Sex for fun: a synthesis of human and animal neurobiology

Janniko R. Georgiadis, Morten L. Kringelbach and James G. Pfaus

Abstract | Sex is a fundamental pleasure, and crucial to the survival of our species. Though not many people would disagree with the proposition that sexual behaviour depends on the brain, the neuroscientific study of human sex is still relatively taboo and much remains to be discovered. On the contrary, excellent experimental animal models (mostly rat) are available that have uncovered major behavioural, neurochemical, and neuroanatomical characteristics of sexual behaviour. Restructuring sexual behaviour into broader terms reflecting behavioural states (wanting, liking, and inhibition) facilitates species comparison, revealing many similarities between animal and human sexual pleasure cycles, some of which can serve as potential avenues of new human sex research. In particular, behavioural and brain evidence clearly shows that motivational and consummatory phases are fundamentally distinct, and that genitally-induced sexual reward is a major factor in sexual learning mechanisms.

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Introduction

Sex has the potential to be both pleasurable and frustrating. Attitudes vary such that, perhaps surprisingly, sexual dysfunctions including sexual desire disorder, anorgasmia, and premature ejaculation are not always perceived as problematic.[1,2] On the other hand, even when their sexual function is well within the normal range, individuals might deem their sexual experiences unsatisfying or their performance inadequate.[3–5] Although crucial to the survival of our species, human sex is clearly more complex than mere reproduction.

Neuroscience can provide a better understanding of the behavioural mechanisms involved in human sex.[6–8] In recent years, increasing emphasis has been put on understanding sexual reward-based learning and sexual incentive motivation. Similar to other forms of learning, sexual behaviour develops over time as people learn to associate stimuli such as bodily features, personality, and contextual cues with genitally-induced sexual pleasure.[7] Adolescence is arguably the most critical phase in sexual development.

The spectacular progress of human functional brain imaging in recent years has not completely bypassed the sexual domain, but the resulting data are often descriptive rather than mechanistic.[6] By contrast, experimental animal (mostly rat) studies have provided invaluable insights into the way the central nervous system organizes sexual reward and sexual incentive motivation,[7–9] although the question of whether animal data can be translated to human sexual behaviour remains unanswered (Box 1).

In this Review we provide a comprehensive description of the available animal and human literature on sexual reward and sexual incentive motivation. We structure our Review around the sexual pleasure cycle, which has phases of wanting, liking and inhibition that map onto the more classical concepts of sexual excitement, plateau, orgasm and refraction. Following this sexual pleasure template, we highlight the major points of convergence and divergence across species, discuss a neural concept of human sexual behavioural control and suggest novel testable hypotheses for future sex research.

The sexual pleasure cycle

Sexual response is at the core of sexual behaviour and is perhaps best conceptualized as the recurring cycle of events and behaviours that, in a heterosexual couple, can potentially lead to reproduction. Excitement (emotional desire, genital arousal), plateau (physical sexual activity and bodily and genital arousal), orgasm, and refraction are the phases of sexual pleasure that are traditionally distinguished.[10] The sexual pleasure cycle adheres to the basic structure of pleasure cycles related to other rewards (such as food), and can therefore also be expressed in terms of motivation–consummation–satiety or wanting–liking–inhibition (Figure 1; Box 2).[6,11,12]

Sexual behaviour is orchestrated by the brain through integration of incoming sensory information with the internal state. This might seem at odds with the fact that erection and ejaculation are organized as spinal reflexes,[13,14] and the fact that these reflexes can be functional in people with complete spinal cord transections;[15] however, sexual behaviour and sexual pleasure require integration of many different types of information, many of which are not genital. For example, the optimal use of sildenafil requires sexual desire, which can be triggered by the presence of a sexual partner or visual erotic stimuli. In the following sections, we discuss what is known about

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Key points

- Restructuring sexual behaviour into broader terms reflecting behavioural states (wanting, liking, and inhibition) facilitates species comparison; similarities between animal and human sexual pleasure cycles can serve as potential avenues of new human sex research
- Sexual wanting in both rats and humans involves interaction between gonadal hormones and external stimuli that become sexual incentives through association with genitally-induced sexual reward; pleasurable genital stimulation is thus a major factor in sexual learning
- In terms of underlying brain networks and neurochemistry identified in both rat and human, wanting sex is something completely different to liking sex
- Sexual inhibition involves similar brain mechanisms in rats and humans
- Rats show a similar pattern of brain activation to humans in response to cues related to sexual reward
- Cortical, limbic, hypothalamic, and cerebellar regions are activated by sex-related stimuli in both humans and rats

Box 1 | Species differences in sexual behaviour

In his intriguing behavioural analysis of sex, Anders Ågmo[16] makes a strong argument that the human is not simply just another mammal. In his view, there are two major reasons for this: social learning (that is, learning from observation) and language (which might be associated with vivid mental representations). Introspection and moral thinking might be additional factors to take into consideration. These functions certainly contribute to any human behaviour and there is no reason to believe that they are not involved in sex.[125] This might explain the divergence in, for example, recruited brain networks during sex between animals and humans. In addition to these factors, Ågmo proposed that in humans all sexual incentive stimuli are learned, whereas animals can at least depend on a fixed set of unconditioned sexual stimuli (pheromones, vocalizations). Some human studies have suggested pheromones are involved in sexual attraction,[126] but the fact remains that humans lack a functional vomeronasal organ (the main pheromone detection organ in rats).[127] The full extent of sexual divergence between species remains to be elucidated, but human sexual behaviours and preferences are certainly extremely versatile, ranging from paedophilia to gerophilia, and from tantric sex to sadomasochistic practices. Under natural conditions, the same sexual variety is not observed in any other species (though some primates show extraordinary versatility).[128] Notably, social perceptions can critically drive sexual preferences in humans (for example, in terms of body shape), and these perceptions vary greatly over time and between populations.[129]

the major brain mechanisms of the sexual pleasure cycle spanning sexual wanting, liking, and inhibition.

Wanting sex

Sexual desire can be induced by virtually any external stimuli, encompassing touch, vision, scent, sound, and also mental representations. Unconditioned sexual stimuli (that is, those for which the pleasurable effect requires no learning) include proximal genital tactile stimulation in humans and distal stimuli such as pheromones, odours, and certain auditory vocalizations in rats.[7,16] Popular belief holds that humans also respond to some distal sexual incentive stimuli (breasts, pheromones) in an unconditioned manner, but this has been difficult to evaluate empirically (Box 1). In the following sections, we discuss the animal and human studies that have improved our knowledge of sexual incentive stimuli.

Animal studies

Most sexual incentive stimuli are conditioned by genitally-induced sexual reward states, such as high sexual arousal and orgasm, such that they become predictors of sexual reward. However, nongenital contextual cues can also become sexual reward predictors, and hence preferred. This means a vast array of stimuli can become sexual in the right circumstances, and can even lead to the development of fetishes, or sexual wanting induced by inanimate objects.[7,17] This, in turn, can have major repercussions for copulatory behaviour. A striking example of this is the use of a rodent jacket as a somatosensory cue. Repeatedly pairing the jacket with each exposure to, and copulation with, sexually receptive females (made receptive at 4-day intervals to approximate the normal ovulatory cycle), leads to the jacket eliciting conditioned sexual reward in male rats, such that paired rats show dramatic copulatory deficits when not wearing the jacket.[7]

Reviewing the animal literature reveals that sexual wanting is stimulated by excitatory neurochemical mechanisms in the brain, including mesolimbic and incertohypothalamic dopamine critical for sexual incentive motivation, oxytocin and melanocortins acting in the hypothalamus and limbic system to stimulate sexual attraction, and ascending noradrenaline acting in hypothalamic, limbic, and cortical regions to augment sexual arousal.[8] Although these systems are activated by sexually relevant stimuli, they are primed for activation by gonadal steroids acting at both genomic and nongenomic levels to create a state of sexual arousability and responsivity.[7,18] This can occur via direct activation of excitatory substrates,[18] or through a process of disinhibition, in which systems that mediate stress, sexual refractoriness, or competing motivational states, are themselves inhibited by steroid hormone priming.[19] Thus, male animals that are not seasonal breeders and do not undergo a seasonal phase of testicular regression have an ambient state of sexual arousability[20] and responsivity, whereas female animals experience cyclic peaks in desire and arousability around the time of ovulation.[21] A similar situation applies to humans.

Human studies

Human brain activity can be measured with neuroimaging techniques (Box 3). Neuroimaging studies of sexual incentive stimuli have mainly employed passive viewing paradigms in healthy men.[6] Women are somewhat under-represented in imaging studies, which could reflect researchers' hesitance to deal with 'female' methodological challenges related to their menstrual cycle, genital responses, attitude towards visual sexual stimulation (VSS), or relative discordance between reported and measured sexual arousal.[6,11,12]

Humans are extremely sensitive to their preferred sexual stimuli; when presented subliminally, VSS can induce both an attention bias[22] and measurable brain responses,[23,24] which are largely observed in the ventral striatum (which includes the nucleus accumbens), the amygdala, the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC).[23,24] Responses to sexual incentive stimuli in the area of the nucleus accumbens and in the ACC are sensitive to pharmacological manipulation of dopamine levels,[24] which suggests an important parallel with rodent physiology.

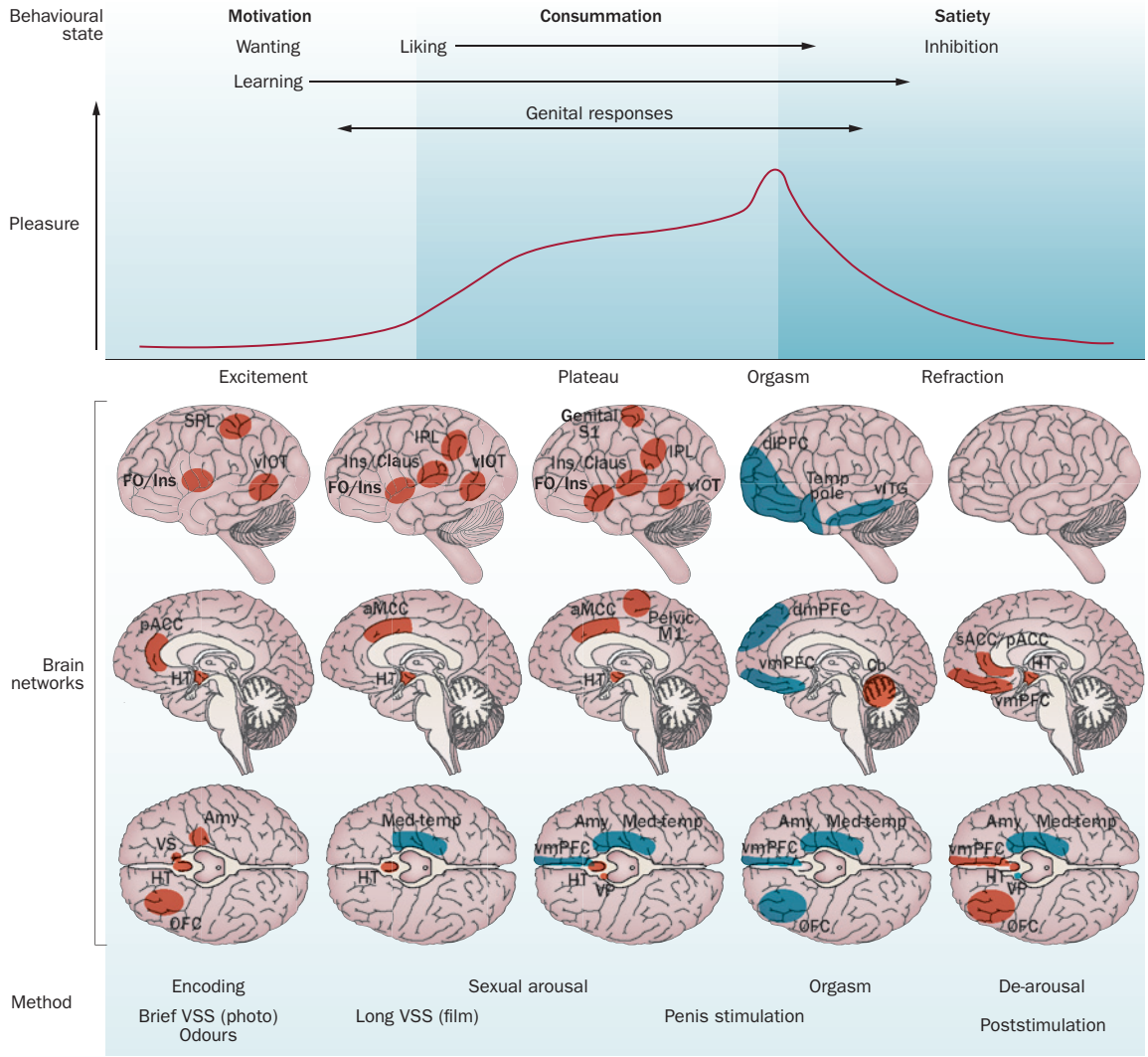

Figure 1 | The sexual pleasure cycle. The sexual response cycle involves phases related to excitement, plateau, orgasm, and refraction, which can also be expressed in terms of wanting, liking and inhibition. Sexual liking typically peaks at orgasm, but is by no means restricted to it. Orgasm (especially in men) tends to signal transition to the satiety phase, which can temporally prevent the individual from entering the cycle again. The sexual response cycle typically occurs over a relatively short time span (from minutes to hours) and may or may not include all of the phases and elements described. Neuroimaging studies have elucidated the key nodes and hubs that are responsible for sustaining and switching between the different phases of the pleasure cycle and can lead to changes in behaviour. VSS paradigms are likely to elicit sexual motivation and wanting. Genital stimulation is usually required to enter the consummatory plateau. The brain regions involved in mediating changes in the sexual response cycle are shown on only one side of the brain but most regions are involved bilaterally. Some regions have multiple roles at different points in the sexual response cycle, for example activity in the amygdala is involved in encoding sexual salience, sexual arousal, orgasm, and poststimulation. Permission obtained from Elsevier Ltd © Georgiadis, J. R. & Kringelbach, M. L. *Prog. Neurobiol.* **98**, 49–81 (2012). Abbreviations: aMCC, middle cingulate cortex (anterior part); Amy, amygdala; Cb, cerebellum; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FO/Ins, frontal operculum/anterior insula; Genital S1, primary somatosensory cortex of external genitalia; HT, hypothalamus; Ins/Claus, posterior insula/claustrum; IPL, intraparietal lobule; Med-temp, medial temporal lobe; OFC, orbitofrontal cortex; pACC, pregenual anterior cingulate cortex; Pelvic M1, primary motor cortex of pelvic floor; sACC, subgenual anterior cingulate cortex; SPL, superior parietal lobule; Temp pole, temporal pole; vlTG, ventral aspect of inferior temporal gyrus; vmPFC, ventromedial prefrontal cortex; vlOT, ventrolateral occipitotemporal cortex; VP, ventral pallidum; VS, ventral striatum/nucleus accumbens; VSS, visual sexual stimulation.

Further evidence for the involvement of mesolimbic dopamine in sexual wanting comes from studies on natural interindividual variations in expression of dopamine-related genes, which can be assessed in either peripheral venous blood or buccal cells from the mouth. Individuals with genetically predisposed high synaptic dopamine not only had the strongest nucleus accumbens activity (measured with functional MRI [fMRI]) in response to to monetary rewards,[25] but also the highest number of sexual partners[26] and the lowest age of first sexual intercourse.[27] Moreover, sublingual apomorphine (a dopamine agonist) could elicit penile erection in men

Box 2 | Terminology of sexual behaviour research

Sexual response has been conceived both in terms of dichotomies that reflect the processes of excitement and inhibition and as a cycle that moves through sequences of sexual or copulatory behaviour. Dichotomies typically reflect initiation and termination of sexual response along a general appetitive (behaviours that increase the probably of achieving a goal) versus consummatory (behaviours engaged with the goal) continuum. Included here are distinctions between courtship and copulation, motivation and performance, among others. The response cycle concept was made popular by Masters and Johnson in their 'EPOR' model,[10] which involves the transition from excitement (a mix of genital arousal and emotional desire for sex) to a plateau of arousal as sexual activity ensues, to an apex of excitement (orgasm), and then to an immediate resolution or refractory phase. In men, the refractory phase is generally longer than in women, especially those who are capable of having a series of orgasms. Superimposed on this are clinical dichotomies of conscious awareness, as reflected in objective versus subjective measures of arousal, desire, orgasm, and resolution. The sexual response cycle has more recently been compared to other well-established pleasure cycles that consist of phases of wanting, liking, and inhibition.[6] In this way, sexual responses follow a pattern similar to other motivations, such as thirst, hunger, and drug addiction, in which an individual wants or craves, likes (or dislikes), and experiences feedback in the form of satisfaction of the need state. These conceptualizations are essentially heuristics that allow researchers to separate sexual responses into the activation of different brain regions or neurochemical systems. Wanting and liking are distinguished by different systems in the brain. Wanting is driven by mesolimbic dopamine[130] that focuses attention and behaviour toward acquiring sexual incentives,[8] whereas liking is synonymous with reward or pleasure, and is driven by opioid and other reward systems.[8] Inhibition as either direct or indirect feedback regulation, is driven by opioid, serotonin, and endocannabinoid systems in the brain.[8] In this way, direct comparisons can be made between men and women, and across species, both in terms of the behaviours that are expressed in each phase and the neuroanatomical and neurochemical systems that underlie them.

with psychogenic erectile dysfunction while they watched a long erotic video, although this did not coincide with measurable mesolimbic activity.[28,29] Indeed, VSS videos >30 s long very rarely yield measurable activity in the nucleus accumbens, suggesting that mesolimbic dopamine is critical for the onset of sexual wanting but not for sustained genital responses.[6]

Natural variations in gonadal steroid levels, between and within individuals, affect both reported sexual desire and the strength of overall VSS-induced brain activity.[30–32] Although these observations support the critical role of sex steroids in sexual wanting, the association is tentative at best until controlled studies are performed, including direct statistical group comparisons or placebo treatment. Better controlled studies have been performed outside the field of sexual medicine. In women, nucleus accumbens activity induced by anticipation of a monetary reward varies over the course of the menstrual cycle,[33] and can be manipulated by exogenous testosterone.[34] Similar interactions between gonadal hormones and mesolimbic dopamine might fuel sexual wanting, as suggested by animal research.[7,18]

Emotional stimuli are better remembered than neutral stimuli and this function depends heavily on the amygdala.[35] The same holds true for VSS; individual differences in VSS-induced amygdala activity can predict differences in recall of those stimuli 4 weeks later.[36] The ability of VSS to make a lasting impression is probably due to its incentive value, which, in turn, might be associated with the magnitude of sexual pleasure induced by such stimuli. Such associations might be instrumental in classical conditioning of sexual responses. In a series of studies performed in women, pleasurable clitoral stimulation (the unconditioned stimulus [UCS]) was paired with neutral visual stimuli (the conditioned stimulus [CS]). After 8–10 trials the neutral stimuli acquired reinforcing properties, meaning that presentation of the CS alone elicited enhanced vaginal pulse amplitude (a genital measure of sexual desire and arousal).[37–39]

Klucken and co-workers[40] revealed a central signature of sexual conditioning in healthy men and women. After pairing two different geometric shapes (CS) with either VSS (sexual reward, UCS) or nonrewarding (neutral) stimuli (non-UCS), volunteers were invited to participate in an fMRI study. While the VSS-predicting geometric shape (CS+) came to produce subjective sexual desire in some of the volunteers, the non-UCS predicting shape (CS–) did not do so in any of the volunteers. Accordingly, watching the CS+, compared to CS–, resulted in increased activity in the OFC, ACC, anterior insula, nucleus accumbens and midbrain. Of note, volunteers who reported that they had inferred the contingency between CS+ and UCS ('aware') showed stronger activity in this network than those who remained oblivious to it ('unaware'). Most aware volunteers were men, and most unaware volunteers were women.[40]

In another study,[41] men were shown visual cues that indicated the likelihood (25% or 75%) of being presented with pictures of attractive young women. The women in the pictures were either naked or wearing a bathing suit, the occurrence of which was also predicted in the cue. Thus, expectancies ranged from a low chance of getting a minor sexual reward to a high chance of obtaining a reasonable sexual reward. When volunteers watched the stimuli in the fMRI scanner, the positive subjective value assigned to the stimuli (which was generally higher for the nude woman reward) correlated with activity in a number of brain regions, most notably the OFC, ACC, anterior insula, nucleus accumbens and midbrain. Importantly, the same set of brain regions were involved in processing the reward prediction error, that is, the degree of incongruence between the reward expected and obtained.[41]

These findings reveal a network of brain regions that are particularly sensitive to sexual incentive stimuli, reward contingencies and expectancy. By extrapolation, therefore, these areas might underlie sexual wanting. However, basically the same network is involved in processing the desire for other incentives, such as food.[6] Moreover, the regions comprising this putative 'sexual interest network' are not—or less—involved when high levels of sexual arousal are involved, suggesting that their role is primarily restricted to recognizing sexual opportunity and directing motivated behaviour accordingly (Figure 1).[6]

Liking sex

Physical sexual activity can lead to enhanced genital and cardiovascular arousal, and genital stimulation can lead to orgasm. Opiates, such as heroin, produce a rush of euphoria followed by a prolonged period of relaxation,[42] a state that has been referred to as a 'pharmacogenic orgasm'.[43]

This opioid reward state induces a dramatic decline in sexual wanting in both men and women, and inhibits the ability to achieve orgasm during subsequent sexual intercourse.[42] It has been argued that a 'natural' version of this state is induced by human orgasm[44] and by certain copulatory behaviours in rats; for example, ejaculation in male rats induces the release of endogenous opioids.[45] Early phases of the sexual pleasure cycle might induce considerable positive affect and carry positive incentive value, although genital stimulation and orgasm in humans, and genital stimulation and ejaculation in male animals, are considered the chief phases that provide positive incentive value.

Box 3 | Methods used to study the brain control of sex in animals and humans

Knowledge of brain activation by sexual stimulation or sex-related cues in rats comes from a variety of techniques, including lesions, electrical recording, and the activation of immediate-early gene products, such as Fos, that are typically expressed in the nuclei of cells that are activated by the stimuli. Additional neuropharmacological manipulations that activate or block specific neurotransmitter receptors in specific brain regions, or that use microdialysis or voltammetry to assess neurochemical turnover in extracellular fluid, have also been used extensively. Molecular studies in brain tissue have revealed hormone-induced transcription factor activation that has had a profound impact on our understanding of how hormones activate genes to make proteins that, when expressed, alter the functionality of brain pathways, making animals attend more to sex-related cues than other external incentives. Human functional neuroimaging works through the mechanism of neurovascular coupling, whereby local neural activity is followed by measurable blood flow, volume and oxygenation changes.[131] PET and functional MRI (fMRI) are the most widely used techniques. Though fMRI clearly outperforms PET in terms of the spatial and temporal (continuous versus intermittent scanning) resolution, and hence popularity, it is important to realize that both techniques measure indirect traces of pooled neuronal activity, often over many seconds. An inevitable consequence of sexual functional neuroimaging experiments is that sex happens at a preset time, in a preset way, and in a preset place. Though natural human sexual activity may also be less spontaneous than we sometimes would like to admit, the current state of sexual functional neuroimaging experiments reflects approximations of real sexual confrontations at best.

Genital source of sexual reward

There are various nongenital methods of achieving orgasm,[46] but the primary source of sexual pleasure is the brain's response to genital stimulation.[8,47] Spinal cord injury does not always completely eliminate genital sensation or functionality because sensory fibres from external and internal genitalia run through four main nerves—one somatosensory (pudendal) and three autonomic (hypogastric, pelvic, vagal)—that enter the central nervous system at different levels.[15]

Sensations that arise from stimulation of the glans of the penis or clitoris are thought to be the most important contributors to genitally-induced sexual reward (Figure 2). Indeed, anaesthetic lidocaine spray applied topically to the glans penis significantly prolongs ejaculation latency time.[48] Likewise, clitoral stimulation is the easiest way for women to achieve orgasm.[49] These similarities are not surprising given that, in mammals, the clitoris and penis follow the same developmental path prior to differentiation,[50] resulting in virtually identical innervation with similar distribution of central nervous system afferents and efferents.[51–53]

The role of the penis glans in sexual liking has been studied much more than that of the clitoris. Millions of years of copulation seem to have resulted in evolutionary pressures that have tailored glans penis morphology and neurophysiology so that it is suited to the stimulatory elements that comprise an aroused vagina: warmth, lubrication, and friction. For example, for bulls to penetrate a rubber tube for semen collection, the tube must be sufficiently warm (>42 °C),[54] suggesting that glans receptors might activate genital reward only within a narrow stimulatory range. Notably, many other types of stimulation, besides vaginal, might fulfill these conditions to provide genital reward. However, our current understanding of the specific receptive properties of the glans is incomplete. Although the sensory threshold of the penis (including glans) to high frequency vibratory stimulation has been assessed,[55] psychophysical studies in humans using more naturalistic stimulation are lacking.

Morphological studies conducted on human and rat penises have shown that the receptor constellation of the glans penis is remarkably similar across species and that it is unlike that of other skin.[56,57] Specifically, the glans penis is remarkable for an abundance of free nerve endings and thin C and Aδ fibres typical of protopathic somatosensation.[56,57] Moreover, it contains coiled receptors—genital end bulbs—that are not found anywhere else in the body.[56,57] These receptors seem to change their orientation during erection,[56] which might conceivably underlie the different sensitivity of the penis under engorged versus flaccid circumstances. Encapsulated mechanoreceptors and thick Aβ fibres, structures classically associated with touch, are virtually absent in the glans,[56,57] leading to the intriguing possibility that friction of the glans, a mechanical stimulus, is processed through the thin fibre protopathic route. Affective touch, that is the speed and pressure associated with a gentle caress, is known to be signalled through C-fibres in the arms and legs.[58,59] Similarly, friction of the glans is a hallmark of affective touch and a critical component of genital reward.

Thus, there is evidence to suggest that sexual liking is deeply encoded in mammalian genitalia, most notably in the glans, which might be considered a specialized sensor for somatosensory stimuli that result in genital reward. Stimulation of other skins areas, such as nipples,[60] is known to incite and augment sexual pleasure, but whether this is unconditioned or learned is an open question. Experimental partial lesions of the spinal cord in rats have demonstrated that sensory information important for ejaculation runs in the ventrolateral (spinothalamic) columns.[61] Indeed, men with injury to the ventral part of the spinal cord are likely to develop anorgasmia.[62] The spinothalamic tract is the main afferent pathway for protopathic information (such as pain), which fits with the concept of penis glans innervation outlined above. Similar studies on the clitoris do not exist. However, animal studies using anatomical tracers injected into penis and clitoris glans seem to indicate that the way clitoral and penile stimulation is conveyed to the brain is likely to be similar.[51,52] Pelvis viscera, including the prostate, the vaginal wall and vaginocervix, probably express different

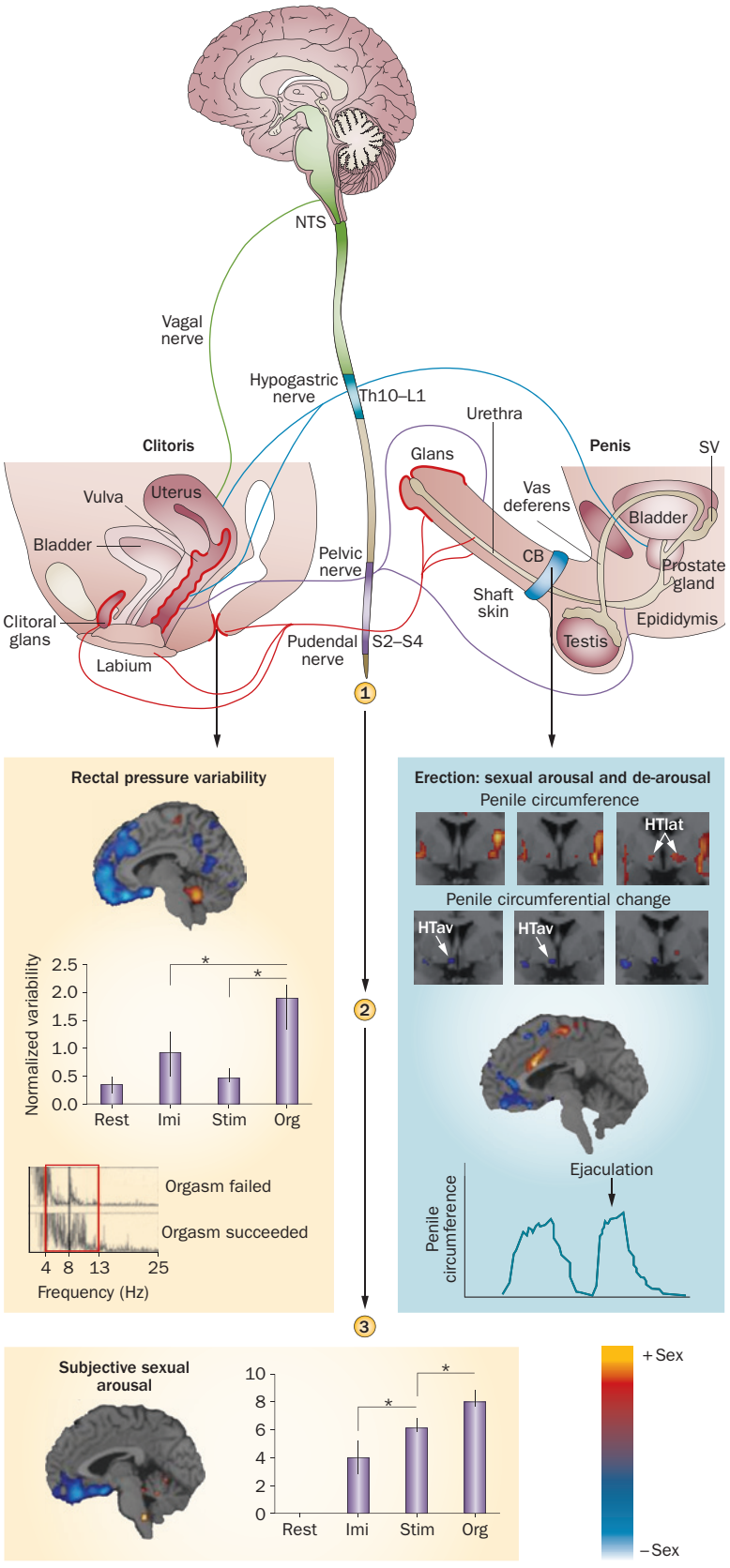

Figure 2 | Partnered stimulation protocols (PSPs) to study the central mechanisms of human sexual consummation. (1) Partnered stimulation of the clitoris or penis was performed with simultaneous measurement of rectal pressure in women or penile circumference in men. The four major genital nerves are also shown, with the pudendal nerve (which innervates penis and clitoris) marked in red. (2) In women, rectal pressure patterns during orgasm had clearly distinguishable fast frequency characteristics, which correlated positively with cerebellar blood flow (orange). Negative correlations were observed in ventral and dorsal parts of the prefrontal cortex (blue). In men, positive correlations with penis stimulation, penile circumference, and the rate of circumferential change, were seen in a number of areas including the middle cingulate cortex (sagittal section, orange) and lateral hypothalamus (top panel, orange). After stimulation ceased, and arousal decreased, a completely different network became active, including ventral prefrontal cortex, rostral cingulate cortex (sagittal section, blue), and the anterior hypothalamus (top panel, blue). Differences between men and women with respect to cingulate and hypothalamic effects may reflect the superior sensitivity of the continuous measurements in the male PSP relative to the intermittent nature of the female PSP. (3) Subjective reports of sexual pleasure in women obtained after each scan correlated negatively with ventral prefrontal (3, blue) and medial temporal blood flow (not visible in section). *Highlights significant differences. Abbreviations: HTav, anteroventral hypothalamus; HTlat, lateral hypothalamus.

receptors, but their role in sexual liking is undisputed. At present, however, this notion is primarily based on popular belief, anecdotal reports and behavioural studies in animals.[63]

The neural basis of genital reward

Animal studies

The neural basis of sexual liking has primarily been elucidated in animal studies. In rats, preferences can be instated through coupling with genital reward, leading, for example, to conditioned preferences for place or partner.[7] In male rats, ejaculation induces the reward state necessary for the induction of both conditioned place preference (CPP) and preferences for partner cues that are associated with the reward states.[7,64,65] In female rats, the ability to control or 'pace' the initiation and rate of copulation induces the reward state. This conditioning is achieved by repeated association of the reward state with a particular set of place cues in the CPP box, or with a particular partner cue (for example, almond odour on the partner). Animals are trained to contrast these cues with a different set of place or partner cues associated with sexual nonreward, such that on the final test day animals are given a choice between place or partner cues of high reward versus cues of lower reward or no reward. Not surprisingly, on the final test animals prefer the high reward cues. The administration of an opioid receptor antagonist, such as naloxone, during training blocks the development of such preferences suggesting that the reward state is dependent on opioid transmission.[65] Furthermore, injections of opioid antagonists can reverse the sexual inhibition displayed by male rats after reaching sexual exhaustion.[66] Similarly, in female rats, CPP is blocked if naloxone is administered during training.[67–71] Manual clitoral or vaginocervical stimulation associated with place or partner cues can induce CPP in sexually naïve rats,[9,72,73] and females selectively solicit

sex from males bearing an odour associated with manual clitoral stimulation.[74]

Interestingly, in male rats, the reward state also requires a critical level of sexual arousal prior to ejaculation to support the conditioned preferences,[75] suggesting an interaction between the intensity of sexual activity prior to ejaculation or orgasm and the degree of reward experienced from it. Indeed, in sexually naïve, but not experienced, male rats, sexual intercourse without ejaculation supports the development of CPP.[76]

Studies examining *Fos* induction (a marker of neuronal activity) in the brains of male and female rats have revealed a common set of regions activated by copulatory stimulation.[77] Additionally, microdialysis has been performed to assess dopamine and glutamate transmission in the nucleus accumbens and hypothalamus during copulation. In both male and female rats, a number of relatively common neural structures are activated by copulatory stimulation, including sensory nerves that innervate the penis or vagina or cervix, by unconditioned olfactory or pheromonal stimuli, or by conditioned sexual incentives. This network includes specific subdivisions of the hypothalamic area, basal forebrain, thalamus, amygdala, and hippocampus, all of which contain classic nuclear hormone receptors.[18] Regions that do not contain classic intracellular steroid receptors, such as the ventral and dorsal striatum, and areas of cortex, are also activated.[77]

Fos has also been found colocalized with the cytoplasmic proteins gonadotropin releasing hormone, glutamate, dopamine, and oxytocin.[77] There is significant overlap in brain regions activated by ejaculation and vaginocervical stimulation in male and female rats, respectively, including the medial amygdala (posterior dorsal part), the subparafascicular (parvocellular) and intralaminar thalamus, the lateral putamen and claustrum, and the ventromedial hypothalamus.[77]

Several cortical regions are activated in both male and female rats by copulatory stimulation, including cingulate, piriform, somatosensory, and entorhinal cortex.[77] The insula is also activated by copulation with a preferred scented partner, and to a lesser extent by the conditioned odour alone. This is of particular interest because those regions are also activated in humans during sexual activity[78] and while observing erotic pictures or films.[79,80] The ability of neutral odours to activate many of these regions following pairing with sexual reward states (induced by ejaculation in male rats and paced copulation in female rats) suggests that they are acting as conditional priming stimuli that generate anticipatory sexual responses in animals.[7]

Dopamine transmission in the nucleus accumbens is a critical substrate for sexual incentive motivation.[81] In both male and female rats, extracellular concentrations of dopamine increase during the presentation of a sexually receptive partner and during copulation. However, in male rats ejaculation produces a dramatic decrease in nucleus accumbens dopamine release that remains low during the absolute refractory phase, but moves back upward during the relative refractory period.[82] A neutral odour paired with the postejaculatory reward state in male rats selectively increases dopamine release in the nucleus accumbens, whereas the same odour unpaired does not.[7] These observations were recently confirmed using single unit recordings from nucleus accumbens shell neurons, as different functional classes of neurons were found to exhibit different firing patterns across the sexual pleasure cycle.[83]

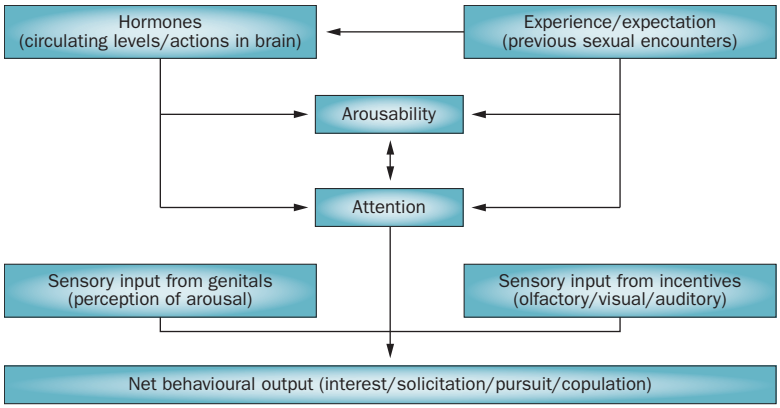

Figure 3 | Scheme representing the most important neurobiological and behavioural elements of sexual responsiveness, as well as the interaction between them.

Taken together with data from lesion, physiological, and neuropharmacological studies, the activation of mesolimbic dopamine systems by unconditioned and conditioned sex cues forms the core of an incentive motivational system that critically links sexual wanting to sexual reward. This system is activated in the presence of priming cues, and also by actual sex partners, especially those that bear stimuli predictive of reward (Figure 3). The brain regions discussed are involved in many different behaviours, but they act together as a 'system' for sexual behaviour.

Human studies

Human neuroimaging research of genital stimulation is much sparser than that of visual sexual incentives.[6] Furthermore, about half of these studies have been performed using PET (Box 3), rather than fMRI. Genital stimulation can be investigated in sexually aroused or nonaroused volunteers, and can be partnered or involve self-stimulation. In a partnered stimulation protocol with sexual arousal, volunteers lying inside the scanner receive manual genital stimulation by their real-life sexual partners.[6,84] Self-stimulatory protocols with sexual arousal have been performed in the context of vaginal self-stimulation, which required the use of custom-made phallus-like device.[85–87] Partnered protocols have a number of important advantages over genital self-stimulation, including less strong head movements, less interference from the experimenters, and sexual interaction with a real-life sexual partner.

Partnered genital stimulation studies (both aroused and nonaroused) have demonstrated that stimulation of the penis and clitoris leads to activity in the full somatosensory matrix. Most of the evidence shows that the penis and clitoris are represented in deep layers of the dorsal primary somatosensory cortex.[78,88–92] Furthermore, the

penis and clitoris also map to the secondary somatosensory cortex, in the parietal operculum.[78,87,88,90,91,93,94] The third area implicated in genital sensory processing is the insula (middle and posterior).[78,88,91,93,94] Of these areas, the posterior insula is most relevant in processing penile tumescence.[77,79,89,95,96]

The most advanced partnered stimulation protocol reported was an fMRI experiment performed in men (Figure 2),[78] which revealed involvement of the lateral hypothalamus, ventral pallidum, middle cingulate cortex, anterior insula, frontal operculum, inferior parietal lobule, and occipitotemporal cortex in both penile tumescence and sexual penis stimulation. The ventral pallidum, known to mediate food liking in rats,[97,98] signalled the onset of penis stimulation and, through decreased activity possibly reflecting inhibitory processes, the absence of penis stimulation.[78] These areas seem to be part of a 'sexual consummation network' that is fundamentally distinct from the earlier mentioned 'sexual interest network'.[6]

Georgiadis and Kringelbach[6] recently identified the substantial neuroanatomical overlap between sexual consummation and sympathetic arousal states induced by music, cocaine, or pain.[6] As mentioned previously, in male rats the intensity of sexual activity (prior to ejaculation) is predictive of the reward experienced,[75] which is supported by recent ideas that sympathetic arousal plays a crucial role in mammalian sexual activity.[99,100] This might explain how people and animals can transfer from a nonsexual high arousal state to sexual consummation, or vice versa if the arousal is not correctly identified as sexual.[8]

Activity in some brain regions decreases as sexual pleasure increases. This is true for the amygdala,[78,88,89] even when the amygdala readily responds to distant visual erotica.[41,101,102] However, prolonged amygdala activity corresponds to heightened vigilance,[103] which promotes avoidant responses and precludes physical interaction.[104] Conversely, people are less sensitive to fearful stimuli, such as white noise, during sexual arousal.[105] Downregulated neural activity associated with sexual liking is observed not only in the amygdala, but also in parts of the medial temporal lobe and ventromedial prefrontal cortex.[78,88,93,106] Intriguingly, all of these areas have been shown to be important for interpersonal judgements.[107]

Human orgasms are difficult to study, primarily because of their unpredictable and uncontrolled nature.[84] The most insightful orgasm data come from a partnered clitoral stimulation protocol in women (Figure 2). Orgasm in women was verified by measuring rectal pressure fluctuations; fast pressure fluctuations probably reflect involuntary pelvic muscular activity,[108] and are a defining feature of orgasm in both men and women.[109,110] In the imaging study, fast pressure fluctuations were indeed most prominent during orgasm.[88,108] The level of activity in ventromedial temporal and prefrontal cortices was lowest during orgasm, when sexual arousal was reported to be highest.[88] During orgasm, activity in prefrontal, but not temporal, areas correlated with the frequency of rectal pressure fluctuations—fast fluctuations were associated with low prefrontal cortex activity. This indicates a relative loss of behavioural control,[111] which is supported by the lack of voluntary pelvic floor motor cortex activity during orgasm.[88]

The brain effect most specific to orgasm was observed in mid-anterior and medial subregions of the OFC.[88] Activity changes in these regions could be used to distinguish between sexual clitoral stimulation and orgasm, which fits with data from other neuroimaging studies demonstrating that similar OFC activity changes represent the subjective pleasure of food intake.[12]

Taking into consideration the temporal resolution of PET, which is about 1 min, the results described here might also be related to postorgasmic sexual inhibition or pre-orgasmic sexual arousal. For the same reason, it is possible that areas active specifically during orgasm might no longer be identified when data are pooled over a 1 min period.

Sexual inhibition

Sexual inhibition can be induced by stressful events or high sexual rewards, such as during the refractory period after ejaculation in male rats, during which reproductive capacity must be regenerated prior to a resumption of copulation,[8,112] and after multiple paced intromissions and ejaculations in female rats that bring about oestrus termination.[113] In both cases, the activation of inhibitory pathways for sexual arousal and desire generates a state of reduced sexual wanting.

Animal studies

In rats, activation of opioid, serotonin and endocannabinoid release during sexual reward is associated with an inhibition of ongoing sexual behaviour. Male rats allowed to copulate (with multiple ejaculations) to sexual exhaustion do not respond to female solicitations for a period of 24–72 h. This inhibition can be reversed by the serotonin 1A agonist 8-OH-DPAT (an autoreceptor agonist that inhibits serotonin release), by the α_2 adrenoreceptor blocker yohimbine, and by naloxone.[114] Thus, blockade of opioid or serotonin transmission, or activation of parasympathetic pathways involved in erection, can overcome the state of inhibition induced by sexual exhaustion.

Yet, somewhat paradoxically, activation of opioid transmission by stress might also play a role in sexual inhibition. Male rats find new environments stressful. In fact, males that are not desensitized to the environment in which they have their first sexual experiences often do not copulate.[115] Pre-exposure to the environment, or treatment with naloxone, increased the proportion of males that copulated on their first trial.[115] Interestingly, sexually naïve males sensitized to amphetamine do not show inhibition during their first exposure to females in a novel environment, despite exposure to the drug being weeks before.[116] Although sexually experienced male rats show signs of fear in novel environments, they do not show subsequent sexual inhibition if a receptive female is placed into the environment.

Together, these data suggest that stress-induced inhibition of sexual response in male rats can be overcome by sensitization of dopamine systems by either sexual experience or exposure to amphetamines, or the blockade of opioid signalling. Indeed, in male rats trained not to copulate with sexually nonreceptive females, a low dose of alcohol or cocaine can disinhibit sexual advances.[117,118]

Interestingly, it has been shown that pairing exposure to a neutral odour with access to sexually nonreceptive females (which is a nonreward) induces *Fos* expression within regions of the medial prefrontal cortex and central nucleus of the amygdala in male rats.[119] In humans, these regions are associated with behavioural inhibition (as a form of executive function) and stress response, and activity in these regions has been shown to correlate negatively with sexual arousal.[78,88,106]

In female rats, a state of sexual nonreward can be induced by sexual frustration (achieved in an experimental setting by application of clitoral stimulation in the presence of an inaccessible male)[7] or by injections of naloxone (capable of eliminating both sexual place and partner preferences[67,67,70,120]) during the females' first sexual experience with a male. Female rats in such a state of sexual nonreward develop an inhibited sexual response.[7] Despite full hormone priming and an injection of saline on the test day, females do not solicit, show low-level lordosis reflexes (the arching of the back and raising of the rump that allows for clitoral and vaginocervical stimulation by male mounts and intromissions), and engage in intense fighting with males that attempt to mount.[7,68]

Human studies

Few human neuroimaging studies have addressed sexual inhibition, and most of those that have, did so by presenting VSS to subjects with low sexual desire. Some of these studies seem to indicate that sexual inhibition correlates with prefrontal hyperactivity in hypogonadal individuals,[31,80] and that this hyperactivity can be downregulated by testosterone treatment.[32] Studies of psychogenic hyposexual patients suggest that increased activity in ventral prefrontal[80,121] and dorsal parietal areas[121,122] and decreased activity in the middle cingulate cortex[121,122] are indicative of differences in sexual arousability relative to healthy controls. Interestingly, male hyposexual patients showed sustained superior parietal activity during an erotic video (and a failure to achieve erection), whereas control patients demonstrated a drop in superior parietal activity and a rise in middle cingulate and posterior insula activity in association with penile erection.[121] Indeed, volitional inhibition of sexual arousal in healthy men elevated neural activity in the superior parietal and ventrolateral prefrontal cortex.[102] These observations seem to suggest that sexual inhibition, be it intended or unintended, is related to exaggerated activity of components of the sexual interest network (including the amygdala, superior parietal lobule, and ventral prefrontal cortex). For some reason this prevents a shift to activation of areas belonging to the sexual consummation network (including the ventral pallidum, posterior insula, and middle cingulate cortex). Importantly, this implies that hyposexual patients might still be able to identify sexual incentives, but these incentives fail to produce a switch to the sexual consummation network.

Poststimulatory de-arousal (including that which occurs during the postejaculatory refractory period) also involves sexual inhibition. A partnered stimulation protocol in healthy men has shown that the amygdala, ventromedial prefrontal cortex, rostral cingulate cortex, and anterior hypothalamus were most active when the rate of penile detumescence was fastest.[78] This is similar to the areas activated in hyposexual individuals presented with VSS. In fact, the anterior hypothalamus is inhibitory to sexual arousal in male rats,[71] while functional connectivity between the anterior hypothalamus and the rostral cingulate cortex might be especially critical in arousal downregulation.[123]

Conclusions

We have finally started to get a better handle on the functional neurobiology of sexual behaviour. In broad terms, the brain integrates sensory sexual stimuli with the internal state, which in turn gives rise to unconditioned or learned expressions of sexual wanting, liking and inhibition. The restructuring of sexual behaviour —and other survival behaviours[124]—into these three phases is critical in order to achieve a meaningful species comparison; although introspection and subjective feelings are major topics in human research, it is impossible to know how animals perceive the world. The structure of the sexual pleasure cycle proposed here and elsewhere[6] renders such differences irrelevant and allows very different incentives and behavioural expressions displayed by animals and humans to be grouped under the same category. Human and animal studies have thus clearly elucidated the different phases and behaviours of the sexual pleasure cycle (Figure 4).

The evidence shows that sexual wanting in both rats and humans involves an interaction between gonadal hormone levels and external stimuli that become sexual incentives through association with sexual reward. The principal source of this reward is genital; in particular, the glans might be considered an extraordinary sensor for somatosensory stimuli that provide sexual reward. Human sexual behaviour involves balancing activity of distinct brain networks over distinct phases of the sexual response cycle, as well as sexual inhibition. As elucidated primarily by animal models, these phases are supported by quite distinct neurotransmitter systems.

Mesolimbic dopamine release is important throughout the pleasure cycle, but perhaps chiefly in sexual incentive motivation and sexual wanting. Human and rat studies seem to largely agree on this point, though the absence of nucleus accumbens activity during sexual consummation in humans is not in line with persistent nucleus accumbens activity in rats during elements of copulation. It is possible that the complex activity pattern of the nucleus accumbens across the pleasure cycle cannot yet be captured by functional neuroimaging methods, or perhaps the fact that rats constantly chase one another during

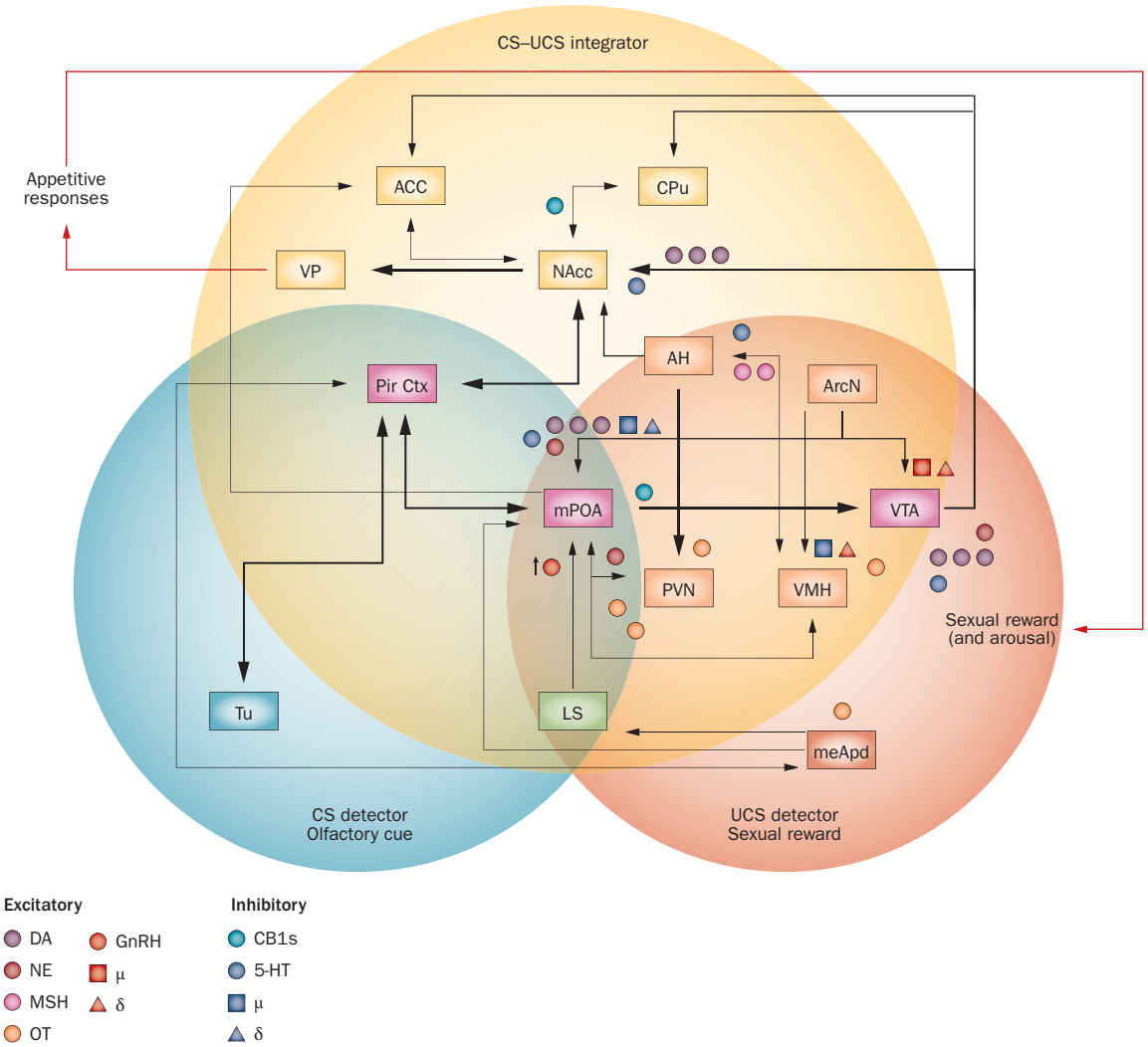

Figure 4 | Neural systems critical for the display of unconditioned and conditioned sexual behaviour in the rat. Appetitive behaviours made toward CS lead to sexual reward that is processed by three interactive systems. Two systems process olfactory stimuli and sexual reward relatively independently, whereas a third, mesolimbic DA system, acts to integrate both the conditioned olfactory cue and its rewarding sexual outcome (UCS). Three common regions, the Pir Ctx, mPOA, and VTA, are activated in male and female rats by conditioned olfactory stimuli. Opioid actions in the VTA potentiate mesolimbic DA activation, whereas opioid actions in the mPOA inhibit sexual arousal and motivation. Opioids can be excitatory in the VTA, inhibitory in the mPOA, or either in the VMH. DA, GnRH, MSH, NE, and OT are excitatory whereas 5-HT and endocannabinoids are inhibitory. Neurotransmitter systems or their receptors in red are excitatory for sexual motivation whereas those in blue are inhibitory. Abbreviations: 5-HT, serotonin; ACC, anterior cingulate cortex; AH, anterior hypothalamus; ArcN, arcuate nucleus of the hypothalamus; CB1, cannabinoid Type 1 receptor; CPu, caudate-putamen (striatum); CS, conditioned stimuli; DA, dopamine; δ, delta opioid receptors; GnRH, gonadotropin releasing hormone; LS, lateral septum; MeApd, posterior-dorsal nucleus of the medial amygdala; mPOA, medial preoptic area; MSH, melanocyte stimulating hormone; μ, mu opioid receptors; NAcc, nucleus accumbens; NE, noradrenaline; OT, oxytocin; Pir Ctx, piriform cortex; PVN, paraventricular nucleus of the hypothalamus; Tu, olfactory tubercle; UCS, unconditioned stimuli; VMH, ventromedial nucleus of the hypothalamus; VP, ventral pallidum; VTA, ventral tegmental area. Adapted with permission from © Pfaus, J. G., Ismail, N. & Coria-Avila, G. A. in *Encyclopedia of behavioral neuroscience (vol. 3)* (eds Koob, G., Thompson, D. & Le Moal, M.) 201–209 (Elsevier, New York, 2010).

copulation requires a continuously activated mesolimbic dopamine system.

Endogenous opioids are released primarily upon ejaculation in rats, which not only temporarily shuts down sexual wanting through manipulation of mesolimbic dopamine, but also creates the sexual reward state that is most efficient at driving future sexual behaviour through learning (Figure 4). Although this learning mechanism is supported by solid empirical proof in rats, in humans virtually nothing is known. Nevertheless, conditioning of sexual responses with pleasurable genital stimulation (without orgasm) is feasible in humans. Sexual stimulation without orgasm induces sexual liking as shown in both rats and humans, and it might be that high sympathetic arousal has an important role in both species. Serotonin is generally inhibitory to sexual responses in both species, which might explain the exaggerated prefrontal activity observed in people with low sexual desire.

Many of the same brain regions are active during human and rat sexual response cycles, including the hypothalamus, amygdala, nucleus accumbens, insula, cingulate cortex, and somatosensory cortex. However, in both species the collection of areas that is active at a given point depends on the phase of the sexual pleasure cycle. At least in humans, the shift from sexual wanting to liking induces a major shift in the balance between brain networks. Very similar network shifts can be found in other pleasure cycles, such as food-related behaviours, suggesting that dominant involvement of these networks reflects general behavioural phenomena.[6] Though the evidence is still limited, it seems that people are able to prevent this shift if responding to a sexual incentive stimulus is inappropriate. Conversely, perhaps sexual desire disorder could be explained by the failure to shift the balance between these networks when faced with sexual incentive stimuli, although obviously other explanations cannot be ruled out, such as negative associations with particular sexual incentive stimuli.

The reasons for the divergent changes in activity in brain areas, as well as brain network shifts, between animals and humans are potentially numerous. The most likely explanation is that humans use mental representations, introspective thinking, and empathy during their sexual pleasure cycle, whereas it is unknown whether this is the case for other animals. The human neuroimaging data discussed here have neither the spatial nor the temporal resolution to make comparisons with the neuroanatomical findings of animal studies.

Currently, animal models of the central control of sexual behaviour are much more advanced than human models. However, human neuroimaging techniques are developing very fast, and advances in both scanner hardware and analytic approaches promise to deliver, in the not-so-distant future, the tools necessary to understand the human central sexual system in a mechanistic way. Examples of such techniques include near-infrared spectroscopy and magnetic encephalography, which not only provide excellent (millisecond) temporal resolution but also allow for behavioural 'freedom' and natural interaction between sexual partners. Given the clear similarities between rat and human sexual response cycles outlined in this Review, we propose that paradigms conducted in, and results obtained from, animal research should guide future efforts in humans. In particular, human neuroimaging paradigms have virtually ignored the role of experience-based sexual learning, the role of contextual cues, and the putative role of genitally-induced sexual reward. Yet, it might be that identifying the mechanisms behind formation of sexual associations will be instrumental to understanding sexual phenotypes such as psychogenic sexual dysfunction and paraphilias.

So, what does the future hold? We hope that the theory of sexual incentive motivation (built around genital reward) will lead to new avenues of human sexual (brain) research, including the investigation of novel paradigms that investigate how the brain mediates sexual learning. Paradigms should be developed to study how the human brain deals with sexual novelty, habituation and expectancy. The human propensity to learn through observation seems particularly accessible with functional neuroimaging techniques. Finally, human sexual inhibition is currently underexplored. In particular, it would be of interest to understand the role of the prefrontal cortex in promoting sexual inhibition. Natural variations in sexual phenotype could be of major importance in all of the above suggested lines of research.

A deeper understanding of human sexual behaviour will only emerge when we get a grip on how the brain, at multiple neurobiological levels, deals with sexual stimuli, and how it interacts with its most important sensors. In time, we hope that this knowledge wil help to develop new and better treatments for sexual dysfunction.

Review criteria

We searched the Thompson ISI Web of Knowledge and PubMed databases. We used the key words "sexual desire", "penis", "clitoris", "vagina", "brain", "stimulation", "genital", "spinal cord", "fMRI", "neuroimaging", "dopamine", "opioids", "sexual inhibition", "learning", "conditioning". We selected publications on the basis of high reputation and quality, which means that we also referenced highly regarded older publications. We also searched the reference lists of articles identified by this search strategy. All papers referenced were published in English.

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