour (eg β-endorphin: Hughes et al, 1997; Stavy and Herbert, 1989) strongly suggest that the hypothalamus in the male is concerned with enabling the expression of sexual behaviour: that is, sexual performance or the 'consummatory' phase. This function is comparable to the role of this part of the brain in other behaviours: for example in eating and drinking (Anand and Brobeck, 1951; Stricker, 1983; Fitzsimons, 1998). In each case, the hypothalamus not only acts as a sensor, detecting changes in the levels of critical signals, (eg angiotensin II, leptin, gonadal steroids) but also contains the neural machinery which is essential for organising and expressing an effective, co-ordinated response to this specific demand. The chemical architecture of the hypothalamus, particularly its rich content of peptides, is a fundamental element in this process (Herbert, 1993).

Sexual Behaviour as Adaptation

Sexual behaviour presents both similarities and differences from these housekeeping functions. The similarities lie in the role of the hypothalamus in the control of the gonads, since these play essential parts (in most species) in the occurrence and performance of sexual behaviour. The fact that the hypothalamus can detect and respond to changes in blood levels of gonadal steroids such as testosterone or oestradiol shows that, in a reproductive context, the hypothalamus retains many of the features characteristic of more usual homeostatic mechanisms. These sensors can be quite elaborate: witness the ability of the hypothalamus to detect the pre-ovulatory surge in oestradiol in order to signal the ovulatory discharge of pituitary LH, an ability which depends not only on monitoring changes in levels of steroid, but integrating these changes across time (Levine, 1997). Setting the hypothalamic feedback system is one potent method of determining the levels of peripheral gonadal steroids, and hence the occurrence or otherwise of sexual behaviour.

I suggest therefore that, in the context of sexual behaviour, rising levels of gonadal steroids act in a similar way to 'deficit' signals in other contexts: that is, they signal to the animal that its current state (no sex) is not the optimal one, in the same way as, say, low sodium or high mineralocorticoids signals the present state as insufficient salt (Fitzsimons, 1998). That is, the hypothalamus uses the current levels of gonadal steroids to monitor, and hence determine, the current levels of sexual interest and behaviour, just as an animals interest in water or saline will be altered by the corresponding deficit state, but moderated by blood levels of sodium, aldosterone and angiotensin II etc. Of course, this is not the only function of gonadal steroids, since they also play essential roles in the well-being of peripheral target structures, such as the uterus, seminal vesicles etc., but it is an important one.

The differences between sexual and other adaptive behaviours (such as drinking in response to water deficit or eating in response to lowered blood glucose) – which may be more apparent than real – lie in the nature of sexual behaviour. This, of course, is a complex activity, and relies upon the receipt and analysis of complex social stimuli from other members of the same species. For example, if a male rat is brought into sexual readiness by rising testosterone, he has to recognise a member of the same species, determine that this individual is a female, and that this female is also sexually attractive and receptive.

Information from the Environment: the Role of the Amygdala

The problem, of course, is that the hypothalamus has no access to the sort of sensory information that is needed to make these decisions. Whereas it can detect changes in the chemistry of the blood, it cannot access sensory input directly, though the exact route by which this essential information arrives at the hypothalamus will depend upon its source. For example, visual information (signalling, say the occurrence of lordosis in a female on heat, or the 'darting' runs characteristic of

oestrous) has to be processed by an elaborate array of cortical and subcortical neural structures (in this case, the visual system) before this information can become useful for sexual behaviour (Hart and Leedy, 1985; Pfaff and Modianos, 1985). However, other sensory categories, particularly olfaction (signalling, say, the presence of oestrous-related pheromones from the vagina) may have more direct access, since the anatomical evidence suggests that olfactory information enters the limbic system (eg the medial amygdala) which is somewhat closer, in neural terms, to the hypothalamus than the pathways taken by entering visual information (Price et al., 1987). In the case of the females of some species (eg rats, cats) there is evidence that sensory information from the skin or external genitalia can access the neural circuits subserving sexual behaviour (eg lordosis) directly (including those in the hypothalamus) (Erskine, 1992), a mechanism that seems very comparable to those also known to be concerned with other motivated behaviours such as eating or drinking. Sensory information from the males genitalia may also play an important part in activating or sustaining his sexual behaviour, by similar pathways (Herbert, 1973).

The fact that olfactory information, upon which sexual behaviour is so dependent in rodents and which continues to play a major part even in primates, enters the amygdala, gives us a clue about how the hypothalamus gains access to this, as well as other sources of information about the environment. The amygdala is, anatomically, situated as a sort of interface between the hypothalamus and the stream of complex (visual) or less complex (olfactory) information required to respond to sexual stimuli (Amaral et al, 1992). I will suggest that the amygdala is needed for sexual behaviour precisely because this activity depends so much on the advent of appropriate stimuli from the environment. However, the essential signal of the 'deficit' state (ie the disparity between the current level of sexual behaviour and some optimal one) is not a primary function of the environment, but of the internal state signalled by the gonadal steroids. Such a separation may be thought to be too simple, but it seems reasonable as an explanation of the first step in determining current levels of sexual behaviour. However, we should remember that the amygdala also contains receptors for steroid reproductive hormones (as do other regions of the CNS, such as the septum and spinal cord), so their function is certainly not limited to activating the hypothalamus. We may suspect that they could influence the way that certain categories of information (eg 'sexual' stimuli) are processed by the amygdala or passed on to the hypothalamus, though the essential puzzle of what determines that a set of stimuli is labelled 'sexual' remains.

It is striking that lesions of the corticomedial amygdala, to which olfactory input is directed, interfere with sexual behaviour in the male rat (McGregor and Herbert, 1992) – specifically by prolonging the precopulatory investigation that characterises the male rats initial phase of sexual behaviour, whereas lesions of the basolateral amygdala (which receive input from the temporal association cortex, and hence complex, highly processed (mainly visual) stimuli) do not. However, as might be expected, basolateral lesions disrupt responding to visual stimuli which have been previously associated (by conditioning) with sexual reward (Everitt et al, 1989).

The Environment and Adaptive Behaviour: some General Features

Although I have stressed the difference between this behaviour and other, more classically adaptive ones, in fact other adaptive behaviours may share several of the features of sexual behaviour. For example, if an animal is made thirsty (by an internal signal representing water deficit) then it has to find a source of water. This may require as much neural processing about the features of the external environment (eg to locate or remember that source) as is needed to identify the source and nature of a potential sexual partner. It is not coincidental, therefore, that the amygdala has been implicated in drinking and eating behaviour (Nitabach et al, 1989). If one reviews the mass of literature on the amygdala, however, it is apparent that much of its relates to the function of this part of the brain in the generation of fear or anxiety responses to environmentally significant signals: ie those predicting imminent danger or adversity (Davis, 1992; LeDoux, 1998). There are those who consider this to be the main, or even the only, function of the amygdala, and that understanding its role in either conditioned or unconditioned fear will unravel its essential function (Maren and Fanselow, 1996). I want to demur from this view: although there is no doubt that the amygdala is closely concerned with the evaluation and response to danger (by which I mean either innate or learned features of the external world that signal threat), this is not its only function. There is also a large (if lesser) literature that shows that manipulations of the amygdala (eg lesions) that can alter fear can also interfere with other categories of response, for example eating or sexuality (Aggleton, 1992), though it is always possible to argue that individual subsections of the amygdala are more closely concerned with one category of behaviour than another. However, I believe that the problem for us is to understand how the amygdala can differentiate sexual from other forms of stimuli (if that, in fact, is what this part of the brain does) and hence ensure that the hypothalamus receives the correct category of information (Kostarczyk, 1986). Or does the amygdala simply carry the elements of some feature such as 'potential reward' or 'potential danger' leaving the hypothalamus (or some other part of the brain) to determine the motivational category?

Evaluating the Social Context and its Implications

But it would be too simple to suggest that there are only two neural components to sexual behaviour: one, based on the hypothalamus, that determines the basic 'deficit' (or 'motivational') state, and a second one, based on the amygdala, that allows the critical features of the environment to be brought into association with the hypothalamic effector mechanism. Sexual behaviour, in all species, takes place within a defined social context. The processes of mate selection, sexual competition and defence of mates, is central to the social structure of many species for much of the time. The fact that this is so costly and risky a business is emphasised by the fact that most species limit the time of the year that they can afford to devote to sexual behaviour and subsequent reproduction; some for only a few weeks, others for much longer. One aspect of human behaviour is that man is liberated from such environmental shackles,

presumably because the benefit of persistent sexual behaviour (and attraction) outweighs the costs, an idea proposed many years ago as an overall explanation of the persistence of human social groups (Zuckerman, 1932), though one that has not stood up too well to subsequent criticism.

However, it remains true that we cannot put forward an overall view of the neural basis of sexual behaviour without taking into account the powerful social forces that shape its expression and control its direction. This is likely to include the activity of those parts of the brain (eg the frontal lobes in man) that are concerned with some of the most complex social behaviours. It is thus satisfying to note that there are profuse anatomical connections between parts of the (orbital and medial) frontal lobes and the amygdala, just as there are between the amygdala and the hypothalamus (Turner and Zimmer, 1984; Amaral et al, 1992).

The Concept of the Limbic System

Both anatomical evidence (that is, the direction and profusion of connections) as well as the results of experimental manipulations (for example, the effects of local lesions or stimulation) suggest that sexual behaviour is represented in the brain by a number of related structures. These structures, including the hypothalamus, amygdala, septum, parts of the brainstem, orbital frontal cortex and hippocampus (there is, in fact, rather little evidence relating the latter to sexual behaviour), constitute the limbic system, as defined by a variety of authors, beginning with Broca (1878), and extending through Papez (1937), MacLean (1990), and many others. The concept of the limbic system has been questioned, mainly on the grounds that its function is ill-defined, or that 'emotion' (sometimes mistakenly taken to be its principal concern) is not credible as a defining function. There are certainly precedents for revising anatomical divisions of the brain; for example, the concept of the reticular formation has been progressively refined as more knowledge about this area becomes available. However, in the case of the limbic system, the reverse is actually the case: as neurobiology has become more interested in functions of the brain that have to do with such aspects as survival, adaptation and homeostasis, it has become apparent that there must be a neural substrate for these functions, and that the limbic system is that substrate (Nieuwenhuys, 1996). This is saying no more than that certain parts of the brain specialise in certain components of overall neural function: for example, the visual system is incontrovertibly the area that deals specially with incoming visual information. However, it is also clear that there are no distinct boundaries separating the visual system from the rest of the brain; nor should there be, since the brain works as a whole.

So it is with the limbic system: the functions that it subserves are so important that it is inevitable that its activity will influence (and be influenced) by large areas of the rest of the brain. This does not argue against our recognition of this system; we are not tempted to abandon the concept of a visual system because visual information flows into the parietal and temporal lobes from the primary visual cortex and merges with other categories of input and other processes. The motor system remains a valid

concept, even though other systems (eg the sensory cortex) contribute to it, and some of its components (eg the striatum) also have functions that extend beyond what is usually regarded as 'motor'. However, if we postulate that the limbic system has special relevance for sexual behaviour we also have to answer two consequent questions: what is the function of the various anatomical regions of the limbic system in sexuality, and how does the limbic system define and separate sexual responses from all the other adaptive events that also concern it? In part, the first question has been addressed by considering the relative roles of the hypothalamus, amygdala, frontal lobes and brainstem in sexual behaviour; the second remains a quandary, though its solution is an essential ingredient of any full understanding of the brain's role in sexual behaviour.

Though the recent debate over the limbic system has been over whether such a concept is still valuable, there has been a more venerable discussion over the boundaries and definition of this system. Papez (1937), of course, famously excluded the amygdala; others have included the amygdala and septal area but not the hypothalamus (Swanson, 1987), though most would regard the hypothalamus as a central feature of any coherent definition of a limbic system (eg Nieuwenhuys, 1996). Other areas of the basal brain are also debated: some would include only forebrain areas, others certain parts of the brainstem (Nieuwenhuys, 1996). Which parts of the cortex to include is also uncertain (Kotter and Meyer, 1992) The hippocampus is generally accepted as a 'limbic' structure, but there is more uncertainly over whether the cingulate gyrus, or the orbital frontal lobe, or both should also be classified a 'limbic' cortex. In fact, one can spend too long worrying over neural boundaries: from what has been said above, it is clear that similar debates, equally fruitless, could be waged over other systems in the brain, even those more securely recognised, such as the motor or sensory systems. The basic argument is whether, if the division of the brain into 'systems' is justified or useful (and I suggest that it is both) then this applies equally to the limbic system as to any other. The anatomical evidence is compelling; the functional evidence is powerful, and the biological need for a neural system to carry out the functions that can only be ascribed to the limbic system (eg adaptation and survival) dictate that a competent brain must have such an assembly. But to attempt to draw precise boundaries round the limbic system is as fruitless as in any other case, and does not invalidate the argument for its existence.

Social Modulation of Sexual Behaviour

I am going to suggest that this anatomical (or 'modular') view of the limbic system (and other, associated parts of the brain) is not an adequate one for us to attempt to answer these essential questions. But before I proceed, let us summarise and extend the evidence we have so far. Sexuality is, in many mammalian species, tightly controlled by steroid hormones, which, if the view put forward here is correct, act as a kind of internal deficit signal. This, like any other deficit, results in changes in the animals behaviour that is directed towards attempts to remedy the deficit, in this case an absence of a sexual partner. However, the means by which this deficit is remedied

also depends heavily on other factors: those within the individual (eg its previous experience, its exposure to steroid hormones during critical stages in its development, perhaps the polymorphic nature of certain critical genes) and its social environment. The latter offers both the means of remedy but also acts as a major controlling element.

One can see this in operation in the social organisation of many species, including primates (Dixson, 1998). The social order (eg the dominance hierarchy) controls access to potential mates just as it does to any other category of desirable and competitive resources. Subordinate male monkeys, for example, seldom mate and show reduced levels of testosterone compared to their more dominant conspecifics (Dixson and Herbert, 1977; Abbott and Hearn, 1978). However, simply injecting them with testosterone, whilst it raises their levels to those of the more dominant males, does not restore their sexual behaviour. Social control has unhitched sexual behaviour from its normal major steroid- control system. Adding to this individual factors, such as personal preferences or specific learning experiences, gives one some idea of the true complexity of sexual behaviour, and the need to invoke correspondingly elaborate neural systems for its control.

An added fact, already referred to, is that sexual behaviour does not occur in isolation in the real world: it is part of behavioural stream that affects the lives on every member of a social group, and the individual has to make choices. For example, how to balance sexuality against eating, drinking, avoiding being eaten, or attack from competitors (or even potential mates); in other words, there has to be prioritisation, since no animal can engage in more than one behaviour at a time. It can now be seen that the point made about the limitations of the information-processing model of sexual behaviour is a real one: studying sexual behaviour by, for example, pairing rats together in an otherwise empty cage may be convenient, replicable and informative, but it underestimates the complexity of sexuality in the real world, and thus the neural machinery required for successful sex.

Implications for a 'Sexual' Brain

The basic point is that sexuality is much too complicated and variable to be controlled by a single chemical signal (gonadal steroids) or a simple neural 'circuit' (eg the hypothalamus-amygdala-frontal connection). Furthermore, as we have already seen, many of the structures implicated in sexual behaviour are also clearly involved in other categories of behaviour. For example, the anterior hypothalamus, long known to be associated with sexual performance, is also implicated in maternal behaviour, in thermoregulation, and in water and salt balance (review by Schulkin, 1999). The amygdala has well-established functions in the generation of fear responses (Davis, 1992) but also in sexual and ingestive behaviour (see above). Whilst it is always possible to try and subdivide each of these structures anatomically, and to propose that individual (and separable) groups of neurons are concerned with each category of behaviour, this is an unsatisfactory approach. Theoretically it leads nowhere: failure to demonstrate behavioural separation at an anatomical level

can always be blamed on technical problems, so that it can never be clear whether such failure represents refutation of the hypothesis, or is a consequence of, say, the lesion size being to large, or its position insufficiently accurate.

The use of the c-fos technique, which relies upon detecting the increased expression of this immediate-early gene as a marker of neuronal activity, has shown that there is distributed activity in the limbic system associated with responses to defined demands. For example, hypovolaemia induces a typical pattern of c-fos expression in the basal forebrain and related brainstem structures (Ueta et al, 1995; McKinley et al, 1994). These include such areas in the basal forebrain as the median preoptic nucleus, the paraventricular nucleus, the subfornical organ, and the supraoptic nucleus; and the regions such as the area postrema, locus ceruleus and ventrolateral medulla in the brainstem. Sexual behaviour hand also induces a distributed pattern of c-fos expression in the limbic system and related regions; but one which is distinct from that of other demands, such as water deprivation (Baum and Everitt, 1992; Dudley et al, 1992; Pfaus et al, 1993; Rowe and Erskine, 1993). Sexual behaviour evokes c-fos in regions such as the medial preoptic area (lateral to that activated by water deprivation), corticomedial amygdala (and the associated BNST) and in part of the upper brainstem. The c-fos technique has also been used very effectively to map the cellular response of different brain areas to various phases of sexual behaviour. In this way, correlative conclusions can be drawn about the contribution that various parts of the brain make to sexual interaction (Heeb and Yahr, 1996). These findings allow two conclusions: there is distributed activity within the limbic system in response to specific demands; these patterns vary with the nature of these demands, and may therefore reflect the organisation of the co-ordinated response to them.

Chemical Architecture of the Limbic System

The conventional organisation of the limbic system, such as that presented above, is a modular one. That is, the system is conceived as being made up of several anatomically recognisable and separable components (modules) for example, the hypothalamus, septum, amygdala etc. Each module would be expected to make a distinct contribution to the overall function of the limbic system – that is, be responsible for a definable sub-set of its activity. For example, in a behavioural context one might look for motivational roles for the hypothalamus, and emotional ones for the amygdala. Within each module there may be further anatomically based functional sub-divisions; for example, within the hypothalamus there are recognisable divisions, such as the preoptic area, or the paraventricular, suprachiasmatic and arcuate nuclei. Each of these structures might have a separable role – for example, one might be concerned with eating, another with sexual behaviour, a third with endocrine control etc. Within each nucleus there may be further subdivisions: for example, the paraventricular nucleus is divided into a number of sub-nuclei (Kiss et al, 1991), each of which might react in a distinct way to different demands and so on. The assumption is that an anatomically-defined area will have a correspondingly discrete role. This is the modular view of the brain.

There is an alternative, orthogonal but not conflicting view of the limbic system as a neurochemical structure. In this view, sub-sets of the limbic system are recognised not by conventional anatomy, but by their neurochemical make-up. Neuronal systems can now be characterised both by their topography and by their neurochemical content, particularly aminoacids, amines, peptides and steroid receptors. The chemical architecture of the limbic system, that part of the brain most closely linked with the expression of sexual behaviour, may be fundamentally different from other parts of the brain – in particular, those systems concerned with cognition in which the neocortex forms an essential and dominant component (though we should recall the arguments presented above against too rigid a definition of the 'system' concept).

Glutamate and GABA are produced widely in the CNS, and their synaptic actions suggest that the mechanisms whereby they act on the post-synaptic membrane are general properties of the brain. The specific role of such neurons resides in their anatomical connections and location, and their function within such a region of the brain is effected by their use of 'fast' transmitters such as glutamate or GABA. These transmitters are not those responsible for the chemical architecture of the limbic system. It is the high concentrations of steroid receptors (particularly those to gonadal steroids), the profusion of peptide-containing neurons, and the rich innervation by monoaminergic terminals that form the bases for its neurochemical organisation (Everitt et al, 1983; Price et al, 1987).

The output of the limbic system seems to be determined by these chemical signals, rather than by the activity of networks typical of neocortical systems. I suggest that the basic control of sexuality resides in the interplay between these three classes of neurochemicals, though individually they play very distinct roles. As we have seen, reproduction is only one category of those activities that are essential for survival, and sexuality can be considered as part of the general context of adaptive processes. One function of the limbic system, therefore, is to match the current response with the current demand or need (sexual or otherwise), and this depends upon the operation of chemical 'codes' within the limbic system. These codes are partly represented by the numerous peptides within it, operating together with steroid hormones but modulated by distributed networks of monoamines. I will argue that a further feature of this coding is that its precise behavioural effect depends not only upon the nature of the chemical message but also upon the anatomical region of the limbic system in which it acts. This reconciles the modular (anatomical) arrangement of the limbic system with its chemical structure.

Peptides and Adaptive Behaviour

Peptides are particularly interesting because they seem to be able to induce rather specific patterns of response. For example, we have already seen that angiotensin II infusions result in one that resembles that observed in response to hypovolaemia. Neuropeptide Y results in responses resembling those following food deprivation (or hypoglycaemia), whereas CRF induces a pattern that resembles the response to

anxiogenic or fear-inducing stimuli (Epstein et al. 1970; Clark et al., 1984; Thatcher-Britton et al, 1986). Interestingly, infusion of the same peptides induces patterns of neuronal c-fos that closely resemble those following the corresponding deficit or demand-state (Herbert et al., 1993; Arnold et al, 1992; Lambert et al, 1995).

It might be expected, therefore, that there would be a corresponding peptide (or peptides) that might 'code' for sexuality. A logical starting place would be LHRH (GnRH), since this peptide activates the anterior pituitary to secrete gonadotrophins and, hence, gonadal steroids. By analogy with other peptides, this might be only one part of a co-ordinated pattern of response: in this case, sexual. Early results seemed to support this idea: intraventicular infusions of LHRH promoted receptivity in oestrogen-treated female rats (Pfaff, 1973; Moss and McCann, 1973), and infusions into the ventral tegmental area (VTA) were also effective (Sirinathsinghji et al, 1986). LHRH also enhanced proceptivity in the marmoset, an index of increased sexual motivation (Kendrick and Dixson,1985). However, it has to be said that subsequent work has not, so far, established a major or convincing role for central LHRH in sexual behaviour.

A number of other peptides have been implicated in sexual behaviour, perhaps not surprisingly for an activity which is so varied, has so many components, and is regulated in many different contexts. There is now considerable evidence that central oxytocin may be important for the initiation of maternal behaviour, a role correlated with its peripheral action on lactation (Pedersen et al, 1982; Kendrick et al, 1987). Recent findings, which are still provisional, point to a role of oxytocin in the sexual behaviour of both sexes. Oestrogen administration alone results in rather low levels of sexual receptivity in ovariectomised rats. However, icv oxytocin added to oestrogen promotes receptivity (Caldwell et al, 1984). Infusions of oxytocin into the MPOA and rostral VMH were highly effective compared to those into either the mesencephalic grey or the midbrain ventral tegmental area (VTA). Following mounting activity, oxytocin-containing perikarya increased in the female's MPOA, an effect presumably related to cervico-vaginal stimulation. In males, for whom oxytocin has had no discernible role, the evidence is less impressive, though there are reports of accelerated ejaculation times following icv oxytocin administration (Hughes et al, 1987b).

A rather different role for oxytocin in sexuality is suggested by Insel and colleagues (Carter et al, 1992; Insel, 1990). These authors propose that oxytocin release promotes social bonding. They support this by showing differences in oxytocin receptor binding in two species of vole. One, the prairie vole, forms monogamous intersexual pairs, actively repels other same-sexed compatriots, and displays high levels of parental behaviour. Higher levels of oxytocin binding were observed in a number of brain sites (including the BNST, basolateral amygdala, and midline thalamus) than in another species, the montane vole, which is polygamous and shows less parental behaviour. Infusions of oxytocin were found to increase pair bonding (Insel and Shapiro, 1992). These findings reinforce the idea that peptides may have multiple roles in sexuality.

A general feature of the peptidergic control of a response is there are inhibitory as well as stimulant peptides. To suppress a behaviour (and associated response) may be as biologically important as inducing it. For example, feeding is reduced by CCK (and

other peptides, such as leptin and MSH); drinking may be suppressed by atrial natriuretic peptide (ANP); fear may be reduced by NPY (review by Herbert, 1993). Sexual behaviour is also reduced by peptides, though the problem is always to determine whether this is a specific action (ie the peptide is exerting a direct control over this behaviour) or whether the effect is indirect (eg either competing behaviours are accentuated, or the animal is so overcome with fear, or aversive states such as 'feeling ill', that sexuality is reduced as a secondary consequence).

Prolactin is the most prominent peripheral peptide that reduces sexual behaviour, in both experimental animals and humans (Bailey and Herbert, 1982; Carini et al., 1996). High levels of prolactin are typically observed in the female during lactation, and in both sexes stress may induce prolactin release. Prolactin from the blood passes into the brain through a carrier-mediated process (as for insulin, leptin and some other peptides) (Martensz and Herbert, 1982; Dubey et al. 1983).

Centrally, β-endorphin, a member of the pro-opiomelanocortin (POMC) family of peptides, suppresses sexual behaviour. Bilateral infusions of minute amounts of β-endorphin into the POA of intact male rats have powerful inhibitory effects on copulation (Hughes et al, 1987). Such males rarely mount females, and almost never ejaculate, but they continue to pursue and investigate the female. Rats trained to bar-press for access to females also show unimpaired enthusiasm for this operant task after POA infusions of β-endorphin, though they fail to copulate once the females arrive (Hughes et al, 1990). There seems to be a separation of 'appetitive' from 'consummatory' behaviour after β-endorphin infusions into the hypothalamus. Infusions into the amygdala, however, gave different results. In contrast to the consequences of hypothalamic infusions, it was the precopulatory phase of the male's behaviour that was disturbed (McGregor and Herbert, 1992b,c). Infused males investigated oestrous females much less than controls, but when they finally copulated this part of the behaviour was no different from controls.

The simple conclusion that β-endorphin produced lesion-like effects in these areas is not, however, the full story. When the infusion into the hypothalamus was delayed until after the male had made a mount (that is, when the 'consummatory' phase had begun) there was no longer any effect: the males continued as if nothing had happened to them. However, if the female was changed for another, the original deficit was reinstated: the males behaviour was once again limited to prolonged investigation, but they failed to mount (Stavy and Herbert, 1989). This result suggests a more complex role either for β-endorphin or the hypothalamus. It seemed as if the male had to match precopulatory information with copulatory activity, and that β-endorphin could disturb this process. An unanswered question remains: is this the function of the preoptic hypothalamic area in sexuality, or is β-endorphin selectively interfering with only part of the POA's role in sexuality?

It remains unclear whether there is a part of the brain that is concerned with the actual expression of stereotyped sequences of behaviour, such as the sexual performance of the male rat. A plausible candidate for such a function might be the ventral striatum. Anatomical evidence suggests that the flow of information from the limbic system passes into this area, and a profusion of clinical and experimental data shows the importance of the striatum in the initiation and control of motor

patterns (including sexual behaviour) (Graybiel, 1990; Cador et al, 1989)). However, if this is the case, either the ventral striatum has some special mechanism for producing stereotyped behaviour patterns (including sexual behaviour) or (and this seems intrinsically more likely) the particular pattern is composed elsewhere, and the ventral striatum 'instructed' accordingly. It is still possible that the hypothalamus is responsible for this instructional role, and β-endorphin interferes with this role.

Similar results were obtained after amygdaloid infusions. When infused males who had successfully begun to copulate with one female were presented with another, they showed a second bout of prolonged investigation before beginning to mount the new female. These results show that amygdaloid infusions of β-endorphin also disturb sexual behaviour, but have a behavioural action quite distinct from similar infusions into the hypothalamus. Furthermore, the nature of these effects correlates well with what we believe may be the overall function of the amygdala (and, to a degree) the hypothalamus. They illustrate some general principles. The first is that peptides have co-ordinated effects on behaviour and upon associated endocrine and autonomic responses. The second is that a peptide's precise effect depends not only upon its chemical structure but also upon the region of the brain in which it acts; many peptides have distributed sites of action, but these can be co-ordinated to produce a biologically relevant set of responses. The contexts in which β-endorphin may influence sexual behaviour are not really well-defined, though stress increases POMC expression. However, it should be noted that POMC peptides are also implicated in food intake (Krude et al, 1998; Fan et al., 1997), so its role in sexuality may be part of a wider function.

Monoamines and Sexual Behaviour

There are marked differences between the aminergic and peptidergic systems, and these have to be clearly recognised if we are to assess their relative contributions to the adaptive role of sexual behaviour. Peptidergic neurons are scattered throughout the brain, sometimes in localised groups (topography varies considerably for different peptides), though the limbic system has the richest content. Many peptidergic neuronal groups interconnect with each other. Aminergic neurons, by contrast, are largely localised to the brainstem (midbrain and hindbrain), from which a rich distributed network of aminergic fibres courses to large areas of the brain. Though aminergic terminals are found throughout the brain, they are not distributed either randomly or equally. For example, it is well established that certain areas (eg the striatum) are rich in DA but poor in NA, whereas the neocortical networks of 5HT and NA are, to some extent, complementary. The same is true of parts of the limbic system; in the hypothalamus, for example, the suprachiasmatic nucleus has a rich 5HT supply, whereas the paraventricular nucleus is distinguished by its NA innervation. The neurochemistry of the peptides and amines is also distinct; amines are relatively simple molecules, and there are rather few of them. Peptides are complex molecules, formed from 2-50 or more aminoacids, and changes in sequence in specific areas of

the peptide can have dramatic effects on function. There are dozens (if not more) peptides in the brain, many with neurotransmitter activity.

The topography of the aminergic systems suggests they might have generalised functions in the brain, and so it has proved. Those working on sexual interaction have been impressed with the marked effects that manipulating the amines has on this behaviour. Blockade of dopamine (DA) impairs sexual behaviour (Malmas, 1973). The precise effect this has depends upon the site of action: DA in the ventral striatum is concerned with precopulatory ('appetitive') behaviour, whereas that in the dorsal striatum affect copulation itself (Pfaus and Phillips, 1989; Everitt, 1990). These results are also obtained if one examines other behaviours, and they tell us two things: first, that DA has an important, but pervasive, role in behaviour; second, that it is important to distinguish the role of DA from that of the region to which it projects. For example, it is likely that the ventral striatum is an area concerned with initiating rewarded motor activity, and the role of DA in this area is to enable this to occur. It is highly unlikely that DA has a specific role in sexual behaviour; this is not to say that it is not important, but that its role has to be assessed alongside other behaviours, and in the context of the overall pattern of neural activity that changes in the DA system might be expected to engender.

Reducing 5HT, by contrast, generally increases sexual behaviour; that is, either heightens its level or increases its likelihood in situations in which it may occur (Gessa and Tagliamonte, 1975). Post-synaptic receptor 5HT antagonists have similar effects, though 5HT 1A receptor agonists may also increase behaviour, probably because they reduce the activity of the intrinsic serotoninergic system (by activating autoreceptors) (Hillegart et al., 1991). Again, it is important to note that many other behaviours show similar alterations in response to manipulations of the 5HT system. This is entirely consistent with the widespread distribution of 5Ht terminals, and the non-specific conditions under which 5HT neuronal groups in the raphe are stimulated.

Noradrenaline (NA) also has pervasive effects on sexual behaviour (Clark et al., 1985), and yohimbine (an $\alpha 2$ adrenergic antagonist) has a clinical reputation a sexual stimulant. The same general features apply to NA as to 5HT and DA: the effects on manipulations are pervasive, and effect many behaviours and other functions); it is important to distinguish pre- from post-synaptic effects; and it is critical to separate the 'function' of NA from that of the region under study. Finally, it is necessary to point out that these three systems interact, so that studying them separately (as it is commonly done) may give an incomplete picture of their real function and complexity.

In the context of sexual behaviour as an adaptive process, the aminergic systems take on a new significance. NA, like 5HT and DA, is activated under many conditions, particularly those associated with 'stress'. Stress, by which is meant the occurrence of unusual demand (with, in most cases, reduced control over the source of that demand) has marked effects on sexual behaviour (Herbert, 1996). Many animals, and even humans, spend much of their life coping with stress to varying degrees of success. There are biological, as well as psychological, reasons why high stress should be inimical to successful sexual behaviour and optimum reproduction; and the interaction between the aminergic and peptidergic systems may provide us with a neurobiological explanation for this observation.

Though it is necessary, in discussions such as this, to separate steroids, amines and peptides on the one hand, and accounts of the different parts of the limbic system on the other, of course there are intricate interactions between them. For example; peptides and amines may co-exist within the same terminals; steroids can induce the expression of peptides in the brain; steroids also change levels of aminergic receptors. Changes in the amygdala will affect the way the hypothalamus responds to internal signals, as well as influencing the processing of external information in the cortex. To understand the functional significance of these interactions fully is not possible at present; but placing sexual behaviour in its biological context is one step towards a theoretical framework for advance in this area.

References

Abbott D.H., Hearn J.P. (1978). Physical, hormonal and behavioural aspects of sexual development in the marmoset monkey. *J. Reprod. Fert. 53*, 155-164.

Aggleton J.P. (Ed.) (1992). *The amygdala*. New York: Wiley-Liss.

Amaral D.G., Price J.L., Pitkanen A., Carmichael S.T. (1992). Anatomical organisation of the primate amygdaloid complex. In: J.P. Aggleton (Ed.), *The amygdala* (pp1-66) New York: Wiley-Liss.

Anand B.K. and Brobeck J.R. (1951). Hypothalamic control of food intake in rats and cats. Yale *J Biol. Med. 24*, 124-140.

Arnold F.J.L., de Lucas Bueno M., Shiers H., Hancock D.C., Evan G.I., Herbert, J. (1992). Expression of *c-fos* in regions of the basal limbic forebrain following intra-cerebroventricular corticotropin-releasing factor (CRF) in unstressed or stressed male rats. *Neuroscience 51*, 377- 390.

Bailey D.J., Herbert J. (1982). Impaired copulatory behavior of male rats with hyperprolactinaemia induced by domperidone or pituitary grafts. *Neuroendocrinology 35*, 186-193.

Baum M.J. (1992). Neuroendocrinology of sexual behavior in the male. In: Becker J.B., Breedlove S.M., Crews D. (Eds.) *Behavioral endocrinology* MIT Press.

Baum M.J. and Everitt B.J. (1992). Increased expression of c-fos in the medial preoptic area after mating in male rats – role of afferent inputs from the medial amygdala and midbrain central tegmental field. *Neuroscience 50*, 627-646.

Beach, F.A. (1942). Analysis of factors involved in the arousal, maintenance and manifestation of sexual excitement in the rat. *Psychosom. Med. 4*, 173-198.

Broca P. (1878). Anatomie comparee des circonvolutions cerebrales: le grand lobe limbique et la scissure limbique dans la serie des mammiferes. *Rev. Anthropol. 1*, 385-498.

Cador M., Robbins T.W., Everitt B.J. (1989). Involvement of the amygdala in stimulus-reward associations: interactions with the ventral striatum. *Neuroscience 30*, 77-86.

Caldwell, Pedersen C.A., Prange A.J. (1984). Oxytocin facilitates the sexual receptivity of estrogen-treated female rats. *Neuropeptides 7*, 175-189.

Carani C., Granata A.R., Fustini M.F., Marrama P. (1996). Prolactin and testosterone: their role in male sexual function. *Int J Androl. 19*, 48-54.

Carter S.C., Williams J.R., Witt D.M., Insel T.R. (1992). *Oxytocin and social bonding*. New York, Academy of Science 652, 204-211.

Clark J.T., Kalra P.S., Crowley W.R., Kalra S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulates feeding in rats. *Endocrinology 115*, 427-429.

Clark J.T., Smith E.R. and Davidson J.M. (1985). Evidence for the modulation of sexual behavior by alpha adrenoreceptors in male rats. *Neuroendocrinology 41*, 36-43.

Davis M. (1992). The role of the amygdala in conditioned fear. In: Aggleton J.P. (Ed.), *The amygdala. Neurobiological aspects of emotion, memory, and mental dysfunction* (pp 255-306). New York: Wiley-Liss.

Dixson A.F., Herbert J. (1977). Gonadal hormones and sexual behaviour in groups of adult talapoin monkeys (*Miopithecus talapoin*), *Hormones and Behavior 8*, 141-154.

Dixson A.F. (1998). *Primate sexuality*. Oxford University Press.

Dubey A.K., Herbert J., Martensz N.D., Beckford U., Jones M.T. (1983). Differential penetration of three pituitary peptide hormones into the cerebrospinal fluid of rhesus monkey. *Life Sci. 32*, 1857-1863.

Dudley C.A., Rejendren G., Moss R.L. (1992). Induction of c-fos immunoreactivity in central accessory olfactory structures of the female rat following exposure to conspecific males. *Molecular and Cellular Neuroscience 3*, 360-369.
Epstein A.N., Fitzsimons J.T., Rolls B.J. (1970). Drinking induced by injection of angiotensin into the brain of the rat. *J Physiol. 210*, 457-474
Erskine M.S. (1992). Pelvic and pudendal nerves influence the display of paced mating behavior in response to estrogen and progesterone in the female rat. *Behav. Neurosci. 106*, 690-697.
Everitt B.J., Herbert J., Keverne E.B. (1983). The neuroendocrine anatomy of the limbic system: a discussion with special reference to steroid responsive neurons, neuropeptides and monoaminergic systems. *Progress in Anatomy 3*, 235-260.
Everitt B.J., Cador M., Robbins T.W. (1989). Interactions between amygdala and ventral striatum in stimulus-reward associations: studies using second-order schedule of sexual reinforcement. *Neuroscience 30*, 63-75.
Everitt B.J. (1990). Sexual motivation: a neural and behavioural analysis of the mechanisms underlying masculine sexual behaviour. *Neurosci. Biobehav. Rev. 14*, 217-232.
Fan W., Boston B.A., Kesteron R.A., Hruby V.J,. Cone R.D. (1997). Role of melanocortinergic neurons in feeding and agouti obesity syndrome. *Nature 385*, 165-168
Fitzsimons, J.T. (1992). Physiology and pathophysiology of thirst and sodium appetite. In: D.W. Seldin, G. Giebisch. (Eds.), *The kidney: physiology and pathophysiology* (pp 1615-1648). New York: Raven Press.
Fitzsimons, J.T. (1998). Angiotensin, thirst, and sodium appetite. *Physiol Rev. 78*, 583-686.
Gessa G.L., Tagliamonte A. (1975). Role of brain serotonin and dopamine in male sexual behavior. In: *Sexual behavior: pharmacology and biochemistry* (pp 117-128). New York: Raven Press.
Graybiel A.M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. *Trends in Neuroscience 13*, 244-254.
Hart B.L. and Leedy M.G. (1985). Neurological analysis of male sexual behavior: a comparative analysis. In: Adler N, Pfaff D, Goy RW (Eds.), *Handbook of behavioral neurobiology*, vol 7, Reproduction (pp 373-422). New York: Plenum.
Hart B.L. (1986). medial preoptic-anterior hypothamlamic area and socio-sexual behaviour of male goats. *Physiol. Behav. 36*, 301-305.
Heeb M.M. and Yahr P. (1996). C-*fos immunoreactivity in the sexually dimorphic area of the hypothalamus and related brain* regions of male gerbils after exposure to sex-related stimuli or performance of specific sexual behaviors. *Neuroscience 72*, 1049-1071.
Heimer L., Larsson K. (1966). Impairment of mating behaviour in male rats following lesions in the preoptic-anterior hypothalamic continuum. *Brain Res. 3*, 248-263.
Herbert J. (1973). The role of the dorsal nerves of the penis in the sexual behaviour of the male rhesus monkey. *Physiol. Behav 10*, 293-300.
Herbert J. (1981). Hormones and the sexual strategies of primates. *Symp. Zool. Soc. Lond. 46*, 337-359.
Herbert J., Forsling M.L., Howes S., Stacey P.M., and Shiers H.M. (1992). Regional expression of *c-fos* antigen in the basal forebrain following intraventricular infusions of angiotensin and its modulation by drinking either water or saline. *Neuroscience 51*, 867-882.
Herbert, J. (1993). Peptides in the limbic system: chemical codes co-ordinating adaptive responses to behavioural or physiological demand. *Progress Neurobiol. 41*, 723-791.
Herbert J. (1996). Sexuality, stress, and the chemical architecture of the brain. *Ann. Rev. Sex Research 7*, 1-43.
Hillegart V., Ahlenius S., Larsson K. (1991). Region selective inhibition of male rat sexual behaviour and motor performance by localised forebrain 5HT injections; a comparison with effects produced by 8-OH-DPAT. *Behav. Brain Res. 42*, 169-180.
Hughes A.M., Everitt B.J. and Herbert J. (1987). Selective effects of β-endorphin infused into the hypothalamus, preoptic area and bed nucleus of the stria terminalis on the sexual and ingestive behaviour of male rats. *Neuroscience 23*, 1063-1073.
Hughes A.M., Everitt B.J., Lightman S.L., Todd K.T. (1987b). Oxytocin in the central nervous system and sexual behaviour in male rats. *Brain Research 414*, 133-137.
Hughes A.M., Everitt B.J. and Herbert J. (1990). Comparative effects of preoptic area infusions of opioid peptides, lesions and castration on sexual behaviour in male rats: studies of instrumental behaviour, conditioned place preference and partner preference. *Psychopharmacology 102*, 243-256.
Insel T.R. (1990). Regional changes in brain oxytocin receptors post-partum: time course and relationship to maternal behavior. *Journal of Neuroendocrinology 2*, 1-7.
Insel T.R. and Shapiro L.E. (1992). Oxytocin receptors and maternal behavior. *Annals of the New York Academy of Sciences 652*, 122-141.

Kendrick K.M., Fabre-Nys C., Blache D., Goode J.A., Broad K.D. (1993). The role of oxytocin release in the mediobasal hypothalamus of the sheep in relation to female sexual receptivity. *Journal of Neuroendocrinology 5*, 13-22.
Kendrick K.M., Dixson A.F. (1985). Luteinizing hormone releasing hormone enhances proceptivity in a primate. *Neuroendocrinology 41*, 449-453.
Kiss J.Z. (1988). Dynamism of chemoarchitecture in the hypothalamic paraventricular nucleus. *Brain Research Bulletin 2*, 699-708.
Kotter R., Meyer N. (1992). The limbic system: a review of its empirical foundation. *Behav. Brain Res. 52*, 105-127.
Kostarczyk, E.M. (1986). The amygdala and male reproductive functions: Anatomical and endocrine bases. *Neurosci. Biobehav. Rev. 10*, 67-77.
Krude H., Biebermann H., Luck W., Horn R., Brabant G., Grutter A. (1998). Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nature genetics 19*, 155-157.
Lambert P.D., Phillips P.J., Bloom S.R., Wilding J.P.H., Herbert J. (1995) *C-fos* expression in the paraventricular nucleus of the hypothalamus following intracerebroventricular infusions of neuropeptide Y. *Brain Research 670*, 59-65.
LeDoux J. (1998). *The emotional brain*. Weidenfeld and Nicolson, London.
Levine J.E. (1997). New concepts of the neuroendocrine regulation of gonadotropin surges in rats. *Biol. Reprod. 56*, 293-302.
Malmas C.O. (1973). Monoaminergic influence on testosterone-activated copulatory behaviour in the castrated male rat. *Acta Physiol. Scand. Suppl 395*, 1-128.
Maren S., Fanselow M.S. (1996). The amygdala and fear conditioning: has the nut been cracked? *Neuron 16*, 237-240.
Martensz N.D., Herbert J. (1982). Relationship between prolactin in the serum and cerebrospinal fluid of ovariectomised female rhesus monkeys. *Neuroscience 7*, 2801-2812.
McGregor A., Herbert J. (1992). Differential effects of excitotoxic basolateral and corticomedial lesionsof the amygdala on the behavioural and endocirine responses to either sexual or aggression-promoting stimuli in the male rat. *Brain Res. 574*, 9-20.
McGregor A. and Herbert J. (1992b). Specific effects of b-endorphin infused into the amygdala on sexual behaviour in the male rat. *Neuroscience 46*, 165-172.
McGregor A. and Herbert J. (1992c). The effects of b-endorphin infusions into the amygdala on visual and olfactory sensory processing during sexual behaviour in the male rat. *Neuroscience 46*, 173-179.
McKinley M.J., Hards D.K., Oldfield B.J. (1994). Identification of neural pathways activated in dehydrated rats by means of Fos-immunohistochemistry and neural tracing. *Brain Res. 653*, 305-314.
McLean P.D. (1990). *The triune brain in evolution: role in paleocerebral function*. New york: Plenum.
Moss R.L., McCann S.M. (1973). Induction of mating behavior in rats by luteinizing hormone-releasing factor. *Science 181*, 177-179.
Nieuwenhuys R. (1996). The greater limbic system, the emotional motor system and thre brain. *Prog. Brain Res. 107*, 551-580.
Nitabach M., Schulkin J., Epstein A.N. (1989). The medial amygdala is part of a mineralocorticoid-sensitive circuit controlling NaCl intake in the brain. *Behav. Brain Res. 35*, 197-204.
Papez J.W. (1937). A proposed mechanism of emotion. *Arch. Neurol. Psych. 42*, 725-743.
Pedersen C.A., Ascher J.A., Monroe Y.L., Prange A.J. (1982). Oxytocin induces maternal behavior in virgin female rats. *Science 216*, 649-684.
Pfaff D.W. (1973). Luteinizing hormone releasing factor (LRF) potentiates lordosis behavior in hypophysectomised ovariectomized female rats. *Science 182*, 1148-1149.
Pfaff D.W., Modianos D. (1985). Neural mechanisms of female reproductive behavior. In: Adler N., Pfaff D., Goy R.W. (Eds.), *Handbook of behavioral neurobiology* (pp 324-493), vol 7, Reproduction. New York: Plenum.
Pfaus J.G., Phillips A.G. (1989). Differential effects of dopamine receptor antagonists on sexual behavior of male rats. *Psychopharm. 98*, 363-368.
Pfaus J.G., Kleopoulos S.P., Mobbs C.V., Gibbs R.B., Pfaff D.W. (1993). Sexual stimulation activates *c-fos* within estrogen-containing regions of the female rat forebrain. *Brain Research 624*, 253-267.
Pfaus J.G. (1995). Neural mechanisms of sexual motivation and performance in females. In: J. Bancroft (Ed.), *The pharmacology of sexual function and dysfunction* (pp 37-54). Amsterdam: Exerpta Medica
Price J.L., Russchen F.T. and Amaral D.G. (1987). The limbic region. II: the amygdaloid complex. In: Bjorklund A., Hokfelt T. and Swanson L.W. (Eds.), *Handbook of chemical neuroanatomy*, vol 5 (pp 279-388). Amsterdam: Elsevier.

Rowe D.W. and Erskine M.S. (1993). C-fos proto-oncogene activity induced by mating in the preoptic area, hypothalamus and amygdala in the female rat: role of afferent input via the pelvic nerve. *Brain Research 621*, 25-34.
Schulkin, J. (1999). *The neuroendocrine regulation of behavior*. Cambridge University Press.
Sirinathsinghji D.J.S., Whittington P.E., Audsley A.R. (1986). Regulation of mating behaviour in the female rat by gonadotropin-releasing hormone in the ventral tegmental area: effects of selective destruction of the A10 dopamine neurones. *Brain Research 374*, 167-173.
Slimp J.C., Hart B.L., Goy R.W. (1978). Heterosexual, autosexual and social behaviour of adult male rhesus monkeys with medial preoptic-anterior hypothalamic lesions. *Brain res. 142*, 105-122.
Stavy M., Herbert J. (1989). Differential effects of b-endorphin infused into the hypothalamic preoptic area at various phases of the male rat's sexual behaviour. *Neuroscience 30*, 433-442.
Stricker, E.M. (1983). Brain neurochemistry and the control of food intake. In: Satinoff, E., Teitelbaum, P. (Eds.), *Handbook of Behavioral Neurobiology*, vol 6 Motivation, (pp 329-366). New York: Plenum.
Swanson L.W. (1987). The hypothalamus. In: Bjorklund A., Hokfelt T., Swanson L.W. (Eds.), *Handbook of chemical neuroanatomy*, vol 5 (pp 1-124). Elsevier, Amsterdam.
Thatcher-Britton K., Lee G., Vale W., Rivier J. and Koob G.F. (1986). Corticotropin-releasing factor (CRF). receptor antagonist blocks activating and 'anxiogenic' actions of CRF in the rat. *Brain Res. 369*, 303-306.
Turner B.L., Zimmer J. (1984). The architecture and some of the interconnections of the rat's amygdala and lateral periallocortex. *J. comp. Neur. 227*, 540-557.
Ueta Y., Yamashita H., Kawata M., Kioizumi K. (1995). Water deprivation induces regional expression of c-fos protein in the brain of inbred polydipsic mice. *Brain Res. 677*, 221-228.
Zuckerman S. (1932). *The social life of moneys and apes*. London: Kegan Paul.

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