Chapter 5

Generalized brain arousal mechanisms and other biological, environmental, and psychological mechanisms that contribute to libido

Donald W. Pfaff and Helen E. Fisher

Abstract

This theoretical essay proposes that underlying the concept of libido is a primitive set of brain mechanisms responsible for the generalized arousal of the central nervous system (CNS) and the activation of all behavioural responses. Having given the concept of 'generalized CNS arousal' an operational definition, we write an equation that describes how specific motivational needs are integrated with generalized arousal to produce an overall state of the CNS sufficient for potentiating behavioural responses. Factor analysis of behavioural data with mice suggest that among all CNS arousal-related influences, generalized arousal contributes about a third of the variance. Many neuroanatomical, neurophysiological, and genomic mechanisms for arousal are reviewed here. Highlighted are large reticular formation neurons in the medulla whose axons bifurcating rostrally and caudally equip them to contribute, respectively, both to cerebral cortical arousal and to autonomic arousal. Their rapid responses would cause sudden changes in CNS state associated with, for example, states of panic or rapid sexual attraction. Consequences of the actions of generalized arousal networks include increased alertness and attention that serve all cognitive functions and all emotional expression. Specifically with respect to psychoanalytic concepts these networks provide the psychic energy necessary for the expression of libido.
Keywords: arousal; noradrenaline; histamine; opioid; prostaglandin; hypothalamus; preoptic area; oestrogen; dopamine; selective proceptivity/courtship attraction; libido.

Introduction

The first part of this paper will document the existence and nature of generalized central nervous system (CNS) arousal while the second part will discuss its relation to motivational concepts. Third, the mechanisms of generalized CNS arousal will be reviewed. Finally, its consequences for the theory of the primitive, physiological component of libido will be presented. We will argue that generalized CNS arousal is required for the activation of any behavioural response; indeed it

Box 5.1 Term definitions

Arousal: An animal or human being with higher levels of central nervous system arousal is (i) more responsive to sensory stimuli; (ii) emits more voluntary motor activity; and (iii) is more reactive emotionally.

Libido: In this chapter, we restrict ourselves to sexual libido. The neural mechanisms we study in experimental animals are limited in their interpretation to the primitive, physiological side of Freud's libido. See also Solms and Zellner, *Chapter 4*, this volume.

Motivation: A motivated response by a laboratory animal or a human being is an approach response toward a stimulus with positive valence or an avoidance response from a stimulus with negative valence. A heightened arousal state is necessary for a motivated response, but is not sufficient.

is necessary for all cognitive functions and all emotional expressions, importantly those associated with the most primitive aspects of libido.

This chapter constitutes an expansion and reworking of a paper in neuropsychoanalysis, with greater emphasis on cathexis, mate choice, and human behaviour.

The existence of mechanisms supporting generalized CNS arousal

Diffuse, global controls over brain arousal have long been recognized in clinical neurology, as their damage leads to disorders of consciousness (Plum and Posner, 1982). Less discussed is their roles in the expressions of emotion and, in the fields of psychology and ethology, the notion that they are necessary for the activation of all behavioural responses. Even under circumstances where they were admitted as important, it was considered that the concept of generalized brain arousal had a vague (and slippery) character. Thus, a complete and precise operational definition has been proposed (Pfaff, 2006) as follows: An animal or human with a greater degree of generalized CNS arousal (i) shows greater responsiveness to sensory stimuli in all sensory modalities; (ii) emits more voluntary motor activity; and (iii) is more reactive emotionally.

Beyond observations from clinical neurology, three new lines of evidence indicate that a generalized arousal function exists in the vertebrate brain. The first line of evidence is statistical: factor analysis (Gorsuch, 1983) of behaviours by mice subjected to a variety of arousal-related assays revealed (Garey et al., 2003) that a generalized arousal factor accounted for about one-third of the variance. The second line of evidence is mechanistic. Generalized arousal is a function for which many of the brain mechanisms are, in fact, already understood (see below). The third line of evidence is genetic: new results suggest that generalized arousal can be bred, producing high-arousal and low-arousal lines of mice (Weil et al., submitted for publication). Further quantitative approaches to CNS arousal functions will comprise an interesting application of structural equation modelling (Bollen, 1989; Kline, 2005).

Regarding the first, statistical, line of evidence, during the past several years we have been seeking to formulate a mathematical description of arousal-related processes in the mammalian CNS. Higher levels of arousal would lead to greater overall activity in the cerebral cortex and in the sympathetic nervous system. They would be due to greater numbers of action potentials in brainstem systems that heighten arousal and fewer action potentials in brainstem systems that reduce arousal. First, a meta-analysis of experimental data from five studies with mice—using principal components analysis (PCA)—yielded the estimate that among arousal-related measures there is a generalized arousal component that accounts for about one-third of the variance (Garey et al., 2003). This analytic result told us that of all arousal-related behaviours emitted by these mice,

about one-third can be attributed to a generalized arousal force. In that same paper we presented the simplest form of an equation portraying the state of arousal in the mammalian brain as an increasing compound function not only of generalized arousal (accounting for about one-third of the data) but also of several specific forms of arousal (sexual, hunger, thirst, salt hunger, fear, pain, etc.; accounting for the rest of the data related to arousal). Working with Professor Martin Braun (at the Department of Mathematics at Queens College, City University of New York, New York, USA) we have improved this equation intended to 'state a set of problems' ripe for molecular neurobiological discovery.

Small changes in the state of arousal (A) of the mammalian CNS can be described as a compound increasing function of a generalized arousal force supplemented by many specific forms of arousal (sexual, hunger, thirst, salt hunger, fear, pain, temperature, etc.). The manner in which these various forces augment each other is not known. Below is a differential equation that hypothetically picture their relations to each other

$$\delta A = F_1(As_1) + F_2(As_2)\ldots + \ldots F_n(As_n) \times F_g(As_g) \qquad \text{Eq. 5.1}$$

Where As_g represents generalized arousal and all of the other terms represent specific forms of arousal such as sexual arousal, fear, etc. The simplest way of writing this equation is in the form of a linear, additive equation, but our theoretical ideas do not depend on additivity. While the A terms designate functions which are momentary, products of the person's or animal's immediate environment, the k terms are intended to reflect an individual's temperament. The mathematics of arousal is open to investigation.

In ordinary English, the equation envisions how many specific need states might augment each other in complex ways and, in turn, have their effects registered in the form of behavioural acts with even greater force because of a powerful generalized arousal force.

Since, in the principal components analysis referred to above (Garey et al., 2003) only 33% of the variance in those experiments with mice was accounted for by a generalized arousal factor, it must be emphasized that a majority of the variance will be accounted for by other factors and that not all measures of arousal will necessarily correlate with each other. As a result, various manifestations of arousal have been pictured (Pfaff, 2006) as 'teamwork', coordinated but not perfectly correlated, adaptive but not identical. Arousal mechanisms have been operated on by natural selection to alert the forebrain (cortical arousal) and the machinery of the body (autonomic arousal) in a manner that meets the challenges of environmental change by activating approach or avoidance responses as necessary.

Pictorial representations of the same ideas as those represented in the equation above may be founding Figures 5.1 and 5.2.

It would be expected from Equation 5.1 that the level of arousal required for normal female sex behaviour would be a function of the teamwork between two systems, generalized arousal and sexual arousal. We will propose that this teamwork also includes other brain mechanisms, specifically a third brain system that functions to produce 'selective proceptivity' or 'courtship attraction' to the sexual partner.

Indeed, the neurochemical and biophysical bases for generalized arousal effects on female-typical lordosis behaviour have been made clear during electrophysiological recordings from neurons of the ventromedial nucleus of the hypothalamus, neurons that are at the top of the lordosis behaviour circuit. Arousal-related transmitters such as noradrenaline and histamine increase electrical excitability in these neurons (Kow and Pfaff, 1987; Kow et al., 1992; Pataky et al., 2005). Noradrenaline effects on these ventromedial hypothalamus (VMH) neurons analysed by patchclamp recording work through alpha-1b receptors, require N-type calcium channels and are

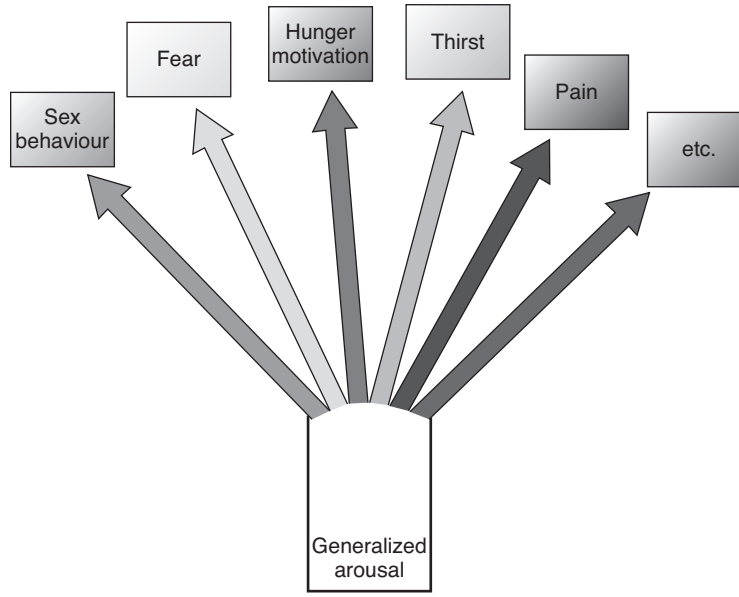

Fig. 5.1 Every biologically regulated motivational state gets its psychic energy from both generalized arousal forces and arousal forces specific to that motivational system.
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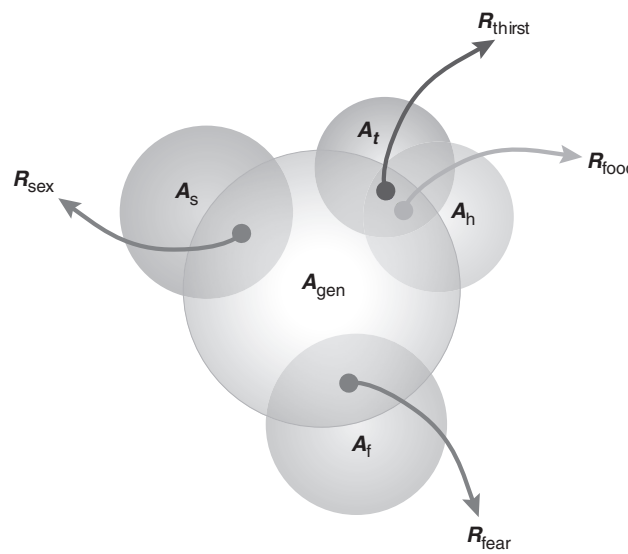

Fig. 5.2 A second way of picturing, using Venn diagrams, of how generalized arousal states and specific arousal states add to produce motivated behaviours.

oestrogen-sensitive (Lee et al., 2008a,b). Histamine effects work through H1 receptors and affect VMH neurons by inhibiting an outward-going potassium leakage current (Zhou et al., 2007). Both of these neurotransmitters, noradrenaline and histamine, would foster sexual arousal by increasing electrical excitability in VMH neurons. In other words, since noradrenaline and histamine, generalized arousal transmitters, increase excitability in the VMH neurons responsible for specific, female-typical sex behaviours, we see exactly how the degree of sexual motivation can build upon generalized CNS arousal. What we do not know yet are the minimal levels of noradrenaline and histamine release onto VMH neurons that would be required for sexual behaviour to proceed.

In the opposite direction, reducing excitability of VMH neurons as studied by patchclamp recording, Devidze et al. (submitted for publication) have found that, through presynaptic actions, mu-opioid receptor agonist reduces activity and even abolishes the activity-enhancing oestradiol effect. Likewise, expression of the gene encoding prostaglandin D synthase (PGDS) in ventrolateral preoptic neurons is associated with a decrease in arousal (Mong et al., 2003a,b). Using antisense DNA oligos to reduce PGDS mRNA function in the preoptic area elevates arousal as well as lordosis behaviour.

With respect to male sex behaviours, mechanisms for the effect of generalized arousal on sexual arousal have been discovered. Muschamp and Hull (1997) have reported that hypocretin/orexin a generalized arousal neuropeptide par excellence is required for normal male sex behaviour. Administration of an orexin receptor antagonist impaired copulatory behaviour in male rats, and the activation of hypocretin/orexin neurons increased markedly during male sex behaviour.

CNS arousal underlies motivated responses

Under what circumstances must we logically infer that motivational forces are driving behaviour (Cofer and Appley, 1964; Pfaff, 1982)? The easiest way to answer this question is to offer an illustration from a laboratory experiment with animals. Suppose we have an animal lacking any sex hormones, performing in a well-controlled laboratory environment. We supply a stimulus animal of the opposite sex to test the experimental animal for its frequency and vigour of mating responses and it emits no mating responses at all. The test animal does not mate. Then, we inject sex hormones. There are no other changes in experimental conditions: not in age, time of day, temperature, stimulus animals, laboratory environment. Now the test animal shows mating behaviour. In the logical equations that describe behaviour, the stimulus and the definition of the response have been held constant. Therefore, the steroid sex hormone injected must have altered another term in the equation, called 'sexual motivation'. The authority Charles Cofer called sexual motivation 'the most powerful factor in energizing and directing behavior'. It depends both on the sex drive of the test animal and the sexual incentive value of the potential sex partner. This 'sexual incentive value' is known to ethologists as selective proceptivity or courtship attraction. We propose that the sex drive and selective proceptivity/courtship attraction are two distinct but overlapping neural systems that operate in tandem with generalized CNS arousal to produce primary aspects of libido.

Motivational concepts are absolutely required to explain a wide variety of biologically regulated responses in animals and humans. Logically, they have the same status in behaviour-CNS equations as the concept of gravity has in Newton's second law. No one has ever 'seen' gravity. It is necessary to explain changes in velocity for a falling body of a given mass. Another analogy: If behaviour was viewed as a vector, then, while the incentive object determines the angle (direction) of the vector then motivation dependent on arousal determines the length (amplitude) of the vector.

In the usual theoretical treatment, motivational concepts are divided into a large number of drive states each of which reflects a particular physical or psychological *need.* In the equation above, each need elevates specific forms of arousal. So-called inter-drive phenomena, shared by

more than one drive state (e.g. hunger and sex, or thirst and fear, or any other combination of needs) by definition in the equation above contribute to the generalized arousal term. As a result of all these factors, motivated *responses* occur. Below we will *first* consider the mechanisms that produce generalized arousal, a force necessary to launch all motivated responses; then we will discuss a primary mechanism that produces selective proceptivity or courtship attraction. Last, we will consider other biological, environmental, and psychological mechanisms that may also contribute to libido.

Explaining mechanisms for motivational states presents a real gift to neuroscientists and behavioural scientists. We will be explaining entire classes of behavioural changes—changes in the state of the brain—instead of working hard just to explain an individual behavioural response. For all of these reasons, neurobiologists, behaviour analysts, and ethologists historically have embraced motivational concepts.

Mechanisms serving generalized CNS arousal

One of the lines of thought supporting the very existence of generalized CNS arousal refers to the fact that we already know of its underlying mechanisms. Since these have been reviewed (Pfaff, 2006) we will cover them briefly here: first, neuroanatomical pathways, then neurophysiological evidence, and finally, functional genomics.

Neuroanatomy: Ascending arousal systems have been described with classical neuroanatomical techniques and include both aminergic and cholinergic pathways (Figure 5.3). Their contributions are not identical to each other. For example, noradrenergic fibres typically innervate the posterior regions of the cerebral cortex more intensely than the frontal cortex and support sensory alertness. By comparison, dopaminergic fibres typically terminate more anteriorly and support the activation of directed motor acts toward salient stimuli.

Descending systems are also important (Figure 5.4). Some of them emanate from the paraventricular nucleus (PVN) of the hypothalamus. For example, corticotrophin-releasing hormone (CRH) neurons project as far posteriorly as the locus coeruleus, while oxytocin- and vasopressin-expressing neurons project not only to the lower brainstem but also down to the spinal cord.

Neurophysiology: Neurons competent to contribute to generalized arousal would be expected to have the capacity to respond to stimuli in more than one sensory modality and, in fact, to have broad receptive fields within a sensory modality. These have been found (and reviewed in Pfaff, 2006) in the reticular formation of the medulla and the pons, among omnipause neurons in the pons and among dopaminergic neurons in the midbrain. In our own lab they have been recorded in freely moving animals and detected among the large neurons in the nucleus gigantocellularis of the medulla (Martin et al., 2007, unpublished data).

Functional genomics: More than 120 genes contribute to the regulation of CNS arousal (reviewed in Pfaff, 2006). Considering genes encoding synthetic enzymes for all the neurotransmitters and neuropeptides involved in arousal, as well as all the genes encoding their receptors, their transporters, and their catabolic enzymes, it is possible to see how the number becomes so large. In our lab, results made it clear, for example, that the gene encoding oestrogen receptor-alpha (ER-alpha) is important for maintaining high levels of arousal (Figure 5.5), while the gene encoding prostaglandin D synthase leads to an enzyme that is involved in reducing arousal state (Figure 5.6). The estrogen receptor result has been followed up with discrete hypothalamic microinjections of an adeno-associated viral vector that produces a small interfering RNA directed against ER-alpha (Musatov et al., 2007).

The major, essential feature of arousal systems in the mammalian CNS is that they are not allowed to fail. Therefore, overlapping functions among genes, neuropeptides, neurotransmitters,

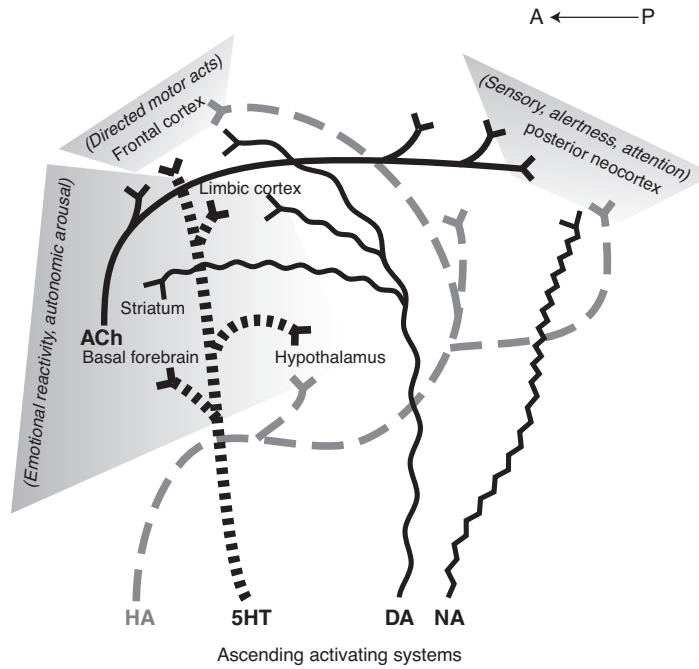

Fig. 5.3 Simplified schematic representation of some major ascending systems present in animal and human brains which serve to support central nervous system (CNS) arousal and activate behaviour. Four sensory modalities feed these systems in obvious ways: touch (including pain), taste, vestibular and auditory. Noradrenaline-containing systems (NA, also known as noradrenergic) tend to emphasize projections to the more posterior cerebral cortex (**P**, except for occipital cortex) and to support sensory alertness. Dopaminergic systems (DA) tend to project more strongly to anterior, frontal cortex **(A)** and to foster directed motor acts. Serotonergic (5HT) neurons project preferentially to a more ancient form of cortex ('limbic cortex') and hypothalamus, and to be involved in emotional behaviours and autonomic controls. Cholinergic neurons (ACh) in the basal forebrain support arousal by their widespread projections across the cerebral cortex. Histamine-producing neurons (HA) likewise have extremely widespread projections which actually originate in the hypothalamus and are strongly associated with increased CNS arousal.
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individual neurons, and nerve cell groups are required. The system's function must be protected against consequences from the loss of individual components. Redundancy is expected in neuroanatomical circuitry, neurophysiological mechanisms, and especially among genes for receptors (Pfaff, 2006).

Bilaterality: In every major respect we can think of ascending arousal systems in the brainstem and descending controls, for example from the PVN of the hypothalamus, are bilaterally symmetrical. The left and the right sides can substitute for each other providing the safety of redundancy in CNS arousal control.

Bidirectionality: Much of the neuroanatomy and neurophysiology literature has emphasized systems ascending from the brainstem and following either a 'low road' through the basal forebrain or a 'high road' through the thalamus to affect the cerebral cortex. But arousal systems are essentially bipolar. They work in both directions essentially at the same time. For example,

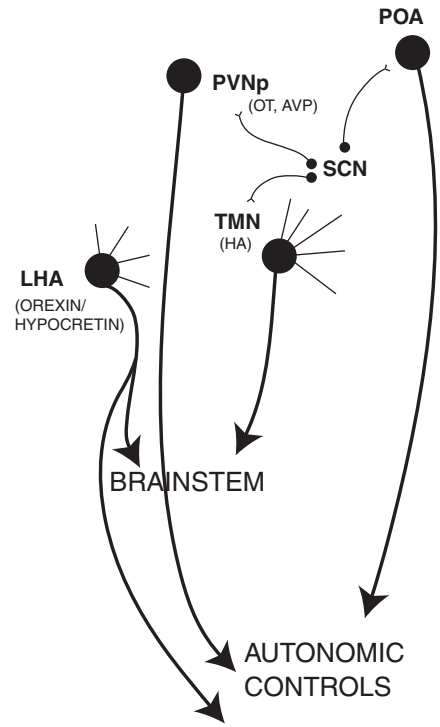

Fig. 5.4 Arousal is controlled top-down as well as bottom-up. Lateral hypothalamic area (LHA) orexin neurons project to monoamine-expressing cell groups in the lower brainstem and even to the spinal cord. Oxytocin (OT) and arginine vasopressin (AVP)-expressing neurons in the parvocellular portion of the paraventricular hypothalamic nucleus (PVNp) control autonomic arousal through the lower brainstem and spinal cord, and affect EEG arousal through projections to locus coeruleus. Histamine (HA) containing hypothalamic neurons in the tuberomammillary nucleus (TMN) have widespread projections, and receive inputs from a 'biological clock', the suprachiasmatic nucleus (SCN). Preoptic area (POA) neurons have descending axons which affect sleep and autonomic physiology. Adapted from Pfaff (2006).

an important hypothalamic cell group, the PVN of the hypothalamus provides a wonderful example, because it is involved in all four forms of arousal: cortical, autonomic, endocrine, and behavioural. Projections to locus coeruleus could have something to do with PVN's alerting effects on the cortical electroencephalogram. And projections to autonomic control centres in the medulla and spinal cord explain some of PVN's effects on autonomic arousal, through vasopressinergic, oxytocinergic and CRH synapses.

Universality: From the comparative neuroanatomy of CNS arousal systems it seems clear that the same basic controls are in place throughout vertebrate evolution, from fish to humans. An especially prominent example of this principle is found in the large reticular neurons in the medial and ventral medulla. These have descending as well as ascending axons (Figure 5.7), thus having the capacity to contribute to autonomic arousal as well as cortical arousal.

Response potentiation: In all cases, arousal systems are necessary for the activation of behaviour. Behavioural responses may be approach responses, but in other cases may be avoidance responses, for example the freezing of an animal that is afraid.

BBURP theory: Trying to address the broadest questions we can possibly ask about CNS arousal systems, we propose a Bilaterally symmetrical, Bipolar (bidirectional) Universal Response Potentiating

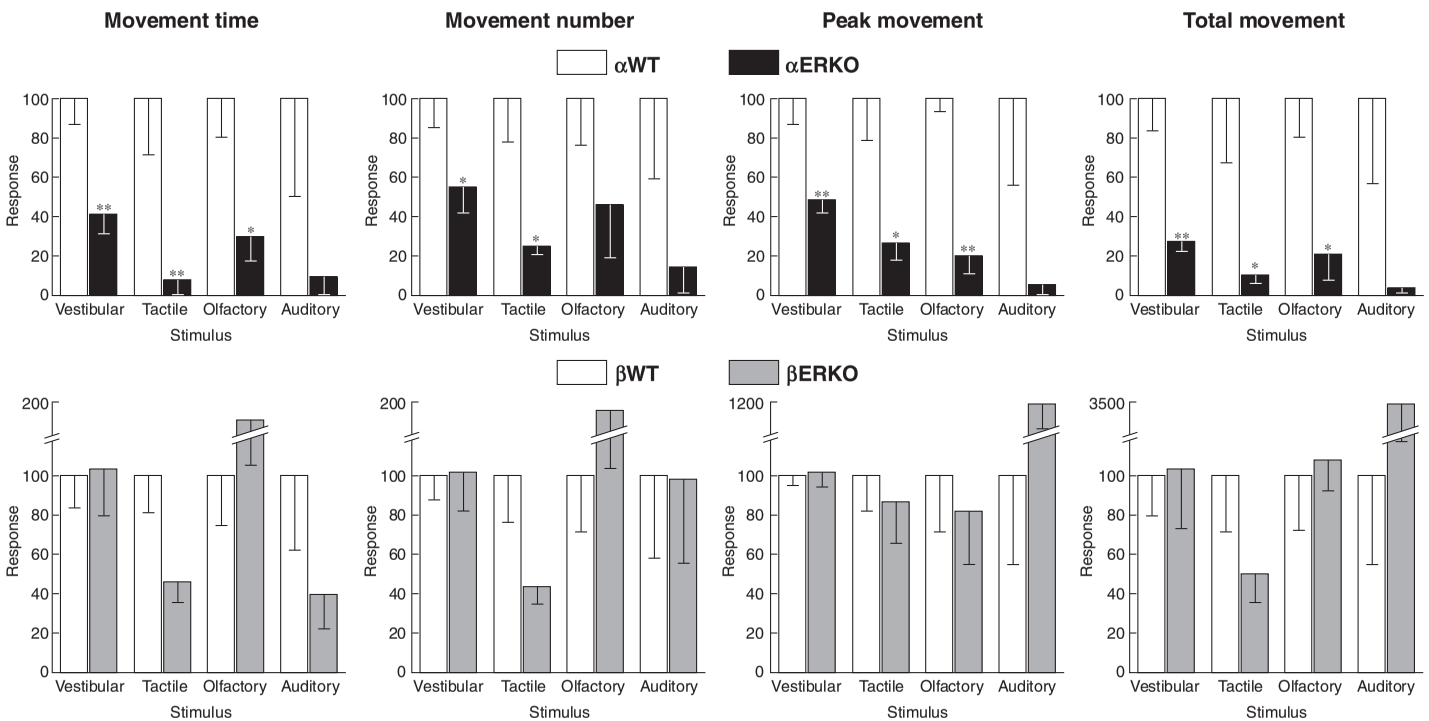

Fig. 5.5 Removing the gene for oestrogen receptor-alpha reduced every measure of arousal in female mice, compared to their wild-type littermate controls. Surprisingly, a likely gene duplication product, oestrogen receptor-beta, did not have the same effect.
Reproduced from Proceedings of the National Academy of Sciences, U.S.A., 100 (19), Genetic contributions to generalized arousal of brain and behavior, Garey, J., Goodwillie, A., Frohlich, J., Morgan, M., Gustafsson, J-A., Smithies, O., Korach, K., Ogawa, S. and D. Pfaff, pp. 11019–22, (c) 2003, National Academy of Sciences, U.S.A.

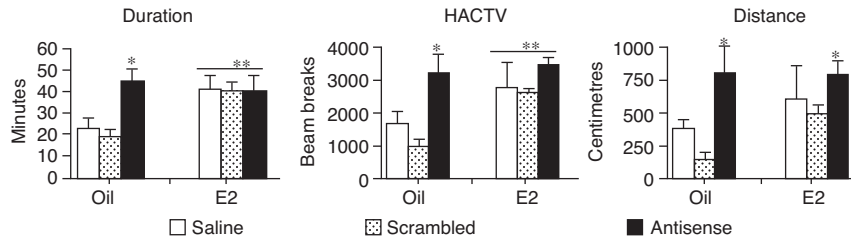

Fig. 5.6 Some genetic effects on arousal go in the opposite direction. Microinjecting an antisense DNA oligo that disables the messenger RNA encoding prostaglandin D synthase in the preoptic area permitted greater arousal in this assay.
Adapted from Mong et al. (2003b).

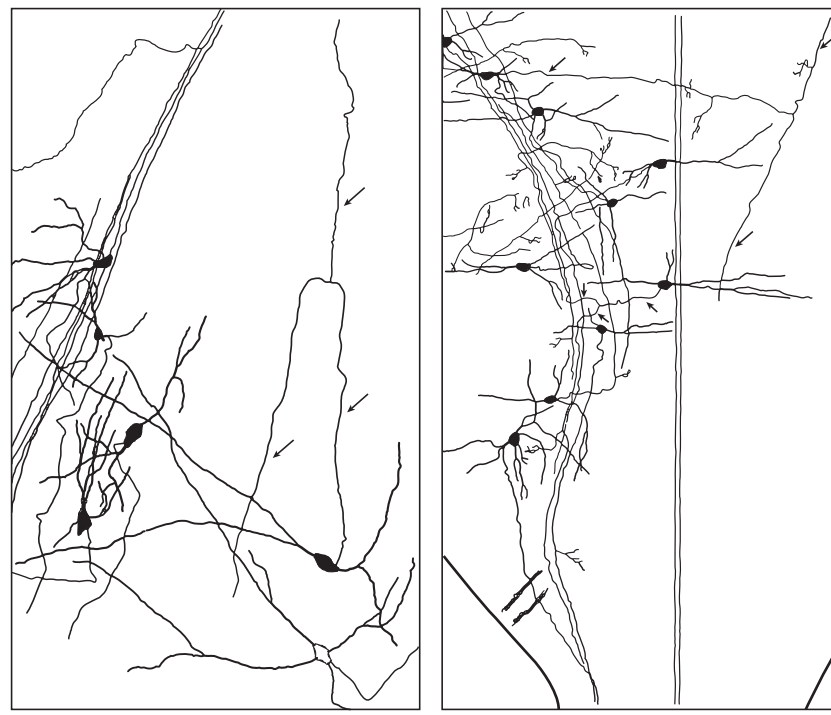

Fig. 5.7 Five examples of large reticular formation nerve cells whose 'trunk line' axons bifurcate into ascending and descending limbs. Such neurons would be excellent candidates to be among my theoretical 'master cells'—primitive neurons influencing arousal going both towards the hypothalamus and cerebral cortex and toward the spinal cord. For each of the five cells illustrated, the bifurcating axonal limbs are denoted by three small arrows.
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(BBURP) system. Among all vertebrates, this system readies the animal or the human to respond to stimuli of all modalities, to initiate voluntary locomotion and to react with feeling to emotional challenges. This is 'BBURPP theory' (Figure 5.8). It is intended to summarize the most generalized features of arousal systems reviewed here.

Not all cells in arousal systems are equally powerful. It appears to us that the gigantocellular reticular neurons pictured in Figure 5.7 constitute a particularly important node for controlling CNS arousal. A considerable proportion of alerting and arousing inputs signal through gigantocellular neurons in the medullary reticular formation, neurons whose extreme levels of activation would signal panic. These cells are interesting because, as discovered by neuroanatomists in the 1950s and 1960s, they receive large numbers of inputs and fan out to large numbers of outputs. We have extended those neuroanatomical findings to a genetically tractable animal, mice (Martin and Pfaff, unpublished observations). As a result of their large scope of inputs and their widespread outputs, their control logic achieves the 'bow tie' (Csete and Doyle, 2004) configuration. This 'bow tie' structure of control engineering is thought by Doyle and his collaborators to have the following advantages : speaking in terms of engineering control principles, arousal mechanisms in this 'bow tie' organizational structure (Zhao et al., 2006) achieve a striking flexibility of control

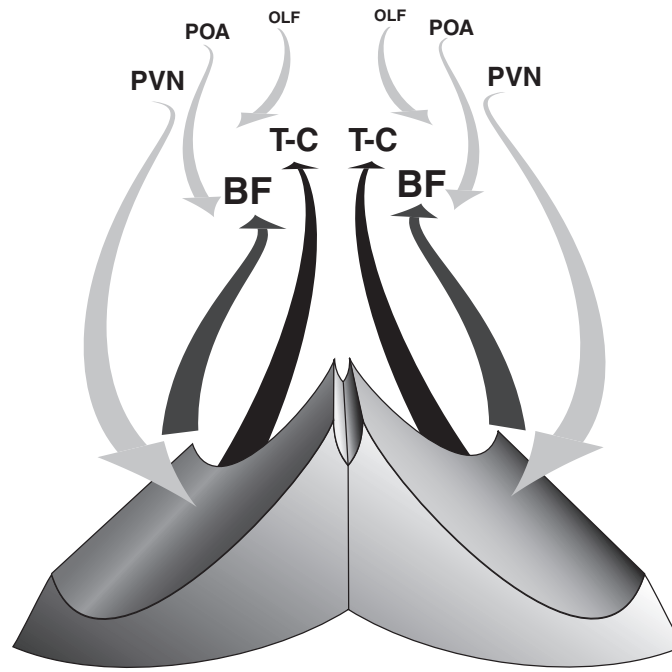

Fig. 5.8 BBURP theory: a **B**ilaterally symmetric, **B**ipolar (Bidirectional, ascending and descending) **U**niversal (among vertebrates) **R**esponse **P**otentiating system. This abstract, theoretical diagram is restricted to the major features of arousal systems which have been conserved throughout vertebrate phylogeny. Arising from an ancient, crescent shaped field of neurons along the ventral and medial borders of the brainstem, arousing signals ascend. However, other important forces for regulating arousal descend from PVN, POA, and OLF. BF, basal forebrain; OLF, olfactory and pheromonal inputs; POA, preoptic area; PVN, paraventricular nucleus of the hypothalamus; T-C, the non-specific thalamocortical systems.
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system performance. The central 'knot' of the bow tie for arousal is thought to these medullary gigantocellular reticular neurons (see above). We seek an understanding of their robustness as control systems performing in variable and uncertain environments (cf. Doyle and Csete, 2005).

Consequences for thinking about libido

These mechanisms regulating generalized CNS arousal are important for us as sexual beings. The founder of psychoanalysis, Sigmund Freud, who began his career as a doctor and neurologist, invented the term 'libido' to describe the urges and desires lying beneath the emotional, physical, and mental energies that go into sexual desire. He always conceived of our libido as having two components: a biological or physiological component, and a complex psychological manifestation (reviewed in Pfaff, 1999).

A modern neurobiologist may not try to explain the psychological side—the full range of mental, artistic, self-conscious expressions of the person in love. However, we can claim to have the mechanisms in hand for the primitive, physiological side of libido. A tremendous number of neuroanatomical, neurophysiological, genetic, and endocrine mechanisms related to sex behaviour have been conserved from the animal brain into the human brain (Figure 5.9). Unless Nature, having evolved a full set of working mechanisms for mammalian reproductive behaviour *threw them all away* and started an entire new set for humans, then we understand well the most primitive mechanisms that drive sexual desire in humans. From the beginning we had been inspired by psychoanalysis to unravel how a simple female sex behaviour is produced, and now realize that the research programme has taken us further than we expected. That is, because of the conservation of mechanisms, therefore, this work with neuroanatomical, biophysical, and molecular techniques (summarized in Pfaff, 1999) has also explained the physiological aspect of the libido concept.

In sum, because generalized CNS arousal is required for the activation of any behavioural response, it must be necessary for those associated with the most primitive aspects of libido.

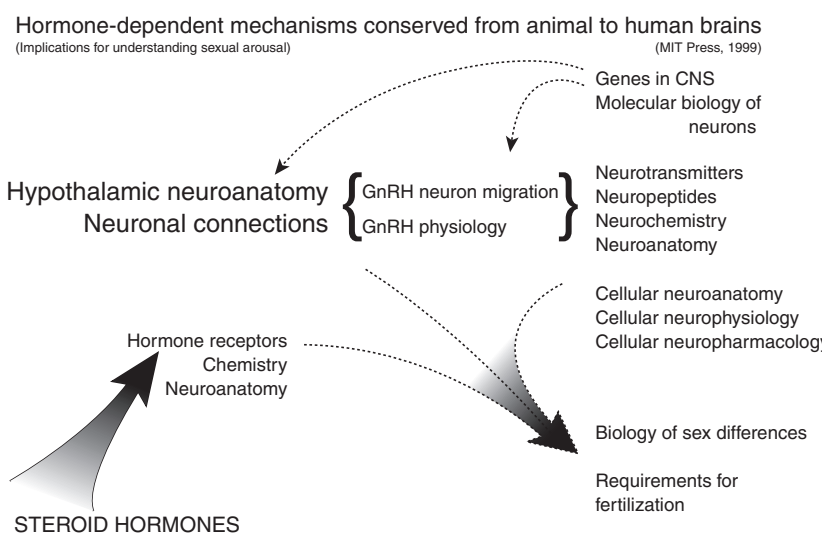

Fig. 5.9 A multitude of mechanisms and systems is conserved from the brains of laboratory animals into the human brain. Therefore, if we have explained sexual arousal and sexual behaviour in such animals, we likely have explained mechanisms underlying the primitive, physiological aspect of Freud's concept of libido. GnRH, gonadotrophin-releasing hormone.

It cannot be equivalent to libido because libido includes the notion of cathected objects and also encompasses aspects of human feelings that have cultural content far beyond the types of CNS mechanisms we have discussed here. Thus, generalized arousal could be considered an obligatory precursor of libido, necessary but not sufficient.

Therefore, we must consider some of the other mechanisms that contribute to libido, including those that are biological, environmental, and cultural/psychological. As mentioned above, the brain appears to operate via teamwork among coordinated neural mechanisms. So we propose that the libido, the physiological craving for sex, operates in tandem with a neural mechanism for attraction, along with several other forces that together contribute to libido.

Animal studies indicate that individuals of many species exhibit mate preferences, focusing their courtship energy on favoured conspecifics. This phenomenon is so common in nature that the ethological literature regularly uses several terms to describe it, including 'female choice,' 'mate preference', 'individual preference', 'favouritism', 'sexual choice', 'selective proceptivity' (Andersson, 1994), and 'courtship attraction' (Fisher, 2004).

Ethologists have traditionally lumped this neural motivation system, selective proceptivity/courtship attraction, together with the sex drive. There are exceptions, however. Beach (1976) made a distinction between the sex drive and courtship attraction, writing that the occurrence of copulation depended as much on individual affinities and aversions as upon the presence or absence of sex hormones, and that proceptive and receptive behaviour in the female may depend upon different anatomical and neurochemical systems in the brain (Beach, 1976). Hutchison and Hutchison (1983) proposed that courtship entailed a sequence of choices each requiring different mechanisms and they questioned whether the sex hormones had any specific role in the establishment and expression of mating preferences. Kendrick and Dixson (1986) have shown that anteromedial hypothalamic lesions block proceptivity but not receptivity in the female common marmoset. Goodall reported that males of many primate species 'show clear-cut preferences for particular females, which may be independent of cycle stage' (1986, p. 446). And Pfaff distinguishes between the hormone-dependent facilitation of sexual arousal and the expression of approach and other courtship behaviours, regarding these as distinct aspects of mating behaviour and physiology (Pfaff et al., 2002).

Mammalian courtship attraction has been associated with a suite of biobehavioural traits, including increased energy, focused attention, obsessive following, affiliative gestures, possessive mate guarding, goal-oriented behaviours, and motivation to achieve sexual union with a preferred mating partner (Fisher, 2004; Fisher et al., 2002). And the following data suggest some of the neural underpinnings of this motivation system. When a female laboratory-maintained prairie vole (*Microtus ochrogaster*) is mated with a male, she forms a distinct preference for him associated with a 50% increase of dopamine in the nucleus accumbens (Gingrich et al., 2000). When a dopamine antagonist is injected into the nucleus accumbens, the female no longer prefers this partner; and when a female is injected with a dopamine agonist, she begins to prefer the conspecific who is present at the time of infusion, even if she has not mated with this male (Gingrich et al., 2000; Wang et al., 1999). An increase in central dopamine is also associated with courtship attraction in female sheep (Fabre-Nys, 1998). In male rats, increased striatal dopamine release has also been shown in response to the presence of a receptive female rat (Montague et al., 2004; Robinson et al., 2002).

The suite of physiological and behavioural traits associated with mammalian courtship attraction can also be seen in *Homo sapiens*, including increased energy, focused attention, obsessive following, affiliative gestures, possessive mate guarding, goal-oriented behaviours and motivation to win a preferred mating partner (Fisher, 1998; Gonzaga et al., 2001; Harris and Christenfeld, 1996; Hatfield and Sprecher, 1986; Hatfield et al., 1988; Shaver et al., 1987; Tennov, 1979). However, this biobehavioural phenomenon is regularly referred to as romantic love.

Romantic love is a cross-cultural universal (Jankowiak and Fischer, 1992) that shares many characteristics with mammalian courtship attraction. So it is parsimonious to suggest that human courtship attraction evolved from a generalized mammalian neural system for attraction.

In fact, recent data indicate that romantic love is also associated with elevated activity of subcortical dopaminergic pathways, as it is in other mammals (Aron et al., 2005; Fisher, 1998; Fisher et al., 2003). To investigate the constellation of neural correlates associated with romantic love, Aron et al. (2005) recruited 10 women and 7 men who were intensely in love. The age range was 18–26 years (M = 20.6; median = 21); the reported duration of 'being in love' was 1–17 months (M = 7.4; median = 7). Each participant was orally interviewed in a semi-structured format to establish the duration, intensity, and range of his/her feelings of romantic love. Each also completed the Passionate Love Scale, a nine-point Likert scale self-report questionnaire which measures traits commonly associated with romantic love (Hatfield and Sprecher, 1986).

The protocol employed photographs and consisted of four tasks presented in an alternating block design: for 30 seconds each participant viewed a photo of his/her beloved (positive stimulus); for the following 40 seconds each performed a countback distraction task; for the following 30 seconds each viewed a photograph of an emotionally neutral acquaintance (neutral stimulus); for the following 20 seconds each performed a similar countback task. The countback task involved viewing a large number, such as 8421, and mentally counting backwards (beginning with this number) in increments of 7. The countback task was included to decrease the carry-over effect after the participant viewed the positive stimulus because it is difficult to quell intense feelings of romantic love. This four-part sequence (or a counterbalanced version beginning with the neutral stimulus) was repeated six times; the total stimulus protocol was 720 seconds (12 minutes).

Group activation specific to the beloved occurred in several regions, including the right ventral tegmental area (VTA), localized in the region of A10 dopamine cells (Aron et al., 2005). The VTA is a central region of the brain's reward system (Martin-Soelch et al., 2001; Schultz, 2000; Wise, 1996), associated with pleasure, focused attention, and motivation to pursue and acquire rewards (Delgado et al., 2000; Elliott et al., 2003; Schultz, 2000). The VTA sends projections to several brain regions (Gerfen et al., 1987; Oades and Halliday, 1987; Williams and Goldman-Rakic, 1998), including the caudate nucleus where group activations also occurred, specifically in the right medial and postero-dorsal body (Aron et al., 2005). The caudate plays a role in reward detection and expectation, the representation of goals, and the integration of sensory inputs to prepare for action (e.g. Lauwereyns et al., 2002; Martin-Soelch et al., 2001; O'Doherty et al., 2002; Schultz, 2000).

A between-subjects analysis also correlating degree of the BOLD response with subjects' scores on the Passionate Love Scale (Aron et al., 2005). While viewing their beloved, those who self-reported higher levels of romantic love also showed greater activation in the right antero-medial caudate body. This result provides strong evidence for the link between a specific brain region and a specific brain function, romantic attraction. However, this specific region is also activated during anticipation of a monetary reward (Knutson et al., 2001), during reward-based stochastic learning (Haruno et al., 2004) and during attention tasks (Zink et al., 2003). Thus, this area of the antero-medial body of the caudate may be specifically associated with the rewarding, visual and attentional aspects of attraction. (Brown reports that because the caudate nucleus has widespread afferents from all of the cortex except V1 (Eblen and Graybiel, 1995; Flaherty and Graybiel, 1995; Kemp and Powell, 1970; Saint-Cyr et al., 1990; Selemon and Goldman-Rakic, 1985) and is organized to integrate diverse sensory, motor and limbic functions (Brown, 1992; Brown et al., 1998; Haber, 2003; Parent and Hazrati, 1995), caudate nucleus anatomy is an appropriate mechanism for integrating the various aspects of this multi-factor physiological and behavioural state, romantic attraction (Brown, personal communication, 2005)).

Using functional magnetic resonance imaging (fMRI), Bartels and Zeki also investigated brain activity in 17 men and women who reported being 'truly, deeply, and madly in love' (Bartels and Zeki, 2000, p. 3829). There were 11 women; all looked at a photograph of his/her beloved, as well as photographs of three friends of similar age, sex, and length of friendship. However, the participants in that study had been in love substantially longer than those in the Aron et al. study (28.8 months versus 7.4 months). They were also less intensely in love. This was established because both study groups were (serendipitously) administered the same questionnaire on romantic love, the Passionate Love Scale. In spite of these differences in protocol, Bartels and Zeki (2000, 2004) also found activity in regions of the VTA and caudate nucleus.

Pfaff's research discussed above, as well as several fMRI studies of human sexual arousal (Arnow et al., 2002; Beauregard et al., 2001; Dixson, 1998; Heaton, 2000; Karama et al., 2002) support the hypothesis that the sex drive is associated with specific networks of brain activation and that these networks are distinct from but overlapping with those associated with human romantic love/mammalian courtship attraction, as well as distinct from those associated with general CNS arousal. These data support our hypothesis that the libido is associated with at least three neural systems: those for general CNS arousal, the sex drive, and courtship attraction.

But there are undoubtedly many additional brain systems involved in libido, including the neural systems for sensory perception, memory, and cognitive and emotional responses. These have not yet been investigated. But we surmise that one's experiences contribute to dimensions of sexual libido beyond the primitive physiological libidinous component studied in lower animals.

Freud proposed that one's parents affect one's sexual choices. Studies with sheep support this hypothesis. Kendrick and colleagues (1998) have 'cross-fostered' baby male goats, placing each with a sheep mother, a parent of a different species. In adulthood, these male goats refused to copulate with females of their own species; instead they sought sex after female sheep, particularly those who had a facial structure much like their foster mother. Female goats that grew up with a sheep mother were more sexually flexible in adulthood: 50% of their mate selections were male sheep (like their parent figure); but the balance of their sexual attractions were directed toward male goats, individuals of their own species. In these cases, juvenile experiences affected the direction of the libido.

In humans, many environmental, social, economic, and psychological forces also contribute to sex drive and sexual preference. Timing and proximity affect mate choice (Fiore and Donath, 2004; Hatfield, 1988; Pines, 1999). Mystery plays a role in attraction: people tend to be less sexually attracted to those they know well, particularly those with whom they have had regular contact as a child (Shepher, 1971). Men and women are sexually attracted to individuals from the same socioeconomic and ethnic background (Buston and Emlen, 2003; Cappella and Palmer, 1990; Pines, 1999), those with a similar level of education and intelligence (Buston and Emlen, 2003; Byrne et al., 1986; Cappella and Palmer, 1990; Pines, 1999), those who share their religious views and have other similar attitudes and values (Krueger and Caspi, 1993; Laumann et al., 1994; Shaikh and Suresh, 1994), those with a similar sense of humour and degree of financial stability (Buston and Emlen, 2003), and individuals with similar social and communication skills (Buston and Emlen, 2003; Byrne et al., 1986; Cappella and Palmer, 1990; Pines, 1999).

Reik and others have proposed that men and women choose mates (presumably also sexual partners) who satisfy an important need, including the qualities they lack, known as 'need complementarity' (Hinde, 1997; Reik, 1964; Winch, 1958). Proponents of 'social exchange theory', a variant of this hypothesis, hold that men and women are sexually and romantically attracted to those who can provide the resources they seek in exchange for the assets they can provide (Blau, 1964; Dryer and Horowitz, 1997; Foa and Foa, 1980; Huston and Burgess, 1979; Murstein, 1976; Roloff, 1981; Sprecher, 2001; Sprecher and Regan, 2002; Walster et al., 1978). Murstein (1976)

hypothesizes that the role one is likely to play in the relationship contributes to romantic and sexual attraction.

Psychologists note that women are sexually/romantically drawn to men with rank, money, and other resources (Buss, 1994; Ellis, 1992) and to those who are self-confident, assertive, and smart (Kenrick et al., 1990), while men are sexually/romantically drawn to women exhibiting signs of youth, health, and beauty (Buss, 1994). Psychologists also propose that men and women tend to fall in love with (and become sexually attracted to) those who are in love with them (Aronson, 1998; Hoyt and Hudson, 1981).

Hazan and Shaver (1987) build on the theories of Bowlby (1969) and Ainsworth et al. (1978), proposing that humans seek an attachment (and most likely also sexual contact) with those who mirror the type of infant attachment they made with mother, be it secure, anxious-ambivalent or avoidant. Harris (1999) hypothesizes that individuals are sexually/romantically attracted to partners who reflect the values, interests, and goals of their childhood friends. And Zentner (2005) proposes that as people grow up they develop a psychological model of their ideal mate, what he refers to as one's Ideal Mate Personality Concept (IMPC). He defines this template as a 'unique ordering and configuration of personality characteristics' that an individual regards as ideal for them (Zentner, 2005, p. 245). This IMPC is not fixed or rigid, however; individuals change their image of their ideal mate over time, being most likely to alter this template when they become dissatisfied with a current partnership (Zentner, 2005).

Biological variables probably also play a role in triggering this triumvirate: general CNS arousal, the sex drive, and courtship attraction. People are sexually attracted to those who show signs of bodily and facial symmetry (Gangestad and Thornhill, 1997; Gangestad et al., 1994; Jones and Hill, 1993), and those with specific bodily proportions (Lavrakas, 1975; Singh, 1993). Women are attracted to men with a different cluster of genes than their own in the major histocompatibility complex (MHC) (Garver-Apgar et al., 2006; Wedekind et al., 1995;). Lastly, Fisher hypothesizes that both sexes also gravitate to individuals with specific genetic profiles in the biological systems for dopamine, serotonin, testosterone, and oestrogen, each associated respectively with different suites of cognitive and behavioural traits (Fisher 2009, Fisher et al., 2010a,b; Fisher et al., manuscript in preparation). These kinds of data indicate that sophisticated neural systems in humans are superimposed on the primitive physiological/sexual libidinal mechanisms studied in lower animals.

Conclusions

We propose that all of the above forces are likely to contribute to the physiological and cathectic aspects of libido, although the intensity of each factor probably varies from one individual to the next. In fact, these data suggest that the libido is associated with a hierarchical lattice of drives,

Box 5.2 Questions for future study

1. Here we have reviewed nervous system research in lower, laboratory animals and experimental results with humans. But, in higher animals, non-human primates, how do primitive aspects of sexuality meld into psychological functions that depend on cultural influences, not hormones?
2. Our mechanistic studies essentially deal with 'bottom-up' approaches to concepts of libido. How do they comport with the 'top-down' regulation that obviously occurs in humans?
3. How can new brain scanning techniques add to our concepts of libido and other aspects of sexually related social affinities?

feelings, and behavioural responses. It is generated by general CNS arousal mechanisms working as a team with the neural systems for the sex drive and courtship attraction. But in humans, and most likely other higher mammals, these neural systems operate in tandem with a host of other biological, environmental and cultural mechanisms to produce a unique sexual response in each individual.

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