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The human sexual response cycle: Brain imaging evidence linking sex to other pleasures

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ABSTRACT

Sexual behavior is critical to species survival, yet comparatively little is known about the neural mechanisms in the human brain. Here we systematically review the existing human brain imaging literature on sexual behavior and show that the functional neuroanatomy of sexual behavior is comparable to that involved in processing other rewarding stimuli. Sexual behavior clearly follows the established principles and phases for wanting, liking and satiety involved in the pleasure cycle of other rewards. The studies have uncovered the brain networks involved in sexual wanting or motivation/anticipation, as well as sexual liking or arousal/consummation, while there is very little data on sexual satiety or post-orgasmic refractory period. Human sexual behavior also interacts with other pleasures, most notably social interaction and high arousal states. We discuss the changes in the underlying brain networks supporting sexual behavior in the context of the pleasure cycle, the changes to this cycle over the individual's life-time and the interactions between them. Overall, it is clear from the data that the functional neuroanatomy of sex is very similar to that of other pleasures and that it is unlikely that there is anything special about the brain mechanisms and networks underlying sex.

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Contents

Abbreviations: Amy, amygdala; pACC, anterior cingulate cortex, pregenual part; sACC, anterior cingulate cortex, subgenual part; ASL, arterial spin labelling; BOLD, blood oxygenation level dependent; Cb, cerebellum; Claus, claustrum; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; FO, frontal operculum; FBA/EBA, fusiform body area/extrastriate body area; HT, hypothalamus; IPC, intraparietal cortex; med-temp, medial temporal lobe; aMCC, middle cingulate cortex, anterior part; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; PERT, post-ejaculatory (orgasmic) refractory period; MI, primary motor cortex; SI, primary somatosensory cortex; SPL, superior parietal lobule; vmPFC, ventral medial prefrontal cortex; VP, ventral pallidum; vPMC, ventral part of the premotor cortex; VS, ventral striatum; vlOT, ventrolateral occipitotemporal; VSS, visual sexual stimulation.

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1. Introduction

Sex is costly as a reproductive strategy, yet crucial for the survival of species (Hamilton, 1964a,b; Morran et al., 2011). Across species there is a great diversity of behaviors associated with reproduction, and while much is known about the sexual behavior of other animals, human sexual behavior has remained mostly elusive.

Yet, sex is one of the driving forces of the human mind, and no other behavior is capable of raising controversy quite like sex. Indeed, sexuality issues such as same-sex attraction or sexual abuse are notorious for causing marked distress and unhappiness. Still, most of us would be inclined to agree that engaging in sexual activity is a source of immense pleasure. Moreover, sexual health and the pleasure gained from it positively predict general health outcome (Jannini et al., 2009), suggesting that there is much to be gained from understanding the underlying principles in order to be able to augment, or at least maintain, a certain level of sexual functionality.

Such underlying principles of sexual behavior must adhere to the adage that "the brain is the master organ of sexual function" (McKenna, 1999) and the focus on this review is to identify and outline the fundamental brain mechanisms. It is not, however, trivial to conduct sex studies in neuroimaging scanners (see Box 1) and there are significant limitations associated with these techniques (see Box 2).

The evidence clearly reveals that while there are some differences between sexual and other behaviors, there are in fact far more commonalities and interactions with pleasure cycles linked to other pleasures such as food.

1.1. The human sexual pleasure cycle and its relation to other pleasure cycles

The term *sexual behavior* is rather broad and includes all behavioral parameters related to sexuality, similar to how *eating behavior* can be construed to include the behaviors related to eating. An interesting feature of these survival-related behaviors is their cyclical nature, whereby the behaviors wax and wane in frequency over time as different goals are identified, desired and consummated (Kringelbach et al., 2012).

Thus, the core of sexual behaviors can be defined as the repeating cycle of events and behaviors that can lead to reproduction, collectively termed the *sexual pleasure cycle* or sometimes the sexual response cycle (Fig. 1). In some species the biological features are such that they can only enter the sexual pleasure cycle at certain times of the year, while other species such as humans have the possibility to initiate sexual behavior year round.

In order to enter this cycle, we must first be motivated to mate, a process that may be triggered by various biological and psychological cues (i.e. sexual incentive stimuli). With sexual desire in place, and given the appropriate context, there may be physical consummation (stimulation of engorged genitalia) of the sexual need, leading to excitation and higher arousal (which may plateau for a while), culminating in ejaculation and/or orgasm. At least in male adult humans, this triggers a period of satiety or transient sexual quiescence after which sexual responsivity can be regained.

The very idea of a predictable sexual pleasure cycle, which is more similar than different for everyone, is of course rather abstract. It may not capture the huge variety of sexual responses and there may be significant differences between men and women, especially related to the orgasm phase. Nevertheless, this model can be rather helpful when aiming to identify the commonalities and differences in the brain networks supporting the different phases of the pleasure cycle, as outlined below. In particular, the cyclical model is useful for identifying the most important nodes and hubs of brain regions driving the functional changes in the brain networks sustaining or switching between the different phases of the pleasure cycle which can lead to changes in behavior.

It will also be clear from the above description that the dynamics of the sexual response cycle are very similar to those

Box 1. Sex in the scanner

The study of the human sexual brain has barely begun. This is in stark contrast to the excellent animal models of sexual behavior available which provide very detailed neurobiological clues about human sexual behavior, not only with respect to its anticipatory (motivation) and consummatory (erection, ejaculation) aspects, but also with respect to cognitive functions like sexual inhibition and sexual learning (see Pfaus et al., 2012 for an excellent overview).

These animal models have some important advantages over current human models: First, animal sexual behavior can be studied in a relatively natural fashion, that is, one can allow animals to naturally interact with each other. Second, it is possible to perform investigations that would be considered unethical in humans, including interventions like genetic knock-outs or lesions, and paradigms that involve e.g. proto-sexual experiences. Third, the models not only provide very detailed neuroanatomical correlates of sexual behavior, but also reveal much of its neurochemistry.

Yet, given that higher-order brain functions critically associated with human sex like morality, introspection, and social learning are not – or poorly – developed in most other animals, it is important that we develop new models for the study of human sexual brain networks. Asking people is not particular informative since it is well known that people are prone to lie about their sexual preferences and habits.

Some valuable structural information can be obtained from brain injury and disease, but it is often not known whether the changes in sexual behavior are primary or secondary to the condition. Alternatively structural brain scans can be performed in normal participants, often using MRI to assess volumetric variations related to some sexuality trait, for instance sexual orientation. These studies do not require participants to achieve sexual desire, arousal or orgasm on demand, but obviously rely heavily on the validity and reliability of their subjectively stated preferences and behavioral sex assessments.

Functional neuroimaging offers a platform to register brain activity online, i.e. *while* subjects are engaged in some aspect of the sexual pleasure cycle, and this approach has been most influential in shaping our current understanding.

Using neuroimaging techniques to study the sexual brain involve major ethical and technical challenges. The lack of ecological validity of the scanner environment is a major obstacle. Still, as shown in this review, it is possible to make experiments with acceptable compromises in terms of research questions, paradigms, and scanning methods. Perhaps most importantly, it is important to take into account the full sexual response cycle, which may vary from one person to the next.

As shown in the review, the *anticipatory phase* has been mostly studied with visual sexual stimulation (VSS) designs (Fig. 2), mirroring the trend seen with in other emotional processing paradigms. Healthy and young heterosexual men represent the vast majority of participants. This bias is driven by practical issues and underlying assumptions such as the higher concordance between genital responses and reported sexual arousal in men, the absence of marked hormonal fluctuations or hormonal contraceptive use, and better accessibility of the male genitalia for behavioral arousal measurements (penis circumference and tumescence).

The main parameters for VSS relate to the content (single nudes and couples interacting), mode (still photos and videos), and duration (sub-seconds to minutes). Sexual interest and desire appear to be best investigated using brief presentations of single nudes, while actual sexual arousal calls for more explicit stimuli (porn video excerpts) and online measurement of genital arousal. Currently only a few studies include these important measurements, despite the fact that MR-compatible devices are available to measure penile circumference and tumescence, as well as vaginal vasocongestion.

The *sexual consummation phase* (arousal, genital stimulation, and orgasm) involves different, but also serious challenges. First, obtaining ethical approval is not easy given the taboos surrounding sexual behavior. Experiments using actual sexual activity appear to be less ethical acceptable than experiments using visual erotica. Second, recruiting normal participants is difficult. Third, with genital stimulation, and especially orgasm, head motion becomes a major issue. While self-stimulation is less complex from a logistical (and perhaps ethical) point of view, it is also more likely to induce strong head movements. Partnered stimulation requires more elaborate preparatory procedures but results in a more realistic sexual setting, and, critically, less head motion. Thus far, partnered genital stimulation paradigms have followed the path of manual stimulation, but this still ensures that identified networks reflect sexual *interaction*. Recent adaptations of this approach include less instructions, enhanced autonomy on the part of the participating couple, less time pressure, and additional online objective and subjective measurements of sexual arousal.

involved in eating behavior (Kringelbach et al., 2012). The feeding pleasure cycle involves motivational (hunger) and consummatory (eating) stages, as well as processes that lead to termination of food intake (satiation, satiety; see Fig. 1). Interestingly, the motor repertoires supporting sexual and eating consummatory behavior, such as for example vaginal thrusting or chewing food, typically involve a high degree of rhythmicity.

Other similarities between the sexual and feeding cycles include how novelty plays an important role. The almost complete loss of sexual motivation immediately after ejaculation is similar the loss of interest in food after a copious meal. Yet, this loss of motivation need not be complete, and the introduction of novel foods may more rapidly reinstate interest for the food (Rolls et al., 1984; Weingarten, 1983), depending on satiety strength. Experimental rodent studies strongly suggest the same situation for sex (Fiorino et al., 1997), though this has never been shown empirically in humans. Certainly, the idea of selective satiation for foods will be familiar to anyone who still has room for dessert after a large main course.

In addition, learning and prediction are central to both sex and food. The very early experiences of food are important for shaping our food preferences and equally proto-sexual experiences are very important in shaping the adult sexual phenotype (Pfaus et al., 2012; Woodson, 2002). Though in the typical pleasure cycle, learning is perhaps most strongly associated after the pleasure is experienced (depicted in Figs. 1 and 6), learning from sex is by no means limited to orgasm or to pleasure. Though orgasm is probably most efficient in this regard, any sexual activity that induces positive or negative affect may be capable of instigating learning mechanisms.

Yet, for all these important similarities between sex and food cycles, there are also interesting differences. First, no one dies from a lack of sex. A second striking difference is the onset of when the full cycle becomes available. Food behavior needs to be ready from birth to aid survival, while the sexual cycle is not needed until puberty and sexual desires are therefore normally largely dormant until puberty. The desires related to food, sex and social pleasures thus vary substantially over an individual's lifetime (Fig. 2).

Other important distinctions are more closely related to the specific nature of the pleasure cycles. First, the pleasure felt during sexual consummation typically increases towards satiation,

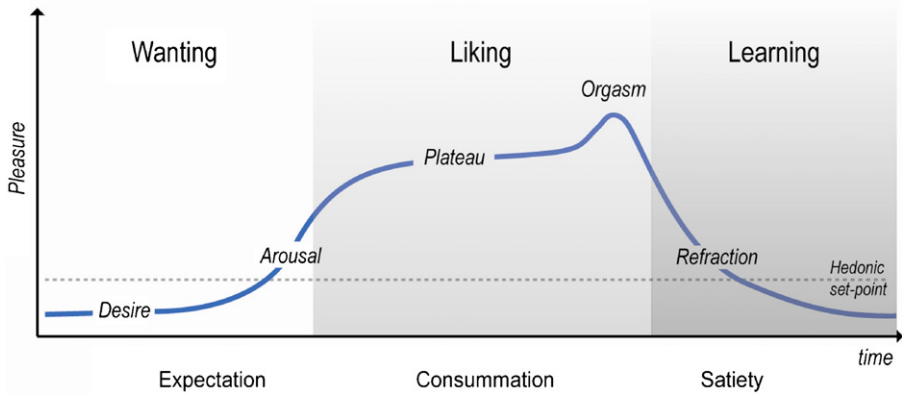

Fig. 1. The sexual pleasure cycle. In the adult human, different pleasure stimuli can elicit sufficient interest for an individual to enter into the appropriate pleasure cycle. This cycle typically exists over a relatively short time span lasting from minutes to hours and may or may not involve part of all of the wanting, liking and learning phases of the cycle. Sexual stimuli will typically elicit desire, leading to arousal and perhaps, if given the appropriate context, consummation. Orgasm can play a part of the consummatory phase and as such, especially in men, may signal the transition to the satiety and satiation phase, which may temporally stop the individual from entering the cycle again. Please note that learning occurs throughout the cycle and that while orgasm appears to be most effective in driving learning processes, sexual learning may thus also occur as a result of sexual experiences involving incomplete sexual response cycles (e.g. if orgasm is not achieved).

reaching its peak in orgasm. This is often not the case during eating – and can at times become reversed such that the first bite is most pleasurable. Hence it is quite possible to prolong sexual activity without becoming satiated as seen in certain sexual practises. Second, the very object of sexual desire is normally other people, i.e. potential sexual partners whether real or imagined. This is not normally the case for food intake, although food usually tastes better when shared with other people. Third, female sexual pleasure does not necessarily conform to all stages of the proposed sexual cycle since female genital anatomy predicts orgasm consistency during copulation to be lower in women than in men (Levin, 2002, 2009; Lloyd, 2005). Finally, gender-specific motor patterns, like those associated with male and female copulatory roles, are not prominent in eating (although social and cultural influences do shape gender roles in eating). Note, however, that these roles are not fixed and that men and women are capable of assuming different sex roles through learning.

Food and sex are among the most basic of all pleasure cycles because they contribute directly to individual and species survival. However, pleasures come in many guises, including non-sensory likings, pleasures of gain and relief, achievement pleasures, social pleasures, activity pleasures, and aesthetic pleasures (Frijda, 2010; Kringelbach and Berridge, 2009). Of those, social interaction is of particular interest to sexual behavior. Solo sexual activity like masturbation does include the entire sexual response cycle, but is often perceived as less pleasurable than – or as a surrogate for – intimate sexual interaction with another person. Thus, intense social interaction amplifies the pleasure gained from sex, which may be related to the evolution of face-to-face sexual interaction (see more in Section 6.2).

Pleasures that involve marked elevations of sympathetic autonomic activity ('rush', 'high'), like physical activity, or certain drugs and music, are important tools to understand the fundamental nature of pleasure (see more in Section 6.3). Sexual activity is a case in point with high arousal as a defining feature (Weil et al., 2010), especially perhaps during orgasm (Mah and Binik, 2005). As such the everyday nature of sexual interactions are highly relevant, because they suggest that there must be substantial overlap between sex and other pleasure cycles in terms of their neurobiological underpinnings.

1.2. Human sexual behavior is a complex interaction between biology and culture

Sexual behavior is a powerful force that ensures survival but is tightly regulated in all human societies. The biological mechanisms underlying sexual behavior are constrained and changed by these cultural forces.

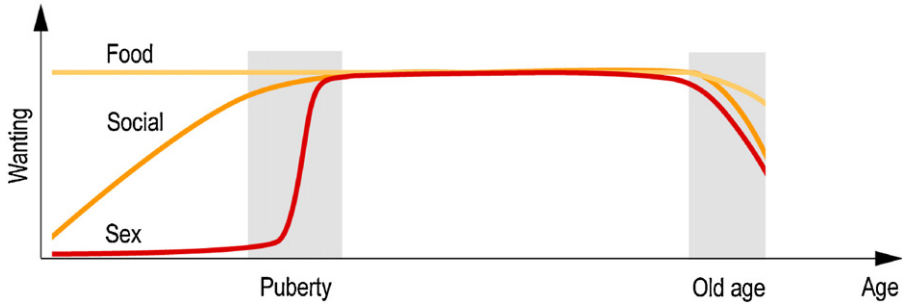

Fig. 2. Life-time evolution of the incentive values of different pleasures. The interest and incentive values of the three main classes of fundamental pleasures evolve over the lifetime of an individual. This allows for the individual to enter into and experience the full pleasure cycle of food, sex and social pleasures. Food wanting is invariably present from birth as this ensures survival, while the social pleasures become more and more important during childhood. At first, the infant will mostly take pleasure in interacting with the primary caregiver but over time interest is slowly extended to a larger peer group. The timecourse for sex is significantly different in that sexual interest is not present at birth but normally only develops during puberty and then rather rapidly. There are natural variations in the interest in different stimuli as the individual tries to balance exploration and exploitation, i.e. find a balance between novel and existing sources of pleasure. Mental illness and the accompanying lack of pleasure, anhedonia, can also significantly change the interest in pleasure over shorter and longer periods. With old age, there is some evidence that the interest in pleasure slowly wanes and that the balance between exploration and exploitation becomes shifted strongly towards the latter.

In general, in all species that employ sexual reproduction, sexual behavior needs to be adaptive, but in humans this versatility interacts with higher human brain functions such as morality. Cultural variations in sexual mores invariably create tension across cultures. Take the practices of 'wife lending' amongst the Inuits or cousin marriage in parts of Asia. Seen from a European cultural context, such practices are considered immoral, yet they might prove to be highly adaptive if seen in the context of environmental factors. In the first case, isolated tribes could potentially benefit from genetic diversity (Kjellström, 1973), whereas, in the second case, inbreeding could be a successful way to build genetic resistance to serious life-threatening diseases such as malaria (albeit at a high cost) (Hoben et al., 2010).

Another defining feature of human sex is that it is confined neither to a particular time of the year nor to the time around female ovulation. Though there is ample evidence that women's sexual interest and sexual attractiveness peaks around the time of ovulation (e.g. Mass et al., 2009; Penton-Voak et al., 1999; Stanislaw and Rice, 1988), it seems safe to state that the relationship between sex and reproduction is less straightforward in humans than it is in any other animal. Yet, as shown in the previous paragraph, this complex relationship gives rise to many cultural practices and formal instructions about sex. In large parts of the world it is even possible to gain (almost) complete reproductive control (and therefore recreative 'freedom') through the use of hormonal and other means of contraceptives. Combined with the virtues of human intelligence, creativity, and precise motor control, human sex is full of practices not aimed at reproduction, while such behavior is rare in most other mammals.

Hence, human sex allows – or maybe even requires – a strong interaction with higher-order brain systems. For instance, the social cognition systems that help us understand other people's actions probably also allow us to become sexually excited by the sight of other people engaged in sexual activity, an ability that feeds a multi-billion dollar porn industry. Clearly, there are countless routes to sexual responsivity, as there are countless cues that may trigger sexual motivation.

Human sexual behavior is thus rather complex. In humans, it is the product of complex interactions between both fundamental biological and cultural mechanisms. Sex is intensely social and as such thrives on complex self-projection, that is, individuals must consider social boundaries and frameworks in relation to one's personal sexual reference and past experiences. This also explains why feelings of shame and guilt, which typically deal with this relationship, are strongly linked to sexuality. The shame felt by those who have suffered sexual abuse is a particularly sad example of this (Feiring et al., 2010).

Overall, human sexual behavior is perhaps best viewed in the light of the dramatic increase in relative brain size and complexity, especially of the frontal regions of the human brain, and associated increased behavioral sophistication that characterizes human evolution (Beach, 1947). In other words, human brain evolution predicts human sexual behavior to be intrinsically more complex than that of other animals. Yet this complexity is not necessarily limited to the brain but can, interestingly, also be predicted from the major anatomical changes during human evolution, like the transition to an upright bipedal position and associated impediments in vaginal accessibility.

1.3. Outline of review

In the following we provide a comprehensive review of our current knowledge of the human brain networks involved in the different phases of the human sexual response cycle, from evoking desire over consummation and orgasm to satiation.

Box 2. Limitations of the neuroimaging of sex

This review covers studies conducted with a number of different neuroimaging methods, most notably functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), since these techniques offer the necessary spatial information to identify brain networks with a reasonable degree of anatomical specificity. However, there will be a set of limitations imposed by hardware and acquisition protocols, some of which hinder what most people would define 'normal sexual behavior'. Importantly, both PET and fMRI have low tolerance when it comes to bodily motion. The scanner design involved for both techniques also largely precludes normal body-to-body sexual interactions.

PET can only be used sparingly since it can potentially lead to significant radiation side-effects. The PET scanner is silent but involves the need for an intravenous injection in the forearm. Because of the half life of the radioactive compounds used, continuous scanning is impossible, and scans are typically separated by 8–10 min of resting.

While MRI has not been been found to elicit significant potential side-effects (at least at low field strengths), the MRI scanner is a cramped and very noisy place.

In terms of measuring in vivo brain neuroanatomy, MRI has excellent spatial resolution which increases with higher field strengths. White matter can be investigated with diffusion tensor imaging (DTI) which is an MRI technique that measures the diffusion of water molecules in tissue. It produces images of white-matter tracts in the brain, allowing analysis of their density and maturation between different populations.

In terms of measuring changes in functional neuroanatomy, PET and fMRI can both be made sensitive to the haemodynamic responses, i.e. make measurements of changes in blood flow, volume and oxygenation. These are in turn linked in yet to be determined ways to actual neural activity in the human brain. Blood oxygenation changes are the major contributor to the so-called BOLD (blood oxygenated level dependent) signal, which can be measured with MRI and has become the dominant neuroimaging acquisition. However, BOLD is not suitable for experiments that encompass long, unpredictable stimulation epochs, slowly developing states, or above-average subject motion, as is the case with human sexual response cycle. A promising alternative is a technique called arterial spin labeling (ASL) which is a fMRI acquisition that performs much better under long and unpredictable experiments (Wang et al., 2003), albeit at the cost of temporal resolution.

PET and fMRI both measure 'slow' haemodynamic responses which are the indirect traces of pooled activity over many seconds. In addition, fMRI paradigms typically involve many repetitions in order to achieve sufficient statistical power.

Other neuroimaging techniques include electroencephalography (EEG) and magnetoencephalography (MEG). EEG directly measures electrical neural activity with high temporal resolution, but often provides insufficient spatial information to localize brain networks. The related MEG technique measures magnetic signals induced by electrical activity in the brain and provides better spatial resolution than EEG, whilst maintaining high temporal resolution. This is a technique with much promise which has not yet been used in sex studies.

The temporal resolution of both fMRI and PET does not come close to the milliseconds oscillations in human brain activity. PET scans typically measure activity over 1–2 min, while fMRI protocols measure signals over 1–2 s. PET also suffers less from the signal artefacts caused by e.g. MR hardware or subject motion.

These limitations mean that there are significant problems associated with trying to measure state changes in the sexual pleasure cycle. For example PET and fMRI are far from ideal when trying to capture the state transition in the brain networks involved in orgasm, given that the sequence of orgasmic events happens over seconds and often involves

excessive head motion with the likely potential to destroy the measured signal.

With regards to the brain changes reported in the studies reported in this review, it is important not to fall into the all too common trap of neo-phrenology. Significant changes in a brain region should not be interpreted such that this or that region is solely responsible for a certain behavior or phase of the sexual pleasure cycle. Rather it is important to realise that brain activity should be viewed in the full context of the dynamical brain changes driving behavior.

This is one of the main reasons why this review uses the sexual response cycle as a structuring device in order to understand the functional neuroanatomy of sex. The neuroimaging findings reflect changes in activity in important nodes and hubs of the brain that are responsible for sustaining or changing the balance between different resting state networks and associated behavior that will vary depending on the different phases of the sexual response cycle. Furthermore, it is important to acknowledge the inherent limitations with neuroimaging which can sometime give misleading and biased results. The results of different studies often use different analysis tools with different statistical thresholds, which may or may not be appropriately corrected to allow for inferences to be drawn to the general population. For this reason we primarily report main effects, i.e. changes in brain regions which are robustly linked to the main study effect. When appropriate we include correlations with subjective and behavioral measures but the reader needs to be aware of the potential for spurious and biased post hoc correlations (Kriegeskorte et al., 2010).

A full understanding of the nature of the functional neuroanatomy of sex is only likely to emerge if all these limitations and potential confounds are taking into account.

First, we review the evidence from neuroimaging studies using different sensory modalities of which most studies have used visual stimuli. We note that while the other sensory modalities are underexplored in the study of human sexual behavior, this may provide exciting avenues for future research. Second, we discuss the neuroimaging findings from the normal consummatory sexual phase, elucidating the brain networks involved in sexual genital stimulation and orgasm in men and women. This is followed by an overview of the brain networks involved in the satiety phase, the so-called 'post-orgasmic refractory period' which is an understudied part of human sexuality. We then review important variations in sexual interest as elucidated by findings related to same sex preference, hyposexual desire and paedophilia.

Finally, we synthesize the findings of the brain networks involved in the human sexual pleasure cycle to provide a comprehensive overview of the functional neuroanatomy involved in human sexuality, which is then compared to other related pleasure cycles involving food, drugs, music, and other people.

2. Wanting: Sensory gateways to sexual interest and arousal

The first phase of the sexual response cycle involves generating a desire or wanting for the particular rewards that can lead to reproduction. This wanting phase is thus partly dependent on sensory triggers and partly on learned, internal cues. The evidence strongly suggests that wanting is associated with the release of dopamine and that wanting is different from liking in terms of the underlying neuroanatomy (Berridge, 1996).

The primary sensory systems can act as important triggers for initiating the human sexual response cycle. This multi-stage recurrent processing changes over time; first using the primary sensory cortices to decode object features, such as identity and spatial location, which are then integrated into multimodal representations in secondary cortical regions. These representations are then evaluated for reward and saliency in higher-order brain networks. In the following we review the evidence from neuroimaging of this processing with a special focus on determining similarities and differences between erotic and other sensory stimuli.

2.1. Auditory, olfactory, gustatory and somatosensory routes

All of the sensory systems offer potential routes to sexual responsiveness. While most human brain imaging studies focus on visual sexual stimulation, this is primarily a reflection of the limitations, challenges and traditions imposed by the neuroimaging environment and community.

The olfactory path to human sexual responsiveness is elusive, yet interesting. Perfume commercials strongly exploit the erotic connotation of scent, which is driven by the biological function of putative volatile sex-specific odours called pheromones. Studies using attractiveness ratings for smell show that men and women are susceptible to pheromones and rate the opposite sex as more or less attractive, depending on their hormonal state and the hormonal state of the opposite sex (Mostafa et al., 2012). Yet, it is presently not clear how pheromones enter and influence the human brain (Van Hartevelt and Kringelbach, 2012).

In many animals the vomeronasal organ is believed to be an important gateway to the brain for species-specific behavior including sex. The observation of synchronization of the menstrual cycle in women living together suggested a similar function of the vomeronasal system in humans. However, recent evidence makes this hypothesis less likely given that the human vomeronasal organ contains very few neurons. Most cells express keratin proteins, specific markers for epithelial cells and no cells express olfactory marker protein (Mast and Samuelsen, 2009).

Additionally, no evidence has been found for a neural connection between the vomeronasal organ and the accessory olfactory bulb, a specific region of the olfactory bulb. Even the presence of an accessory olfactory bulb in humans is doubtful. Studies investigating the role of the vomeronasal organ in pheromone detection have shown that androstadienone is detected by the olfactory epithelium and not the vomeronasal organ. Individuals with functional occlusion of the vomeronasal organ or without a visible vomeronasal organ showed no difference in perception or detection of androstadienone compared to controls (Mast and Samuelsen, 2009).

Note, however, that the notion that the human vomeronasal organ is not functional does not imply that humans are unable to detect pheromones or social chemical signals. Detection of pheromones could be achieved through the olfactory epithelium in a similar way as in the olfactory system in mice.

A series of PET studies have suggested that (artificial) pheromones can change the activity in the hypothalamus in a sexual orientation-specific way (Berglund et al., 2006, 2008; Ciumas et al., 2009; Gulyas et al., 2004; Jacob et al., 2001; Savic et al., 2001, 2005).

Recent advances to these findings include the use of fMRI and more naturalistic stimuli (male sexual sweat), providing more convincing evidence for distinct involvement of the anterior hypothalamus in processing male pheromones in heterosexual women (Zhou and Chen, 2008). Importantly, smelling pheromones also changed activity in regions beyond the hypothalamus, including amygdala, occipitotemporal cortex, and orbitofrontal cortex (OFC) (Berglund et al., 2006; Gulyas et al., 2004; Savic et al., 2001; Zhou and Chen, 2008). As shown in the next sections on visual processing, this network of brain regions is also strongly implicated in processing visual erotica, suggesting that sexually-salient odours are another route into the same brain network. In both cases, activity of this network may serve to allocate attention resources for a state of readiness needed to prepare for further

exploration of the potential mate, which in turn may eventually lead to sexual arousal and consummation.

Touch is another highly interesting modality given the hedonic properties of particular classes of skin receptors, which seem to be abundant in the so-called erogenous zones. It has recently been demonstrated that pleasant touch in humans is served by a system of low-threshold mechanoreceptive tactile C-afferents (CT-afferents) that project to the insular and orbitofrontal cortices (Löken et al., 2009; Olausson et al., 2002). When hairy skin is stroked at speeds corresponding to a caress, the CT afferents increase their firing rate proportional to the subjective ratings of pleasantness (Löken et al., 2009). It is not currently known whether these receptors are found on the genitals and other erogenous zones.

Nevertheless, nipple stimulation has been found to lead to sexual pleasure (Levin and Meston, 2006) which is particularly intriguing given its original function in early development during breast feeding and mother–child bonding, adding evidence to the idea that other pleasures may augment sexual pleasure. Neuroimaging studies of genital touch have been performed either outside an erotic context (Kell et al., 2005; Mäkelä et al., 2003; Michels et al., 2010; Pukall et al., 2005) or in the context of sexual stimulation with high sexual arousal and orgasm (Georgiadis et al., 2006, 2010a; Georgiadis and Holstege, 2005).

Unimodal auditory stimuli with erotic content have to our knowledge only been used in one study so far, which found that the auditory erotic stimulation led to enhanced recruitment of the auditory cortices (Miyagawa et al., 2007), much in the same way the visual cortices have been shown to be recruited in visual erotica. Clearly, there is much room for progress in this area, as hearing just an erotic voice – or erotic content – is a very effective means of instigating sexual arousal.

To the best of our knowledge gustatory erotic stimuli have not yet been used in neuroimaging. The aphrodisiac effect of gustatory stimuli is mostly anecdotal in humans, but the sexual repertoire of male *drosophila* relies heavily on their probing of gustatory cells present on the abdomen of the female (Koganezawa et al., 2010). Given numerous similarities between eating and sex (see further in Section 6.1), one would expect gustatory stimuli to have the potential of initiating the sexual pleasure cycle in humans as well.

2.2. The visual route

The overwhelming profits made by the porn industry probably best illustrate the strong visual bias in human sexual behavior. Exquisite and robust recognition of visual sexual cues is a quality shared by all primates, which is seen for instance in the way sexual colouration drives mate selection in some monkey species (Ghazanfar and Santos, 2004). Indeed, visual erotic content readily captures the brain's attentional resources, perhaps even more so than aversive visual stimuli (van Lankveld and Smulders, 2008). Sexually-salient visual features also readily tap into the brain's motivational circuits, which can be seen as a biological necessity in the face of sexual opportunity. This could explain intriguing observations of very rapid decoding of visual erotic stimuli outside conscious awareness (Childress et al., 2008; Jiang et al., 2006).

Because of the strong visual bias in human perception most brain imaging studies in the sexual domain have turned to visual sexual stimulation (VSS) paradigms to gain access to central mechanisms mediating sexual desire and arousal. These studies have provided interesting, though often puzzling, findings, which is perhaps not surprising given the large variety of visual images that are not always well-controlled. On the one hand, there is ample evidence for subcortical involvement, which is interesting as it may be the only tangible link with rodent models of sexual behavior. On the other hand, watching erotica likely requires multiple levels of central processing, involving not only subcortical brain areas but also neocortical systems that have unknown counterparts in other animals.

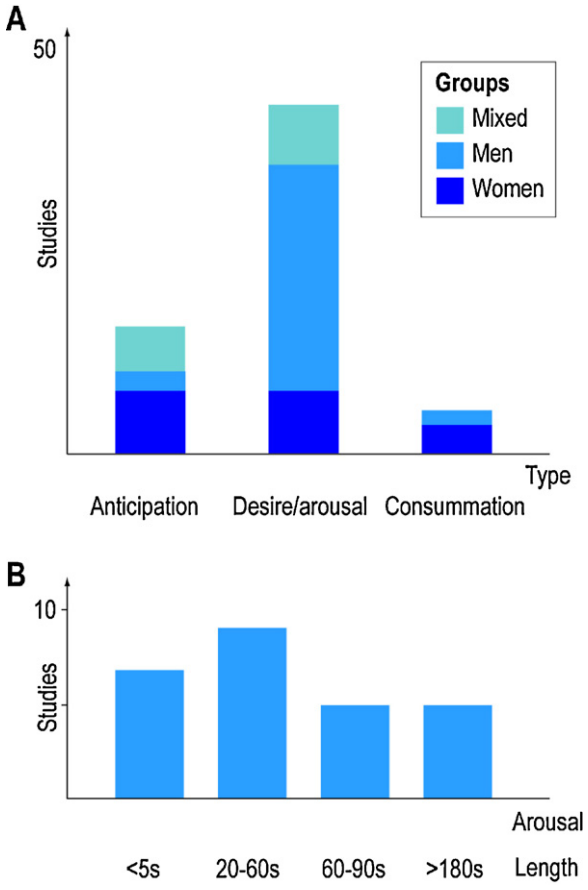

Fig. 3. Categorizing sexual neuroimaging studies. (A) Our comprehensive review categorizes the included studies in three different categories: (1) Anticipation without sexual arousal (studies measuring sexual, preference and salience using visual, auditory, and olfactory stimulation), (2) Desire with or without sexual arousal (Visual sexual stimulation, VSS, studies), and (3) Consummation (studies with genital stimulation and orgasm; partnered and self-stimulation). Colours refer to gender of the groups: men (light blue), women (dark blue), mixed men-women (light green). (B) The largest category (VSS in heterosexual men) is further analyzed. Studies with short VSS epoch lenghts mostly used photos of single nude women, whereas long VSS epochs usually comprised porn videos of couples. Typically short stimulus duration led only to sexual interest/desire, while longer stimulus duration also led to sexual arousal.

In the following, we will outline the consistent brain findings that can be distilled from the studies in the literature (Fig. 3), first focusing on heterosexual men which is the most studied group. We then compare the responses in heterosexual males to the VSS-induced brain responses in other groups (e.g. women). Note also again that various limitations and potential confounds should be considered. The visual erotic and control stimuli vary enormously across studies (Fig. 3B) and were not always well controlled in terms of e.g. visual features and duration times. The reported changes in brain activity could thus equally reflect these uncontrolled factors rather than main effects. Any changes are also likely to reflect only the most important nodes and hubs of brain regions that are driving the functional changes in the brain networks sustaining or switching between the different phases of the sexual response cycle.

2.2.1. VSS in heterosexual men: Early object processing

It is paradigmatic in neuroscience that the early parts of visual processing is a multi-stage process, reflecting the different aspects of the visual stimuli such as spatial location and identity which are thought to be spreading from the primary visual cortex in the back

of the brain via dorsal and ventral routes, respectively (Milner and Goodale, 2008).

The ventral visual stream includes ventral and lateral occipitotemporal cortices (vlOT). Like other emotional stimuli (Mourao-Miranda et al., 2003; Sabatinelli et al., 2004) erotica readily evoke occipitotemporal responses, even when compared to control stimuli that match the VSS for some confounding elements like colour or number of participants (Buhler et al., 2008; Ferretti et al., 2005; Hamann et al., 2004; Redouté et al., 2000; Schiffer et al., 2008b; Walter et al., 2008a). Further, while the vlOT responds to very brief VSS presented outside conscious awareness (Oei et al., 2012), the strength of the vlOT response also tracks with external factors like VSS duration (Buhler et al., 2008), and internal factors like the level of plasma testosterone (Stoleru et al., 1999). The exquisite occipitotemporal sensitivity to sexual features is further underlined by the finding of fast (<200 ms) event-related potentials recorded over this area that distinguish between nude and barely dressed women (Hietanen and Nummenmaa, 2011) and between desired and non-desired sexual stimuli (Ortigue and Bianchi-Demicheli, 2008).

Eye tracking studies have demonstrated that men watching VSS attend mostly to female genitalia, faces and bodies (Rupp and Wallen, 2007). It is well-known from other studies that brain regions that preferentially respond to body parts and bodily shape are located on the lateral fusiform and ventrolateral inferior temporal gyrus (fusiform body area and extrastriate body area, FBA/EBA) (Downing et al., 2001; Orlov et al., 2010), whereas neurons responding to faces are located more medially (Kanwisher et al., 1997). VSS paradigms consistently give rise to changes in activity in these occipitotemporal areas, especially when the VSS consisted of movie excerpts of explicit sexual interactions (Buhler et al., 2008; Ferretti et al., 2005; Paul et al., 2008; Redouté et al., 2000). According to a recent brain imaging meta-analysis of action observation and (mental) imitation paradigms (Caspers et al., 2010), an area corresponding with the location of EBA/FBA shows a clear bias towards action imitation, a propensity it shares with the ventral part of the premotor cortex (vPMC) and the intraparietal cortex. Other areas like the superior parietal lobule and dorsal premotor cortex are tuned towards action observation (Caspers et al., 2010).

This literature on the brain processing of faces and bodies and the link to action observation and imitation is highly relevant for understanding VSS-induced activity patterns. First, all of these areas are very often activated by VSS paradigms (Section 6.3). Second, the brain responses to photos of nudes and explicit movies depicting couples reflect some of the anatomical segregation between action observation and imitation networks, respectively (Caspers et al., 2010). Areas vicariously recruited when participants perceive and understand the emotional states of others include the vPMC, anterior insula, intraparietal cortex, and vlOT (Keysers and Gazzola, 2009), a constellation of areas that overlaps considerably with the action imitation network (Caspers et al., 2010), and with areas biased towards video/couples VSS processing (Buhler et al., 2008; Ferretti et al., 2005; Paul et al., 2008; Redouté et al., 2000). Note that video/couples VSS is most likely to induce sexual arousal in subjects (see Box 1).

In other words, the fact that erotic movies are generally perceived as highly arousing may be due to the fact that these classes of visual images are highly likely to give rise to changes in brain imitation of the sexual scenes.

2.2.2. VSS in heterosexual men: Subcortical effects

The cortical changes in activity related to VSS are invariably accompanied by subcortical changes in activity. Perhaps the most consistent finding is that the ventral striatum including the nucleus accumbens (VS/NAcc) is active both exclusively and consistently in studies that entailed relatively short presentations of still erotic images, primarily depicting single nude women (Childress et al., 2008; Ferretti et al., 2005; Hamann et al., 2004; Heinzel et al., 2006; Klucken et al., 2009; Oei et al., 2012; Ponseti et al., 2006; Safron et al., 2007; Sartorius et al., 2008; Schiffer et al., 2008b; Sescousse et al., 2010; Stark et al., 2005; Walter et al., 2008a).

Interestingly, the VS/NAcc has not been found to be active during movie clips depicting couples having sex and does not appear to correlate with subjective or genital indices of sexual arousal. On balance, the evidence points to the VS/NAcc being primarily involved in early rather than later stages of the human sexual response cycle. Yet, it is important to realize that fMRI and PET provide indirect measures of brain activity and that the lack of significant activity in a brain region is not necessarily informative with regards to the actual brain activity (see Box 2).

One neuroimaging study tried to extract specific erotic effects from VSS-induced brain responses, and found that the VS/NAcc could be dissociated from processing general elements such as 'nakedness' and 'arousability' (Walter et al., 2008a). This line of evidence is supported by VS/NAcc responses to preferred relative to non-preferred aroused genitalia (Ponseti et al., 2006) or erotic interactions (Stark et al., 2005). Interestingly, the VS/NAcc region was active following presentation of a geometric figure predicting a subsequent erotic image, but only in participants who were aware of this contingency (Klucken et al., 2009). This finding emphasizes the role of the VS/NAcc as being involved in conditioning of, and making internal predictions about, erotic stimuli, i.e. sexual learning.

A recent study confirmed this finding, showing that the VS/NAcc not only processed the hedonic value related to female nudity, but also the reward prediction error (difference between expected and received outcomes) (Sescousse et al., 2010). Importantly, the same study made clear that the VS/NAcc also processed the prediction error related to monetary gains, arguing against specific erotic processing in the VS/NAcc (Sescousse et al., 2010). Similar conclusions can be drawn from a study using subliminal presentations of a number of salient stimuli, demonstrating the sensitivity of the VS/NAcc to rewarding stimuli regardless of sexual load (Childress et al., 2008).

Thus, VSS-induced VS/NAcc responses strengthen theories that place its function in the context of anticipation, motivation, and desire (Berridge, 1996; Jensen et al., 2003). Assuming that dopamine neurotransmission mediates these hemodynamic responses seems reasonable given that the VS/NAcc is a major target of midbrain dopamine. Indeed, variations in dopamine-related genes both predict ventral striatum responsivity (Forbes et al., 2009; Yacubian et al., 2007) and sexual motivation, the latter indicated by reports about the number of sexual partners (Guo et al., 2007) and age of first sexual intercourse (Guo and Tong, 2006). A very recent fMRI paper provided further proof, demonstrating that VS/NAcc responses to subliminally presented VSS are enhanced by the dopamine agonist levodopa and depressed by the dopamine antagonist haloperidol (Oei et al., 2012).

Another important region is the amygdala where the responses are largely similar to those found in the VS/NAcc. These findings support the notion that the amygdala is a putative area for rapid and robust detection of salience, including 'hidden' sexual signals, (Childress et al., 2008; Savic and Lindstrom, 2008). Further, most studies found that the amygdala is rarely associated with subjective sexual arousal or genital responses. These similarities in the activity in the amygdala and VS/NAcc are supported by the existence of strong anatomical (McDonald, 1991) and functional (Passamonti et al., 2009; Stuber et al., 2011) connections between the two areas.

Despite their putative coupling in the context of reward-seeking behavior (Passamonti et al., 2009; Stuber et al., 2011), amygdala and VS/NAcc contributions in the context of human sexual behavior also differ in important ways. Emotional memory strongly depends on amygdala function (Roozendaal et al., 2009), which is seen in enhanced recall of erotic stimuli predicted by the level of VSS-induced amygdala activity recorded four weeks earlier (Hamann et al., 1999). Another difference is that whereas the VS/NAcc does not distinguish between erotic and monetary stimuli (Sescousse et al., 2010), the amygdala shows a clear preference for primary over abstract reinforcers (Knutson et al., 2001; Sescousse et al., 2010) and punishers (Moll et al., 2005). Conversely, processing the reward prediction error, which relies heavily on expectation, does not seem to depend on amygdala function (Sescousse et al., 2010).

The hypothalamus is another important region. In animal research sub-regions of the hypothalamus have been connected to virtually all phases of the sexual response (Pfaus, 2009; Veening and Coolen, 1998). In humans too, hypothalamus involvement has been reported in a variety of studies, including those focusing on sexual encoding and sexual interest (Brunetti et al., 2008; Childress et al., 2008; Paul et al., 2008; Safron et al., 2007; Stark et al., 2005; Walter et al., 2008a), as well as those searching for brain responses related to sexual arousal and penile tumescence (Arnow et al., 2002; Brunetti et al., 2008; Karama et al., 2002; Miyagawa et al., 2007; Paul et al., 2008). Most of these studies do not have the required spatial resolution to reliably resolve hypothalamic nuclei and it is thus entirely possible that different clusters of neurons were involved in these different aspects of sexuality. For instance, the paraventricular nucleus most likely controls the hormone release implicated in sexual arousal (Burri et al., 2008), whereas neuronal density in a subpopulation of the preoptic area is associated with same sex preference (Swaab et al., 2001).

Effects reported in other subcortical areas like the midbrain, thalamus, and dorsal parts of the striatum are more difficult to interpret. Walter and colleagues focused on thalamic function associated with VSS, using very high resolution (7 T) fMRI, and were able to identify distinct thalamic nuclei associated with sexual expectancy (intralaminar, centromedian, parafascicular) or general arousal (mediodorsal). The head of the caudate was connected with both elements of VSS processing, and both the thalamic nuclei and the caudate nucleus showed functional associations with cingulate and insular cortex (Metzger et al., 2010; Walter et al., 2008b).

2.2.3. VSS in heterosexual men: Evaluative reward processing

Following early processing of visual features such as object identity and spatial location, the brain evaluates the visual stimuli in terms of reward, salience and their potential to cause behavioral change. This important evaluative processing takes place in subcortical and higher-order cortical regions of the human brain.

This difference between identity and evaluative processing is reflected in how nude bodies are processed in the brain. While nude bodies per se is a particular important and salient sexual visual category, they do not as effectively evoke differential activity in brain regions linked to body processing such as the above mentioned regions of occipito-temporal cortices and vPMC. Rather, the existing body of evidence from other fields of reward processing would suggest that the critical evaluative processing of nude bodies and other erotic stimuli would take place in a network subserved primarily by higher order evaluative regions such as the insular, cingulate and orbitofrontal cortices.

This prediction has been borne out in that virtually every VSS study has reported activity changes in the insular and anterior cingulate cortices (ACC). However, not many studies have reported activity in the OFC. This is not surprising given that the OFC is very susceptible to poor signal in fMRI due to its close proximity to the nasal air sinuses, which can only be avoided with dedicated acquisition protocols (Wilson et al., 2002).

Most VSS-induced cingulate responses were found in an area stretching from the posterior border of the anterior part of the middle cingulate cortex (aMCC) to the ventral border of the pregenual anterior cingulate cortex (pACC). A closer look at the data when taking into account the differences in VSS, revealed a clear pattern of activity changes in the various parts of the cingulate cortex (Fig. 6), one that moreover respects well-established cytoarchitectonic boundaries (Vogt, 2005).

Responses recorded in the aMCC tended to be associated with penile responses or long blocks of explicit video-type VSS (Arnow et al., 2002; Karama et al., 2002; Moulier et al., 2006; Mouras et al., 2008; Redouté et al., 2000; Stoleru et al., 1999). By contrast, images of single nudes, or erotic images presented for a brief period of time, clearly bias activity towards the pACC (Hamann et al., 2004; Heinzel et al., 2006; Ponseti et al., 2006; Schaefer et al., 2006; Schiffer et al., 2008b; Sescousse et al., 2010; Walter et al., 2008a). Moreover, the pACC showed no convincing activity correlating with indices of sexual arousal like penile tumescence.

A similar, though less striking, dichotomy was observed in the insular cortex. The rostroventral (anterior, agranular) part of the insular cortex was the only part of the insula to respond to brief depictions of single nudes (Childress et al., 2008; Oei et al., 2012; Sescousse et al., 2010). Dysgranular (middle) and especially granular (posterior) divisions showed a clear association with penile tumescence or long blocks of explicit video-type VSS (Arnow et al., 2002; Ferretti et al., 2005; Karama et al., 2002; Moulier et al., 2006; Mouras et al., 2008; Redouté et al., 2000; Stoleru et al., 1999). Of note, tumescence-related responses were also found in the anterior insula.

These observations seem to be in line with intimate connections between pACC and anterior insula demonstrated by anatomical studies in non-human primates (Mesulam and Mufson, 1982; Vogt and Pandya, 1987) and functional connectivity studies in humans (Taylor et al., 2009). Good evidence exists for anatomical connections in primates between middle/posterior insula and dorsal cingulate cortex including MCC (Mesulam and Mufson, 1982).

VSS-induced pACC activity was independent of sexual arousal levels, which is perhaps best illustrated by the finding that pACC was more active when participants were asked to suppress their sexual arousal when they watched a porn movie (Beauregard et al., 2001). This evidence suggests a possible role of the pACC in evaluating external sexual stimuli with regards to personal sexual reference, which, in turn, may be determined by contextual factors, as well as previous sexual experiences and current internal state. This potential role of the pACC is supported by a number of observations: (i) pACC showed a specific association with the perceived 'sexiness' of bodily depictions (Walter et al., 2008a); (ii) in non-paraphilic men, the pACC was one of the few regions to respond to naked women more than to naked under-aged girls (Schiffer et al., 2008b); (iii) pACC activity predicted reported self-relevance of erotic pictures, but not of non-erotic emotional pictures (Heinzel et al., 2006); (iv) pACC activity reflected prediction errors and hedonic value (Sescousse et al., 2010); (v) Tract-tracing studies in primates have demonstrated strong reciprocal anatomical connections with OFC, anterior insula, and amygdala (Mufson et al., 1981), areas heavily implicated in reward value representation (Kringelbach, 2005), interoceptive (visceral) experience (Craig, 2002), and emotional memory (Roozendaal et al., 2009), respectively.

The posterior subdivision of the insula is held to be important for somatosensory representations, multisensory integration, pleasant touch, and homeostatic afferent information (Craig,

2002; Olausson et al., 2002). In the case of penile erection there is a clear change in penile shape and sensitivity, paralleled by enhanced general arousal. Both processes might be processed through the posterior insula (see Section 3.1.3).

The aMCC, which showed a very similar association with penile tumescence, is known to regulate bodily states of arousal to meet behavioral demands (Critchley et al., 2003). This is a key requirement for sexual arousal, but the aMCC has also been linked strongly to cognitive functions, including response selection, decision making, anticipation, and error detection (Bush et al., 2002; Devinsky et al., 1995). The thought that aMCC activity reflects transient alterations in cognitive and conscious state experienced during sexual arousal is interesting, but remains to be investigated.

As mentioned above, only some of the studies reported activity in the OFC, probably due to signal drop-out issues. The reported changes in activity in the OFC were almost exclusively associated with images of single nudes or short stimulation epochs (Buhler et al., 2008; Childress et al., 2008; Klucken et al., 2009; Oei et al., 2012; Ponseti et al., 2006; Schiffer et al., 2008b; Sescousse et al., 2010; Walter et al., 2008a). Almost all of these OFC effects were localized in the posterior and lateral OFC (areas 47/12l and 47/12 m, Kringelbach, 2005).

This anterior–posterior gradient in the OFC is functionally relevant, because abstract reinforcers are represented anteriorly in the phylogenetically most recent part of the OFC, whereas primary reinforcers are represented posteriorly (Kringelbach, 2005; Kringelbach and Rolls, 2004).

Recently, this proposed anterior–posterior distinction in the OFC between a primary reinforcer such as sexual stimuli and more abstract reinforcers such as monetary reward was demonstrated for the first time in a single study. It was shown that the hedonic value of, and prediction error related to, monetary rewards and images of nude women correlated with activity in the anterior and posterior OFC, respectively (Sescousse et al., 2010). The posterolateral OFC may be a critical region in assessing reproductive viability (or sexual attractiveness), as it showed a preference for women with biologically optimal waist-to-hip ratios (Platek and Singh, 2010), and a stronger activity to images of young adult women compared to underaged girls (Schiffer et al., 2008b). Interestingly, the latter OFC effect was absent in heterosexual paedophiles (Schiffer et al., 2008b; Walter et al., 2007). Finally, this OFC region responded to geometric figures that predicted a subsequent erotic image only in participants who reported to be aware of this contingency (Klucken et al., 2009), supporting its role in expectation. Facial attractiveness, another defining feature of mate selection, seems to be related to activity changes in a more medial OFC region (Kranz and Ishai, 2006).

2.2.4. Summary of heterosexual male VSS effects

The data from the three previous sections on heterosexual male VSS-induced brain responses show how the interacting phases of object identification and evaluative processing point to a partly dissociable 'sexual interest network' and 'sexual arousal network' in the human brain (Fig. 6).

The parameters for presentation of the visual sexual stimuli are not surprisingly very important in bringing about changes in brain activity. Briefly presented photos of nude women elicit a spatial brain signature which is distinct from that associated with long presentations of movie clips depicting explicit male–female sexual interactions. At least part of this effect appears to be related to stimulus duration, as seen for instance in the relatively high responsivity of the OFC in event-related designs with brief stimulus epochs (Buhler et al., 2008).

However, our systematic review of VSS-induced brain responses demonstrates that differences in content are equally important. At the behavioral level, diverging stimulus properties emphasizing novelty are most effective either in eliciting instant sexual interest, or in bringing about a state of sexual arousal, including genital responses. By taking into account these different properties, we demonstrated a systematic effect of largely spatially separate pathways predominantly associated with sexual interest and arousal in the cingulate and insular cortices.

The 'sexual interest network' is primarily associated with briefly presented and simple erotic stimuli (nude women) and includes the VS/NAcc, amygdala, OFC, pACC, SPL, hypothalamus, and anterior insula (Fig. 6). Studies from other fields of reward processing including food intake have implicated these brain regions in the evaluations of salience and hedonic value encoding, as weighted against internal and environmental factors (see Section 6.1). It has also been shown that these regions have strong anatomical connections between them. As such it could be argued that their concerted interplay enables sexual motivation to follow sensory stimuli.

In general, the regions in the 'sexual interest network' were not found to be associated with genital responses or high levels of sexual arousal, suggesting that their role is primarily restricted to recognizing sexual opportunity and directing motivated behavior accordingly. It should, however, be noted that in some studies the hypothalamus and anterior insula did show correlations to measures of arousal, and as such may act as nodes to facilitate the change between the phases of the sexual response cycle.

Sufficiently strong sexual interest invariably leads to arousal, which suggests the existence of a 'sexual arousal network'. During prolonged video-type VSS (depicting complex scenes of couples interaction), men typically experience higher levels of sexual arousal indicated by penile tumescence and enhanced cardiovascular arousal. This behavioral shift coincides with a shift from predominant midline activity to predominant cortical convexity activity. At the regional level, there was a remarkable posterior and dorsal shift in the activity found in dissociable regions of the cingulate and insular. The 'sexual arousal network' (Fig. 6) includes the regions of the vlOT, vPMC, IPC, aMCC, and posterior insula, as well as in the hypothalamus and anterior insula which also showed an association with penile tumescence. Changing sensory inflow that results from penile tumescence and enhanced levels of general arousal may explain the shift in brain networks. However, prolonged periods of VSS also allow for more elaborate processing, which might explain the major involvement of areas on the cortical convexity. Hence, at least in neuroanatomical terms, sexual arousal seems to be a distinct phase of the sexual response cycle.

The identification of VSS-dependent functional pathways and networks thus has the potential to be used as a framework to understand the intricacies of different stages of the sexual response, and the associated stage-specific dysfunctions or disorders. For instance, psychogenic sexual dysfunctions may be traced back to a lack of proper sexual encoding, lack of contingency awareness or the formation of negative sexual associations (i.e. sexual interest network), but also to mislabelling of the sympathetic arousal that accompanies sexual arousal (e.g. as anxiety, see Section 6.3).

2.2.5. VSS in heterosexual women: Menstrual cycle influences and gender differences

VSS neuroimaging studies have predominantly been carried out in men and only a few studies have been conducted in women (Box 1). In addition, the studies that have included female participants have mainly done so in search of gender, orientation, or menstrual cycle influences on VSS-related brain responses. In the following, we review the similarities and differences between heterosexual men and women, using the sexual pleasure cycle and underlying

networks found in the much larger body of evidence from heterosexual men.

Studies with mixed male–female participants have mainly employed designs with brief erotic photo presentations, primarily depicting single nude persons or genitalia (Hamann et al., 2004; Klucken et al., 2009; Ponseti et al., 2006; Stark et al., 2005; Walter et al., 2008a). By definition, therefore, the findings presented in these studies apply to both men and women, like the VS/NAcc involvement typically related to the 'sexual interest network'.

While it is more difficult to infer from the often statistically underpowered within-gender analyses and the paucity of results, the female and male brain respond in a largely similar fashion to longer periods of video-type VSS that could lead to sexual arousal (Arnow et al., 2009; Gizewski et al., 2006; Karama et al., 2002; Salonia et al., 2009).

It is important not to confound these VSS studies with other studies in women which are designed to investigate non-immediate sexual issues, like partner risk assessment (Rupp et al., 2009a,b), and emotional closeness of the relationship (Bianchi-Demicheli and Ortigue, 2007, 2009).

One larger body of research in women concerns the influence of the ovulatory cycle. It is well established that hormonal fluctuations during the menstrual cycle influence sexual interest (Clayton et al., 1999), predict future sexual interest (Wallen and Rupp, 2010), and may strengthen or weaken implicit sexual associations (Rudski et al., 2011). Regarding VSS, there is evidence that pictures of naked men induce greater interest and positive affect during ovulation (Mass et al., 2009), and one could therefore predict VSS-induced brain activity patterns to change across the menstrual cycle.

Such modulations have been identified (Gizewski et al., 2006; Zhu et al., 2010), but there is no real consensus in the field regarding the neuroanatomical correlates of these influences. Evidence from studies outside the sexual domain have found that arousal- (Goldstein et al., 2005) and reward-related (Ossewaarde et al., 2010) processing in the brain is clearly influenced by the female hormonal milieu during the menstrual cycle. These changes are most notable in regions like the OFC, amygdala, cingulate cortex, insula, and VS/NAcc, all of which, as we saw earlier, have been seriously implicated in VSS processing.

Interestingly, when women look at male faces this leads to an increase in activity in the medial OFC/vmPFC during the late follicular relative to the luteal phase. This activity is correlated with the perceived attractiveness as well as individual estradiol to progesterone ratio (Rupp et al., 2009a), suggesting a key role for the OFC in mate selection. Another study using a go/no-go paradigm with male faces suggested differential inhibitory control mechanisms during late follicular and luteal phase, which was linked to aMCC functionality (Roberts et al., 2008). In a similar vein, the aMCC was more strongly active to male faces perceived as posing a low sexual risk versus high risk men (Rupp et al., 2009b).

In addition to these hormonal studies, sexual neuroimaging studies in women have contributed to our understanding of how different brain networks are involved when distinguishing between different kinds of sexual activity. The results suggest that regions of the vlOT and vPMC are linked with memories of partnered intercourse, but not of clitoris stimulation (Bianchi-Demicheli and Ortigue, 2009). In contrast, activity in the left insula was correlated with the memory for both activities (Bianchi-Demicheli and Ortigue, 2009), as well as the overall quality of orgasms (Bianchi-Demicheli and Ortigue, 2007). These findings of involvement of brain regions known to be involved in social cognition could reflect the more intimate interpersonal interaction during sexual intercourse. It is not currently known if men make a similar distinction between various levels of sexual intimacy.

Overall, the evidence suggests that there are no consistent and conclusive gender differences in VSS-related brain processing between men and women. When gender differences are reported, they invariably seem to be biased towards men (Gizewski et al., 2006; Hamann et al., 2004; Karama et al., 2002; Klucken et al., 2009; Sabatinelli et al., 2004). This could be indicative of the presumed greater role of visual stimuli in human male sexual behavior (Laumann et al., 1994). Yet, women's sexual responses are typically less conspicuous, and may be triggered by a much wider variety of stimuli than men would respond to (Chivers et al., 2007). In addition, women show a relative lack of concordance between their reported sexual arousal and physiological arousal, though this may also vary widely between female individuals (Chivers et al., 2010). As we have discussed earlier, the menstrual cycle – or factors influencing it like contraceptive use – further complicate matters. All these factors are important because they imply more behavioral noise in the female sexual response relative to its male counterpart, which, in turn, is likely to result in male-biased VSS-induced brain activity when comparing both gender groups.

What remains is the observation that women do achieve sexual interest and arousal, but may follow a different path to sexual responsiveness than men (for an overview, see Rupp and Wallen, 2008). In the case of visual erotica, there is evidence that women, relative to men, are more interested in context (Rupp and Wallen, 2007), habituate less easily to visual sexual stimuli (Laan and Everaerd, 1995), show less specific preference for opposite sex stimuli (Chivers et al., 2004; Costell et al., 1972), and are less sensitive to sexual conditioning and sexual contingencies (Klucken et al., 2009). An evolutionary perspective would argue that this evidence reflects fundamental biological differences underlying typical male and female roles in sexual behavior, like women's more thoughtful approach with regard to mate choice, as opposed to the more instinctive nature of the male sexual response. However, it is questionable whether biological factors can fully account for sexual behavioral differences. The impact of learning, resulting from social mores and values regarding sexuality, is certainly not trivial nor negligible.

3. Liking: Sexual arousal, consummation and climax

Sexual consummation is an important phase of the sexual response cycle which has to happen if reproduction and thus species survival is to be achieved. In most mammals, including humans, reproduction requires coital intercourse between a male and a female. Note, however, that sexual consummation covers a host of sexual activities, most of which will never lead to reproduction. In the event of sexual opportunity, and under the appropriate circumstances, this activity naturally follows sexual interest and arousal.

Strong feelings of pleasure and euphoria, as well as marked alterations in cognitive processing, self-referential thought, and physiological arousal are defining features of sexual consummation, especially during orgasm (Mah and Binik, 2001). These processes promote inter-individual intimacy and approach, and degrade the interference of external distractors (Koukounas and McCabe, 2001), both of which are necessary requirements to engage in sexual activity (and procreate). The extraordinary mental state and pleasure experienced during sexual activity may be the main reason why sex is so powerful and why e.g. sexually transmitted diseases and sexual abuse are so difficult to control. On the other hand, even when we relish sex, we are still capable of precise motor control, talking, postponing pleasure, and more.

Given the description above, it would seem reasonable to assume that higher-order brain functions participate in sexual consummation. Some of these may be similar to cortical control

processes seen in e.g. rodents (see e.g. Pfaus et al., 2012), others may be unique to humans.

As mentioned above, the evidence shows that liking and wanting have different underlying neuroanatomy. They have, however, proven difficult to tease apart in behavioral studies and there is an ongoing debate regarding how to best dissociate them (Havermans, 2012). One of the best examples of a dissociation is the phenomenon of "persistent miswanting" (Berridge, 2012). In such cases, wanting persists even when stimuli are disliked such as seen e.g. in drug addicts after bad drug experiences. It is conceivable that similar persistent miswanting is found in the sexual domain. E.g. some intriguing evidence from the Netherlands suggests that up to 40% of premenopausal women who experience pain during intercourse show inadequate pain behaviour, that is, they continue to attempt having intercourse at least once a week (Laan, personal communication).

Most of the evidence for the dissociation between wanting and liking comes from other animals where wanting and liking can be successfully dissociated by various pharmacological manipulations of e.g. dopamine levels in select brain regions (Smith et al., 2011). In humans, it is more difficult to dissociate wanting and liking but a potentially important behavioral wanting-liking paradigm has recently been introduced where human participants indicate their subjective liking of a stimulus as well as their wanting measured by the amount of effort they are willing to put in to prolong or shorten the duration of the exposure to the stimulus (Parsons et al., 2011a,b). For example, this paradigm has been used to demonstrate that even though men and women differ in their liking ratings of baby faces, they show similar viewing times (as a measure of wanting by exerted effort to influence viewing times, Parsons et al., 2011a). This paradigm would seem to lend itself well to detailed sex studies.

Unfortunately, the popular fascination for sexual activity is not paralleled by the amount of human neuroscientific research in this area and much data is currently missing (Box 1). Nevertheless, in the following we will try to synthesize the findings from the existing neuroimaging literature.

3.1. Arousal: Sexual genital stimulation

Penis and clitoris are organs designed for reproduction and sexual pleasure. Their innervation is unlike that of other skin or viscera, and their input to the central nervous system, especially when engorged and aroused, gives rise to unique qualities of sensation comprising powerful incentives for engaging in sexual activity. Additionally, strong sexual feelings may be perceived by stimulation of internal genitalia, like the vagina and prostate, given an appropriate sexual context.

3.1.1. Sensory receptors in the human sexual organs

Most if not all of the data on sensory receptors in the sexual organs have been conducted in other animals and so are not necessarily transferable to humans. Here we briefly review the most pertinent findings from this literature.

Animal experiments have shown that the penile epithelium is extensively innervated by free nerve endings, most of which are terminations of thinly myelinated Aδ fibers conveyed by the somatosensory dorsal penile nerve (Halata and Munger, 1986; Johnson and Halata, 1991). Sensory receptors in the glans (distal end of penis) are highly sensitive to vibration (Johnson et al., 1986) and warm temperature (Johnson and Kitchell, 1987). However, they may also respond to penile erection alone. Receptors around the cavernous bodies respond specifically to penile tumescence (Halata and Munger, 1986; Johnson and Halata, 1991). Because of their common embryonic origin, these morphological and functional properties are likely to also apply to the clitoris, though hard empirical evidence is lacking (Marson and Murphy, 2006). These different penile sensory features seem to be largely preserved at the level of the spinal cord. Dorsolateral and ventrolateral columns convey information relevant for ejaculation, whereas dorsal columns mainly convey information about penile touch (Hubscher et al., 2010). Evidence for a similar organization in humans is provided by the observation that spinal cord injuries involving the ventrolateral columns lead to anorgasmia despite intact dorsal columns (Beric and Light, 1993).

The empirical evidence outlined here is at least suggestive of differential encoding of penile sensory inflow under flaccid and rigid conditions. A similar logic might apply to the clitoris under engorged and non-aroused conditions. This is important, yet challenging when considering how genital afferent inflow can contribute to the unified sexual experience.

3.1.2. Brain representation of genitals and pelvic floor motor control during sexual activity

Ever since the dawn of modern neuroscience, studies have diverged with regard to where the external genitalia are represented on the postcentral gyrus (primary somatosensory cortex, SI). Without any doubt, Penfield's view of SI organization ('sensory homunculus') is the most influential (Penfield and Rasmussen, 1950). In this model, the genitalia are represented on the interhemispheric surface directly dorsal to the cingulate cortex, and this corroborated earlier work (Foerster, 1936).

However, the first documented study argued for a location of genitalia on the dorsal surface of SI (Pfeifer, 1920). What is important to emphasize here is that these neurosurgical studies relied heavily on patients' self-reports, making interpretations quite venturesome given strong sexual taboos in those days. Contemporary non-invasive investigations have continued to support either the ('Penfield') interhemispheric (Allison et al., 1996; Guerit and Opsomer, 1991; Mäkelä et al., 2003; Nakagawa et al., 1998) or the dorsal location (Bradley et al., 1998; Georgiadis et al., 2010a; Georgiadis and Holstege, 2005; Kell et al., 2005). Most studies performed in women found a dorsal location for the clitoris (Georgiadis et al., 2006; Mehnert et al., 2008; Michels et al., 2010), except for one study which concurred with the interhemispheric location (Komisaruk et al., 2011).

When reviewing this evidence, it is essential to remember that pelvic floor and perineal muscles are important for specific sexual motor actions. The primary motor cortex (MI) of these muscles is on the interhemispheric surface in the paracentral lobule (Blok et al., 1997; Georgiadis et al., 2006; Kuhtz-Buschbeck et al., 2007; Seseke et al., 2006), very close to Penfield's original description of genital SI, and this fits well with the finding that the postcentral gyrus only rarely reaches the interhemispheric fissure (Grefkes et al., 2001). This raises the possibility that neurosurgical stimulations induced pelvic muscular contractions which, in turn, triggered genital feelings. In rats, such genital sensorimotor coupling is evident, because penile erection is reinforced by perineal muscular contractions induced by penis stimulation (Giuliano and Rampin, 2000). In humans, partnered sexual stimulation of penis (Georgiadis et al., 2010a; Georgiadis and Holstege, 2005) and clitoris (Georgiadis et al., 2006) created activity in *both* the 'dorsal SI' and the 'interhemispheric MI' locations. Along with MI, premotor and supplementary motor areas strongly correlated with objective and subjective indices of sexual arousal (Georgiadis et al., 2010a), underscoring the relevance of motor function in sexual arousal. The most illustrative clinical example of this function is premature ejaculation, which is strongly associated with poor central motor control (Rosenbaum, 2007).

The auxilliary somatosensory areas regions are found in the parietal operculum and in the posterior insula, both of which have

been shown to respond to penile touch (Kell et al., 2005; Mäkelä et al., 2003), penile erection (Ferretti et al., 2005; Moulier et al., 2006; Redouté et al., 2000, 2005), and sexual genital stimulation (Georgiadis et al., 2009, 2010a). In a study focusing on vaginal pain, insula and parietal operculum activity tracked with the perceived discomfort of vaginal stimulation (Pukall et al., 2005), supporting the idea that emotional load modulates activity in the parietal operculum (Ploner et al., 2002). Indeed, in a design where touch and arousal/erection effects of sexual penis stimulation could be disentangled, parietal operculum activity was found to depend on both (Georgiadis et al., 2010a). The parietal operculum may be one of the nodes that creates a unified sexual experience depending on how genital sensory inflow is coupled to e.g. emotional information from the medio-temporal cortices (Friedman et al., 1986) and frontal motor areas (Eickhoff et al., 2010).

3.1.3. Penile erection: Critical contributions of the posterior insula–claustrum complex?

Given that the penis is thus represented in the primary somatosensory areas, it could be predicted that penile erection would lead to activity in these regions. Yet, penile erection per se is not sufficient to trigger activity in the primary somatosensory areas (Arnow et al., 2002; Georgiadis et al., 2010a; Moulier et al., 2006). This suggests the existence of a separate cortical pathway for tumescence-related information, reminiscent of similar specialization at the level of the penis and the spinal cord. A primary candidate is the middle/posterior insula, where activity has been found to be correlated with VSS-induced penile tumescence (Arnow et al., 2002; Ferretti et al., 2005; Karama et al., 2002; Moulier et al., 2006; Mouras et al., 2008; Redouté et al., 2000; Stoleru et al., 1999). This fits with the observation that tumescence-related activity is not confined to the insular cortex, but extends medially to the claustrum (Redouté et al., 2000), which was confirmed by studies using partnered sexual penis stimulation (Georgiadis et al., 2010a; Georgiadis and Holstege, 2005). Of note, activity in this cluster did not distinguish between penis stimulation and the period immediately after stimulation (Georgiadis et al., 2010a), making it unlikely that the posterior claustrum–insula process complex penile touch. Additional evidence comes from a direct gender comparison between sexual penis and clitoris stimulation, showing that the right claustrum was significantly more active in men (Georgiadis et al., 2009). Possibly, this reflects the fact that women are generally less aware of clitoral engorgement than men of their penile tumescence, and associated therewith, the greater biological significance of penile erection relative to clitoral engorgement.

3.1.4. Waves of sexual arousal and de-arousal with self-limited partnered penis stimulation

Despite its primal nature, sexual activity is subject to large inter-individual differences regarding e.g. what stimuli or practices people may like (or dislike), and how long they take to go through a full sexual response cycle. To accommodate for some of these confounds, Georgiadis and colleagues developed a paradigm (Fig. 5) that allows for inter-individual differences in the amount of penis stimulation sufficient to reach ejaculation, thus fulfilling a critical aspect of sexual consummation under normal, non-experimental conditions. This design typically yields 'waves' of sexual arousal and de-arousal for every participant (Georgiadis et al., 2010a).

The relatively natural sexual responsiveness made feasible by employing this design has proven to be highly beneficial, resulting in the discovery of distinct networks supporting high sexual arousal and post-stimulatory de-arousal. It was found that partnered sexual penis stimulation recruited aMCC, posterior insula–claustrum, anterior insula–frontal operculum, intraparietal cortex, and occipitotemporal cortex, a network that showed considerable overlap with the visually-induced 'sexual arousal network' (see Section 2.2.4), despite the absence of visual input. Post-stimulatory de-arousal showed activity in pACC and sACC, but also in vmPFC, amygdala, and parahippocampal gyrus, suggesting a switch towards self-referential ('default-mode') processing (Gusnard and Raichle, 2001; Heinzel et al., 2006) after sexual activity ceased. Intriguingly, this pattern of activity is not unlike that of the 'sexual interest network' identified on the basis of VSS studies shown above (Section 2.2.4; Figs. 4 and 6). These results strongly suggest that similar to erotic visual stimulation, penis stimulation may serve as gateway for eliciting a transition between the different phases in the sexual response cycle. Under normal circumstances there is also a strong synergy between visual and penis stimulation. Please do note, however, that visual stimulation is rarely enough on its own to bring about the transition to orgasm but requires stimulation of the sexual organs.

In addition to these findings, some areas seem to do double duty in sexual behavior. The amygdala, for instance, readily responds to distant visual erotica (Beauregard et al., 2001; Ferretti et al., 2005; Gizewski et al., 2006; Hamann et al., 2004; Karama et al., 2002), but under conditions of sexual genital stimulation its activity decreases markedly (Georgiadis et al., 2006, 2009, 2010a; Georgiadis and Holstege, 2005). Again, this suggests that anticipation and consummation are fundamentally distinct. Note that the amygdala is not only important for identifying (sexual) salience, but also of objects or events that are rewarding or detrimental for survival (Amaral, 2002; Davis and Whalen, 2001; Rauch et al., 2000). Hence, amygdala suppression may lower vigilance and make normal body boundaries dissolve, which is a prerequisite for sexual intimacy. Indeed, post-traumatic stress disorder has been associated with both chronically enhanced amygdala activity (Rauch et al., 2000) and severe sexual difficulties (Letourneau et al., 1997). Arousal-related decreased activity is also seen in parts of the medial temporal lobe and ventral prefrontal cortex (Section 3.2.4).

The self-limited partnered stimulation paradigm also revealed a novel, dual role for the hypothalamus in sexual consummation. The activity in lateral hypothalamus correlated with penile tumescence, whereas the anteroventral hypothalamus was active only during penile detumescence after stimulation ceased. Remarkably, this result is exactly in line with well-established animal data demonstrating that these hypothalamic subregions regulate arousal and de-arousal states (Saper et al., 2005). Recent theories emphasize the importance of generalized arousal to initiate behavioral activation (Pfaff et al., 2008), and this may be particularly pertinent in sex (Weil et al., 2010). In this regard it would be interesting to know which forebrain regions interact with these hypothalamic autonomic gateways (Sutcliffe and De Lecea, 2002).

A prime candidate for this interaction is the cingulate cortex, because cingulate subregions also showed an opposite functional association with arousal (aMCC, arousal; sACC, de-arousal), one that furthermore supports existing ideas about cingulate cortex and autonomic control (Critchley et al., 2003; Nagai et al., 2004). Functional connectivity analysis revealed a very specific sACC-anteroventral hypothalamus functional pathway (Georgiadis et al., 2010b). This finding is in line with well-established anatomical connections between sACC and anterior hypothalamus (Johansen-Berg et al., 2008; Ongur et al., 1998). Further, the functional association between sACC and anteroventral hypothalamus in relation to de-arousal after sexual activity is supported by experimental observations that both areas possess arousal-inhibiting properties (Lu et al., 2006; Mayberg, 1997).

Besides the hypothalamus, other interesting dynamics were identified with the self-limited partnered paradigm. The basal

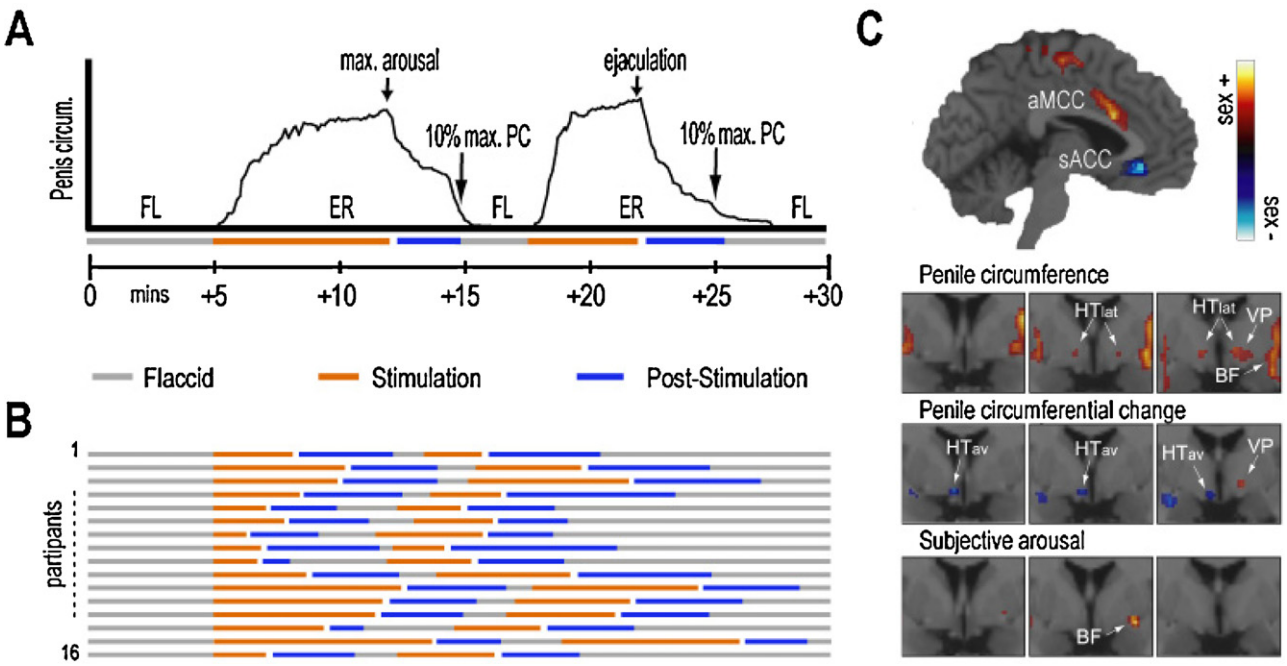

Fig. 4. Paradigm for neuroimaging of the sexual response cycle. The perhaps most effective way to study the functional neuroanatomical changes related to the different points of the sexual pleasure cycle is the so-called *Self-limited partnered stimulation protocol* (Georgiadis et al., 2010a). This paradigm has been specifically designed for ASL fMRI of the male sexual cycle, and entails two periods of partnered penis stimulation (by real-life sexual partner), which can last up to 10 min each. The first period ends when the subject indicates ejaculation is imminent (i.e. upon maximal arousal), and the second period ends when the subject achieves ejaculation. (A) The time course of penile circumference for one participant is plotted. Note that this time course drives subsequent analyses in that it determines baseline (flaccid, light grey), stimulation (orange), and post-stimulation (blue) blocks. The latter was characterized by penile detumescence and decreasing arousal. (B) There are large inter- and intra-individual variation in stimulation duration (orange bars), which confirms the ecological validity of the design. (C) The paradigm has helped to dissociate stimulatory (red-yellow) and post-stimulatory (blue-light blue) effects in subregions of cingulate cortex and hypothalamus (Georgiadis et al., 2010a). Please note that this paradigm has not yet been used in women but it is easy to adapt.

forebrain, an area rich in cholinergic neurons, showed the strongest correlation with perceived sexual pleasure/intensity, which offers some support to the theory that acethylcholine release is important for sexual pleasure (Heath, 1972). The ventral pallidum (VP), an area believed to be instrumental in processing stimulus liking (Berridge, 1996; Miller et al., 2006; Smith and Berridge, 2005), showed rather ideosyncratic involvement. VP activity correlated with the slope of penile tumescence, which was very steep shortly after stimulation onset, but dropped below baseline levels after sexual stimulation ceased. Hence, it seems that VP signalled penis stimulation onset, but also, through decreased activity possibly reflecting inhibitory processes, the absence of that same hedonic stimulus.

The vlOT showed similar activity dynamics, which is remarkable as this happened in the absence of external visual input. This supports the theory that the vlOT is not 'merely' a visual area, but a key center for multisensory integration (Beauchamp, 2005). In case of genital stimulation, it could reflect concomitant visual imagery (Kosslyn et al., 2001). In the case of watching VSS, genital feelings might enhance activity in this area. Sexual occipitotemporal involvement may be more important in men than in women (Georgiadis et al., 2009; Sabatinelli et al., 2004), possibly reflecting the presumed greater role of visual processing, or imagery, in male sexual behavior (Laumann et al., 1994).

3.1.5. Sexual clitoral and vaginal stimulation

The self-limited partnered sexual genital stimulation paradigm has not yet been applied to women. Reviewing the findings on clitoral stimulation must therefore rely on data from other, less reliable paradigms. Some of the results have been mentioned above, such as the involvement of primary somatosensory cortex and parietal operculum, which women share with men (Georgiadis et al., 2009).

The most robust finding related to clitoris stimulation has emerged from a direct gender comparison. Clitoral stimulation in women was found to elicit stronger activity in the left posterior parietal cortex and left dorsal MI and premotor cortex (Georgiadis et al., 2009) compared to penile stimulation in men. This pattern is hard to reconcile with a strictly somatosensory explanation, and instead might reflect the possibility that female participants, more than their male counterparts, were creating a mental representation of the situation (manual clitoral stimulation), or that they blended more with the stimulation. Both tentative explanations are possible and would correspond to women's proposed empathic 'talent' (Baron-Cohen et al., 2005), but to be resolved would require acquisition of data on perspective taking during genital stimulation.

The location of the clitoris in the perineum prevents it from becoming sufficiently stimulated during vaginal intercourse (Levin, 2002). This would seem to indicate that coital thrusting precludes female sexual pleasure which is obviously not the case. Vagina and vaginocervix are extensively innervated by visceral sensory nerves, which travel to the spinal cord along the parasympathetic and sympathetic motor nerves (Sipski et al., 2001). Because this part of the genital afferent inflow enters the central nervous system at levels superior to the sacral cord, some genital sensation, and even orgasmic ability, may be preserved in low spinal cord lesions (Komisaruk et al., 1997; Sipski et al., 2001).

Information about the central processing of vaginal afferent inflow in a sexually-relevant context (penetration) is very limited. Though effects have been reported in hypothalamus, amygdala, cingulate cortex, insula, and brainstem using a design in which participants self-stimulated with a vibrator (Komisaruk et al., 2004; Whipple and Komisaruk, 2002), these reports lack the necessary detail to determine the robustness and exact location of the effects, precluding any reliable comparison with other studies.

3.2. Orgasm

Orgasm is derived from the ancient Greek word οργασμός, which roughly translates into being 'excited' or 'swollen'. This phase is a natural progression from sexual interest and arousal, yet it feels very different from the other phases of the sexual response cycle.

The physiological and mental transitions during orgasm are phenomenal, and include involuntary muscular contractions, sharp peaks in cardiovascular arousal, loss of control, feelings of release, altered states (and even loss) of consciousness, and altered sense of space and time (Kinsey et al., 1953; Mah and Binik, 2001; Masters and Johnson, 1966). The evidence is still not clear on how brains come produce this extraordinary experience but some interesting evidence has recently come to light.

One important observation is that orgasms may occur independently of any kind of genital stimulation. Imagery or mentalizing might do the trick, just like brain pathology, most notably temporal lobe epilepsy (Baird et al., 2002; Janszky et al., 2002, 2004). Early experimental studies also hint at a role for higher cortical systems in orgasm. Using EEG, paroxysmal activity was found (Janszky et al., 2004), and these waveforms resembled convulsive discharges seen with epileptic seizures (Calleja et al., 1988). Other studies showed that during orgasm, but not during a "faked orgasm", electrical activity was right-lateralized (Cohen et al., 1976), and that orgasm was associated with a depression of alpha power, a well-known but non-specific marker of attentional shifts (Graber et al., 1985).

The first study on brain metabolism related to human orgasm was conducted with Single Photon Emission Computed Tomography. Injections of radioactive tracer were administered to the male participants when they indicated that orgasm was imminent, and orgasm-related perfusion decreases (relative to baseline) were found in most neocortical areas except for the right prefrontal cortex (Tiihonen et al., 1994). It is difficult to interpret the results of this early study. The time lag of several seconds between injection and cerebral labelling could imply that the observed pattern is most likely attributable to the end of orgasm and possibly even the onset of the post-orgasmic phase rather than orgasm per se.

The subsequent advent of the neuroimaging techniques, such as PET and fMRI, has represented a major advance in terms of spatial and temporal resolution. As would be expected, the orgasm phase of the sexual response cycle has been linked to a number of regions. We have subdivided our discussion into regions related to the pleasure of orgasm, the pelvic contractions and the general sexual arousal. We also mainly review experiments during which men and women underwent tactile sexual genital stimulation, and attempted to reach orgasm. The focus is primarily on orgasm in women because the existing experiments were most informative as a result of additional subjective and objective measures.

3.2.1. A special note on orgasm in women

For obvious biological reasons, the coupling between male ejaculation and orgasm is very stable. Women, however, do not commonly reach orgasm through unassisted coital intercourse, and according to some studies, around 30% of women never do (Hite, 1976). In marked contrast, an estimated 90% of women can reach orgasm through clitoral stimulation (Lloyd, 2005). This contradiction is known as *the female orgasm paradox*: The clitoris is the primary locus for inducing orgasm in women, but it is not located in a strategic position for it to become sufficiently stimulated during coital intercourse (Levin, 2002; Lloyd, 2005). As a consequence, it seems highly unlikely that orgasms in women serve the same procreative function as their male counterpart. Obviously, their recreative purpose is undisputed, and we believe this makes the following sections especially intriguing.

Note also that the lack of a reliable indicator of female orgasm means that they have been shrouded in much mystery. Yet, contrary to popular knowledge, solid scientific behavioral measures exist that can reliably establish the onset and termination of orgasm. The key is to focus on the fast fluctuations in rectal pressure as a reliable measure of pelvic muscular activity (Bohlen et al., 1980, 1982). Spectral analysis can reveal strong high frequency characteristics in orgasm-related rectal pressure signal (Van Netten et al., 2008), which in turn reflect involuntary muscular spasms, a defining feature of orgasm. For orgasm in women, therefore, we concentrate on a brain imaging study that used this behavioral measure together with participants' self-reports, in combination with clitorally-induced orgasm (Georgiadis et al., 2006).

There is one fMRI paper in the literature on vaginocervical self-stimulation leading to orgasm (Komisaruk et al., 2004) which will need independent verification by at least one other study. The existing study has potential problems in that the orgasms occurred at the end of minutes of continuous vaginal stimulation, leaving the possibility of random artifactual activity because of signal drifts typical of BOLD acquisition (Smith et al., 1999).

3.2.2. Orgasm-specific activity in orbitofrontal and other prefrontal regions

The available neuroimaging studies in the literature have provided a rich set of data related to the brain networks involved in orgasm. These changes have been reported as increases and decreases from a control state. It is important to realize that the signs of such changes are not necessarily meaningful as they depend on having a carefully matched control state. As we have stressed in this review, the changes have to be seen in the context of changes between the various network states of the sexual response cycle. This means that the studies will have measured the pivotal nodes that are involved in changes concomitant with these state transitions.

It is therefore of considerable interest that some of the most prominent orgasm related activity has been found in the prefrontal cortex (Fig. 5). Specifically, prefrontal decreased activity occurred when orgasm-related perfusion was compared to that during sexual genital stimulation (Georgiadis et al., 2006, 2007, 2009), which is the contrast with the smallest difference in perceived sexual arousal (Georgiadis et al., 2006).

The strongest orgasm-related changes in activity was seen in the mid-anterior portion of the left OFC (at MNI coordinates $[-36.0 \pm 2.0,\ 38.0 \pm 6.0,\ -17.3 \pm 1.2]$) and medial OFC (at MNI coordinates $[3.0 \pm 1.4,\ 44.0 \pm 14.1,\ -25.0 \pm 4.2]$) (Georgiadis et al., 2006, 2007, 2009) (see Figs. 5C and D). Furthermore, these changes in OFC were not unilateral but bilateral when comparing orgasm and imitation (Georgiadis et al., 2006).

The peaks of these orgasm-related changes fits well with the emerging literature implicating the OFC in pleasure and reward processing (Kringelbach, 2005). Especially the activity within the mid-anterior subregion of the OFC is interesting, since previous research has shown that activity correlates with the subjective pleasure of different rewards, e.g. food (Kringelbach et al., 2003), drugs (Vollm et al., 2004), chocolate (Small et al., 2001), and even music (Blood and Zatorre, 2001). Perhaps most importantly, mid-anterior OFC activity tracks changes in subjective pleasure, such as a decline in palatability when the reward value of one food was reduced by eating it to satiety (while remaining high to another food) (Kringelbach et al., 2003). The mid-anterior subregion of the OFC is thus a prime candidate for the coding of subjective experience of pleasure (Kringelbach, 2005) and the findings of orgasm-related activity in this subregion supports this notion.

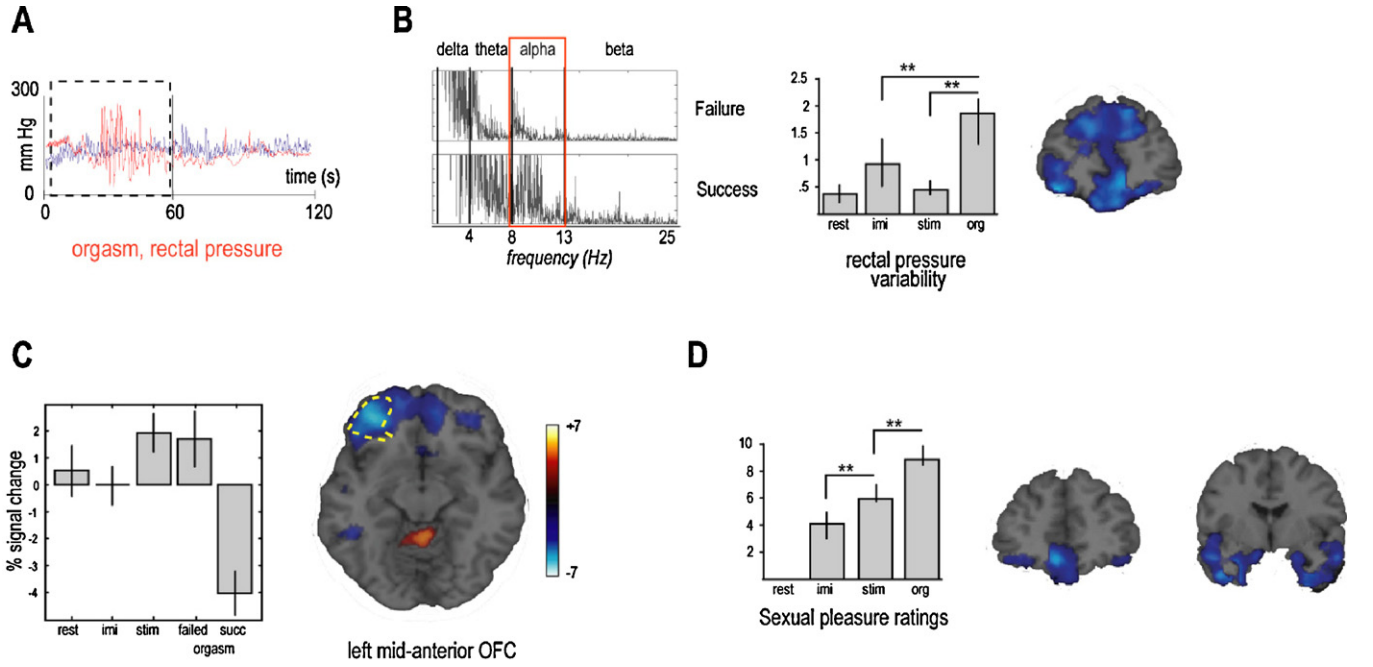

Fig. 5. Orgasm-related changes in women. Making behavioral measures of orgasms in women is challenging and requires the insertion of a rectal probe to measure involuntary pelvic contractions indicative of orgasm. (A) The graph shows data from a single individual in the changes in rectal pressure over two minutes. The signal was most variable during orgasm. (B) Further spectral analysis of the rectal pressure signal reveals that orgasm is especially related to signal changes in the alpha band, which distinguished it even from failed orgasm attempts (Van Netten et al., 2008). The presence of such high frequencies is indicative of involuntary muscular contractions. This variability in rectal pressure is correlated to widespread blood flow changes in the prefrontal cortex. (C) Specific orgasm-related changes are found in the mid-anterior orbitofrontal cortex (OFC) which show remarkable changes in blood flow during real orgasm compared to sexual clitoral stimulations and failed orgasm attempts (Georgiadis et al., 2006). This fits well with the proposed role of the mid-anterior OFC in representing subjective pleasure. (D) Subjective sexual pleasure was found to correlate to changes in medial OFC and vmPFC, as well as ventromedial temporal lobe, including amygdala. Orgasms were timed exactly in the first minute of a ^{15}O-water PET scan, which is visible by the rectal pressure pattern (shown in A).

Similarly the peak in the medial OFC (ventromedial prefrontal cortex, vmPFC) is interesting given that previous research has identified the medial regions of the OFC as a coding site for positive hedonics with activity related to the valence of positive and negative events (Kringelbach and Rolls, 2004), contrasted to lateral portions that have been suggested to code unpleasant events (O'Doherty et al., 2001). It should be noted, however, that activity in lateral OFC may reflect a signal to escape the situation, rather than displeasure per se (Hornak et al., 2003; Iversen and Mishkin, 1970; Kringelbach et al., 2003; Kringelbach and Rolls, 2004). This medial-lateral hedonic gradient interacts with an abstraction-concreteness gradient in the posterior–anterior dimension, so that more complex or abstract reinforcers (such as monetary gain and loss) are represented more anteriorly in the orbitofrontal cortex than less complex sensory rewards (such as taste or sexual stimuli) (O'Doherty et al., 2001; Sescousse et al., 2010; Small et al., 2001). Yet, this medial region of OFC has not been shown to change its activity with reinforcer devaluation, and so may not reflect the full dynamics of pleasure.

Pertinent to these findings of different functional roles of subregions of the OFC is the finding that, at least in women, failed orgasm attempts significantly enhanced left lateral OFC activity (Fig. 5C), suggesting that orgasm could not be reached because of excessive behavioral suppression (Georgiadis and Kortekaas, 2009; Salonia et al., 2009). This is in turn allows for the additional interpretation that the orgasm-related OFC dynamics could reflect one of the main features of orgasm, the 'loss of control' (Mah and Binik, 2001).

In addition to these activity changes in the OFC, it was found that prefrontal, but not temporal, perfusion was inversely coupled with rectal pressure fluctuations indicative of fast ('orgasm-like') pelvic muscular contractions (Georgiadis et al., 2006). This was true both for dorsal and ventral PFC divisions, most of which (except vmPFC) did not show a clear association with sexual arousal, suggesting that the decreased PFC activity is 'specific' to orgasm (Fig. 5B).

These marked decreases in prefrontal metabolism support an immense body of literature underscoring the critical role of the PFC in behavioral and emotional control (e.g. Bechara, 2005). Successful prefrontal regulation may be key to reaching orgasm, a notion that is backed by several experimental reports of exaggerated prefrontal activity and correlated decrements in sexual function (Arnow et al., 2009; Redouté et al., 2005; Stoleru et al., 2003), and clinical reports demonstrating the opposite (Damasio et al., 1994; Lapierre et al., 1995; Yang et al., 2005).

3.2.3. *Pelvic muscular contractions and the cerebellum*

Apart from the OFC and prefrontal regions, also the cerebellum has been implicated in the transition to the orgasm phase of the sexual response cycle. The involvement of the cerebellum is an interesting but challenging finding.

Studies have found that a cluster encompassing the left anterior vermis and deep cerebellar nuclei as the only brain region showing reliable orgasm-related blood flow increments, and it did so in men and women alike (Georgiadis et al., 2006, 2007, 2009). Key figures in the history of neuroscience have linked the cerebellum to reproductive behavior (Gall, 1822), but besides incidental reports (Heath, 1972), the cerebellum has since not been deemed relevant in this context. However, recent animal models of the human sexual response has led to reconsideration of the role of the cerebellum (Garcia-Martinez et al., 2010; Paredes-Ramos et al., 2011).

The 'axial' cerebellar preponderance seems to faithfully reflect the somatotopic organization of the cerebellum, in that it may represent axial muscles (perineal muscles, pelvic floor) and genitalia which are most strongly implicated in sexual

activity. At least in women it was shown that blood flow in this cluster strongly correlated with fast fluctuations in rectal pressure (Georgiadis et al., 2006), Interestingly, activity in putative pelvic floor MI did not show an association with this peripheral measure (Georgiadis et al., 2006), providing further support for the idea that orgasm-related pelvic contractions are controlled differently.

The correlation with rectal pressure fluctuations by no means excludes a role in non-motor behavior, as the cerebellar vermis has been strongly implicated in cognition, autonomic regulation, affect, and emotional memory (Critchley et al., 2000; Middleton and Strick, 1994; Schmahmann, 2004; Snider and Maiti, 1976).

3.2.4. Sexual arousal linked to temporal and ventral prefrontal regions

In addition to regions with orgasm-specific activity, there were other regions which change their activity in non-specific ways during orgasm. In both men and women, orgasm produces profound, widespread, and bilateral blood flow decreases in the temporal lobe and PFC, relative to a non-sexual resting state (Georgiadis et al., 2006, 2007, 2009). In ventral and medial parts of the temporal lobe (e.g. amygdala), and in the vmPFC, this effect started to emerge before orgasm (Georgiadis et al., 2006, 2009, 2010a). Accordingly, these areas showed a remarkable negative association with objective (Georgiadis et al., 2010a) and subjective (Georgiadis et al., 2006) sexual arousal (Fig. 6), which in turn corresponds with clinical observations of hypersexuality following temporal lobe damage (Aloni and Katz, 1999; Baird et al., 2002). Similarly, psychogenic hyposexual desire is associated with vmPFC hyperactivity (Arnow et al., 2009; Cera et al., 2012), while both medial temporal lobe and vmPFc exhibit enhanced activity after the cessation of genital stimulation (Georgiadis et al., 2010a).

It is of considerable interest that these areas belong to the so-called default mode network, one of the main resting state networks that have been implicated among other functions in self-referential thought (Gusnard et al., 2001; Lou et al., 1999). The altered state of consciousness characteristic of sexual activity, and especially orgasm, could well be the result of altered default mode network functionality. In more general terms, suppressing components of the default mode network seems important for task performance and behavioral arousal, and this suppression becomes less efficient with advanced age (Persson et al., 2007). At least to some extent, this could contribute to age-related decrements in sexual function and the ability to experience arousal. Further, decreased default mode network functionality may be associated with feelings of relief, as evidenced by the changes in vmPFC and amygdala associated with alleviating fearful feelings (Hariri et al., 2000).

3.3. Summary of brain responses related to sexual consummation

Sexual consummation is an important phase of the sexual response cycle during which orgasm and the ejaculation necessary for reproduction may or may not occur. It is often accompanied by strong subjective pleasure which may be prolonged for as long as the phase last. Sexual consummation can follow on naturally from the sexual interest and arousal phase. If orgasm is obtained, the phase is invariably followed by the satiety or post-orgasmic refractory period (at least in men).

Sexual genital stimulation is most often the first part of the sexual consummation phase. In the neuroimaging literature, this phase has been investigated in greater detail in men than in women, and has been shown to overlap greatly with most of the 'sexual arousal network' identified on the basis of VSS studies (Fig. 6). It thus includes the aMCC, posterior insula, intraparietal cortex, vlOT, ventral pallidum, lateral hypothalamus, and frontal operculum/vPMC. In addition, putative somatosensory areas are activated, as well as primary and higher-order motor areas that correlate with pelvic muscular contractions supportive of a sexual arousal state, probably through concerted genital sensorimotor activity.

The weight of the evidence shows that contrary to textbook knowledge, the somatosensory representation of penis and clitoris is likely to be located on the dorsal surface of the primary somatosensory cortex. This is important information, given that this may be an important gateway into the sexual system.

Afferent inflow related to penile erection takes a largely segregated route to reach the central level, and the posterior insula–claustrum complex may be particularly relevant in this respect. The ventral pallidum seems to signal both onset and termination of genital stimulation. Critically, the high sexual arousal state during genital stimulation was associated with marked decreased activity of amygdala and other medial temporal lobe areas, ventral temporal cortex, and vmPFC.

Currently, orgasm is most reliably investigated in women. The most specific effect to orgasmic events is the change in activity in subregions of the OFC. The findings of activity in mid-anterior and medial OFC fit very well with data from other neuroimaging studies that have demonstrated that the pleasure of rewards is represented in these subregions of the OFC.

In addition, the evidence shows that the level of activity in ventromedial temporal cortices, as well as in vmPFC, correlated negatively with subjective arousal, which was highest during orgasm. Conversely, prefrontal areas showed the strongest negative coupling with rectal pressure fluctuations, a measure of involuntary pelvic muscular contractions, indicating a relative loss of behavioral control related to prefrontal deactivity. In the same vein, involuntary axial movements may explain the positive coupling with rectal pressure fluctuations in the vermis of the cerebellum.

4. Satiety or post-orgasmic refractory period

The final phase of the sexual response cycle is the satiety phase – or post-ejaculatory (orgasmic) refractory period (PERT) as it is known in the field of sexual science. Similar to the pleasure cycles for other rewards, there is invariably a phase where animals become unresponsive or much less responsive to a given reward. Yet, very little is currently known about the brain correlates of this phase.

All animals that employ sexual reproduction have a refractory phase during which they are sexually unresponsive. The duration of this period varies considerably across species, and, in humans, also across and within individuals. Moreover, there may be fundamental gender differences. In men the PERT is a robust biological event that occurs in virtually all men. As a consequence, achieving multiple orgasms in a single sexual session is quite rare in men.

The female post-orgasmic period is far less ubiquitous, and women may be able to achieve multiple orgasms in one session (Levin, 2009). The robustness of PERT strongly indicates that temporary unresponsiveness is likely to be more significant, biologically, for men than for women. In any case, PERT is remarkable for the rather dramatic shift in mental state, and discovering the responsible brain mechanisms would be highly interesting, not only from a neurosexological perspective, but also more generally, to understand consciousness processes.

The closest we have currently come to understand the PERT-related brain responses come from two studies. One fMRI study tried to specifically address the PERT-related brain responses, scanning men during the period 3–30 min post-ejaculation

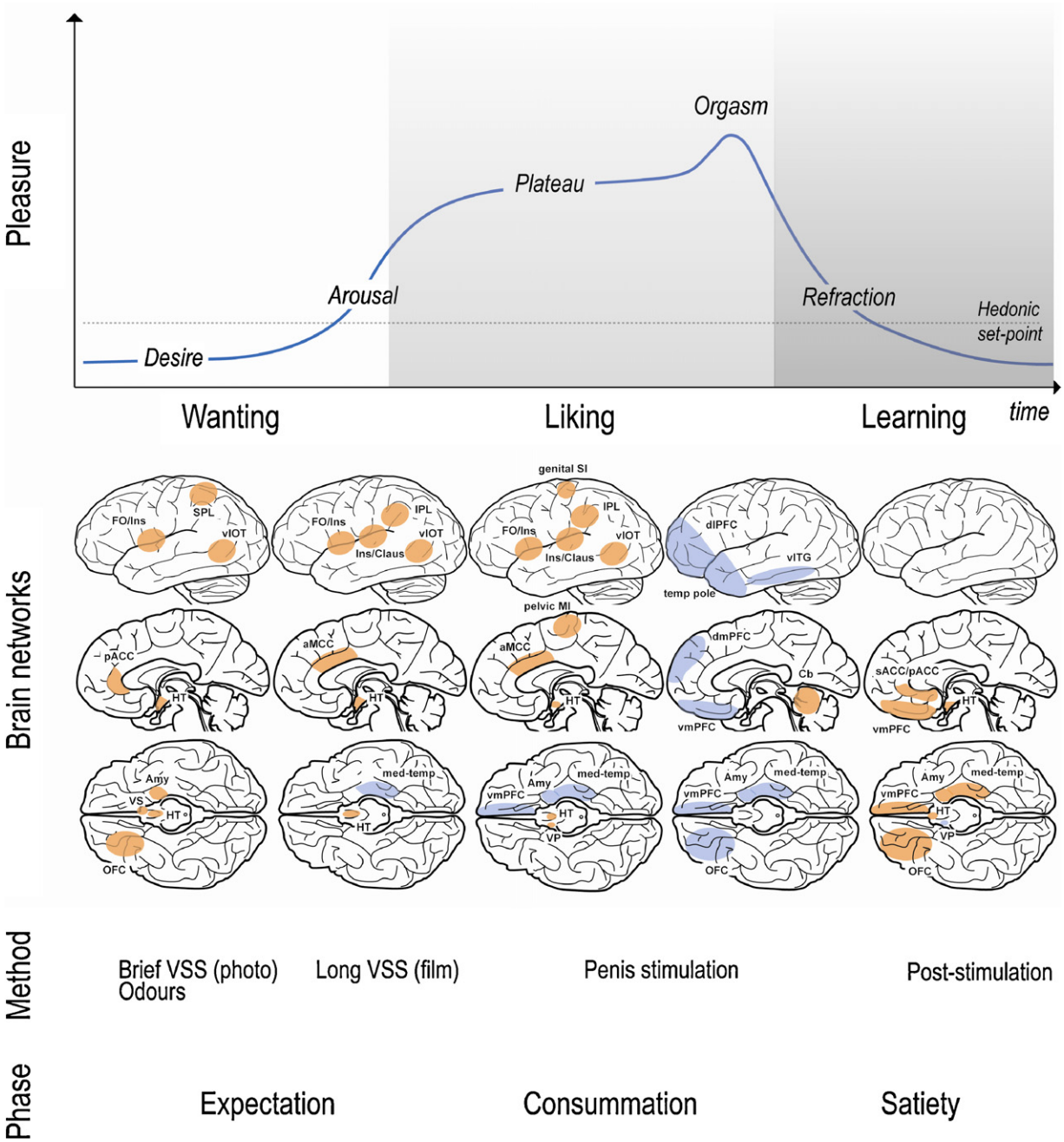

Fig. 6. Functional neuroanatomy of the human sexual response cycle. Neuroimaging studies have elucidated the key nodes and hubs that are responsible for sustaining and switching between the different phases of the pleasure cycle which can lead to changes in behavior (also listed in Table 1). The figure summarizes the findings from the neuroimaging literature as they relate to the different stages of the human sexual response cycle: desire, excitement, plateau, orgasm, and refraction (top panel). Different methods of stimulation are required for a state change to occur (bottom panel). Visual sexual stimulation paradigms will elicit sexual interest and wanting. Still sexual images are less likely than moving videos of sexual activity to cause a change from wanting to liking associated with higher arousal. However, in order to enter the consummatory plateau, sexual genital stimulation is usually required. The brain figures show the important areas mediating these changes in the sexual response cycle as described in the text (showing the region on only one side of the brain but most regions have bilateral involvement). Please note that some regions have multiple roles at different points in the sexual response cycle, e.g. activity in the amygdala is involved in different ways in encoding sexual salience, sexual arousal and orgasm, and post-stimulation.

(Mallick et al., 2007). This study found the septal area (which is close to anterior hypothalamus), temporal lobe, and amygdala involved. However, the very lengthy stimulation epoch seems not suitable for this purpose, possibly causing artifactual results (Smith et al., 1999).

A more recent and better controlled study found a similar pattern of activity (Georgiadis et al., 2010a) in a network related to post-stimulatory de-arousal was demonstrated, comprising the amygdala, parahippocampal gyrus, vmPFC, sACC, pACC and anterior hypothalamus (Georgiadis et al., 2010a). Unfortunately, this study required perfusion images during the post-ejaculatory phase to be pooled with images from post-stimulatory phases without ejaculation, making it impossible to determine very precisely PERT-related brain responses.

In summary, post-stimulatory activity has thus far only been investigated in men and was most prominent in vmPFC, sACC, pACC, anterior hypothalamus, amygdala, and parahippocampal gyrus (Fig. 6). This is indicative of a switch to default mode network activity after stimulation. Moreover, evidence was found for a sACC–anterior hypothalamus functional pathway that could be

key factor in de-arousal, possibly including the post-orgasmic state (Georgiadis et al., 2010b).

5. Variations of human sexual interest

In this review, we have used the sexual response cycle as a template for understanding the brain networks involved in sex as the only unassisted way to produce offspring. It is important to realise, however, that while the template works well for much sexual behavior, there is also a significant amount of sexual behavior that does not conform to this template.

Sexual variations within the template of the sexual response cycle can take many forms but typically relate to the object of desire, and in particular to sexual interest which is reproductively maladaptive. One example is sexual paraphilia where the object of desire is non-human. Other sexual variations include sexual interest in partners of the same sex which is common in the general population, with up to 5–10% of men and about 5% of women in the USA self-reporting at least a bisexual preference (Laumann et al., 1994; Xu et al., 2010a, 2010b). Surprisingly, given the high incidence in the general population, homosexual and bisexual preferences are regarded by some segments of the population as hugely controversial and are even criminalised in some societies.

Sexual variations are driven by both biological and psychological factors. Biological predisposition to gender identity and sexual preference have been well established since the seminal studies conducted by Gorski and colleagues highlighted the importance of hypothalamus morphology (Gorski et al., 1978). Some have taken such findings to the extreme by claiming that sexual variations are solely the product of biological predispositions, which is both controversial and not supported by the current scientific evidence (Pfaus et al., 2012).

In contrast to this deterministic view, it is a fact that humans are extremely adaptable to a whole range of different environmental situations and conditions, of which mate availability is of special importance to sexual behavior. This adaptability in itself strongly implies that learning from experience must play a critical role in sex (Woodson, 2002). In fact, a number of animal studies have demonstrated that learning is the critical link between biological predispositions present in the womb and mature sexual preferences and behaviors (Ismail et al., 2008; Koksal et al., 2004; Nash and Domjan, 1991; Pfaus et al., 2012). Under optimal conditions, sexual learning leads to 'reproductively normal' sexual outcome, but under unusual conditions reproductively maladaptive sexual strategies may develop, perhaps linked to sexual learning (Woodson, 2002). While largely ignored in human neurosexological research, sexual learning in the context of the lifetime changes in the sexual response cycle can provide a framework for understanding how paraphilic sexual preferences like paedophilia may develop.

Sexual dysfunction provides another source of variability in human sexual responsiveness. Note that sexual dysfunction is defined as the inability to execute a sexual response in a satisfactory manner. Many sexual dysfunctions exclusively and directly affect the genital apparatus or gonadal hormone release, but there is a class of sexual dysfunctions that is likely to originate from neurogenic and/or psychogenic factors. This is likely the case for hyposexual desire, premature ejaculation, erectile dysfunction, anorgasmia, hypersexual desire, retarded ejaculation, and vaginismus.

Again, it is helpful to think about how, over time, variations in sexual interest gain access to the sexual response cycle. In particular this is helpful when thinking about the variations in brain networks. While the evidence is not entirely clear at this point, it may well be possible that early sexual learning predisposes a certain shift of balance in the sexual response cycle which subsequently manifests itself in certain sexual behaviors.

In the following sections we review brain data related to the most-studied variations in sexual interest: homosexual preference, hyposexual desire disorder, and pedophilia. It is important, however, to realise that the available knowledge is largely based on VSS paradigms, which is only a small part of the full sexual response cycle.

5.1. Homosexual preference

Sexual preference for individuals of the same gender (homosexuality) is a common variation of sexual interest and trying to understand the origin of this natural variation has led to the pursuit of a number of questions. One key question has related to whether there is a neuroanatomical difference leading to homosexuality. In the following, we briefly review this highly controversial data, while noting that, in contrast, very little research has been done investigating the role of learning in homosexuality.

Post-mortem investigations of human brain tissue have suggested that the volume of certain hypothalamic subnuclei is determined not only by gender (Allen et al., 1989; Hofman and Swaab, 1989), but also by sexual orientation (Levay, 1991) and gender identity (Kruijver et al., 2000; Zhou et al., 1995). MRI investigations of living human brain structure have provided some evidence for gender-related volumetric variation in many other human brain regions, including striatum, amygdala, medial PFC, and hippocampus (Goldstein et al., 2001; Mechelli et al., 2005), although evidence for sexual dimorphism in the size of brain regions is far less pronounced in humans than it is in animals.

In contrast, there is only very limited evidence for structural changes with regards to sexual orientation. Homosexual women (and heterosexual men) were found to have decreased grey matter density in the left perirhinal/parahippocampal cortex compared to heterosexual women (Ponseti et al., 2007). Some corroborating evidence for this finding comes from clinical observations of late-life transvestite behavior (Gautier-Smith, 1980), and even homosexual paedophilia (Mendez et al., 2000), following hypometabolism of the medial temporal lobe.

With regards to differences in functional brain activity, only a few studies have addressed the question of whether same sex preference gives rise to differences in VSS-induced brain activity. The evidence so far is that there are no significant differences compared to brain activity seen in heterosexuals (Hu et al., 2008; Paul et al., 2008; Safron et al., 2007).

Some evidence points to differences in how the brain processes preferred or non-preferred visual sexual stimuli across sexual preferences. For instance, a cluster of brain regions encompassing VS/NAcc, hypothalamus, medial thalamus, and pulvinar, was more active irrespective of sexual preference when participants viewed preferred aroused genitalia, as compared to their non-preferred genital category (Ponseti et al., 2006).

A very similar sexual preference-driven VS/NAcc response was demonstrated in a study in which participants with and without sado-masochistic preferences participated (Stark et al., 2005). The vPMC, an area possibly related to 'sexual embodiment' (Sections 2.2.1 and 6.2), showed a similar bias to preferred core sexual stimuli, as did the superior parietal lobule (Ponseti et al., 2006). Watching non-preferred genitalia (Ponseti et al., 2009) and non-preferred VSS video excerpts (Paul et al., 2008) was associated with completely different networks.

The fact that brain responses to preferred and non-preferred sexual stimuli are so distinct can potentially be exploited, for instance by using machine learning techniques to automatically classify homo- or heterosexual participants on the basis of their

VSS responses (Ponseti et al., 2009). Though somewhat over the top as assessment tool for homosexual preference, such techniques do hold high promise in the profiling of people with dangerous preferences, particularly pedophiles (Ponseti et al., 2012).

5.2. Hyposexual desire

The lack of sexual desire is all too common and affects the well-being of far too many people. While hyposexual desire disorder is most common in women, it may also manifest itself in men as psychogenic erectile dysfunction. These sexual disorders are linked to complex psychological and biological factors that are very difficult to tease apart.

Yet, less complex causes of hyposexual desire exist such as deficits in putative neuromodulators. The most important examples are hyperprolactemia (e.g. in women who breastfeed), Parkinsonism, and male hypogonadism. It has been proposed that testosterone and dopamine enhance sexual interest, whereas serotonin, prolactin, and opioids generally have the opposite effect (Clayton, 2010; Hull et al., 2004; Pfaus, 2009). As a result, most of the pharmacological treatment strategies for hyposexual desire disorder focus on targeting these neurotransmitters.

VSS neuroimaging studies focusing on hyposexual desire disorder find that hyposexual individuals have altered VSS-induced global brain activity compared to control participants, which can be 'normalized' by pharmacological treatment (Archer et al., 2006; Hagemann et al., 2003; Montorsi et al., 2003; Redouté et al., 2005; Schaefer et al., 2006). However, these observations are tentative at best, given that most studies did not perform a direct statistical group comparison, or use a placebo control condition. Moreover, these studies have not provided precise insights as to which regions or mechanisms might mediate diminished sexual interest. The causes for these shortcomings are legion and can be linked to probable divergences between VSS paradigms, hyposexual disorders, and the treatment compounds delivered.

The studies where direct comparisons between hyposexual individuals and healthy controls were performed seem to suggest that increased activity in ventral prefrontal (Arnow et al., 2009; Cera et al., 2012) and dorsal parietal areas (Bianchi-Demicheli et al., 2011; Cera et al., 2012), and decreased activity in the aMCC (Bianchi-Demicheli et al., 2011; Cera et al., 2012), are indicative of differences in sexual arousability. Interestingly, whereas male patients showed sustained SPL activity during a long erotic video (and a failure to achieve erection), a drop in SPL activity and a rise in middle/posterior insula activity coincided with penile erection in controls (Cera et al., 2012). These observations seem to relate to the sexual arousal network identified earlier (see Section 2.2.4), and suggest that hyposexual patients fail to activate this network.

Similar to what we have described in the previous sections, VSS effects in the prefrontal cortex were rather inconsistent across studies, apart perhaps from the OFC which showed a rather clear bias towards the still VSS images (see Section 2.2.3). Still, some studies, especially those using rather lengthy porn movie excerpts, reported results that associate prefrontal *hyper*activity with *hypo*sexual behavior. This would seem to support the alleged connection between sexual disinhibition and PFC damage suggested by neurological cases (though less consistent than often claimed, see Rees et al., 2007). One study demonstrated that effortful suppression of VSS-induced sexual arousal was associated with enhanced activity in the left lateral PFC, pACC, and SPL (Beauregard et al., 2001).

Testosterone may be a critical factor in prefrontal regulation: in healthy men plasma testosterone negatively predicted VSS-induced blood flow in vmPFC and left lateral PFC (Stoleru et al., 1999), and in hypogonadal men testosterone treatment down-regulated activity of the left lateral OFC (Redouté et al., 2005). These findings were supported by a recent study showing exaggerated VSS-induced responses in these prefrontal areas in individuals with hyposexual desire disorder (Arnow et al., 2009). On the other hand, a study in depressed participants showed enhanced PFC responses (including lateral PFC) to briefly presented erotica that correlated with amelioration of the depressive symptoms (Schaefer et al., 2006). A potential explanation of this discrepancy is that recognition of sexual salience – the most likely scenario in the case of brief VSS – requires a different kind of PFC/OFC involvement than sexual arousal and genital responses which may be expected after prolonged exposure to a porn movie under normal conditions.

5.3. Paedophilia

The parent–infant relationship is the source of much social pleasure and it is clear that we have natural tendency to be drawn to infants (Parsons et al., 2010). Yet, this natural love of children has a very dark side, in the form of paedophilia.

Though the aetiology of child sex offending is not known, neurodevelopmental mechanisms are likely to be heavily implicated (Seto, 2004). Indeed, some studies have shown that brain regions shown to be involved in adult VSS processing like the amygdala, hypothalamus, VS/NAcc, and OFC have reduced grey matter density in paedophiles compared to non-offending controls (Schiffer et al., 2007; Schiltz et al., 2007). However, another study comparing paedophiles to nonsexual offenders found no regional differences in grey matter volume, but instead identified significantly lower white matter density in two bundles (fronto-occipital and arcuate fasciculi) in paedophiles (Cantor et al., 2008). These major fiber bundles connect most of the areas implicated in sexual interest and arousal, suggesting that decreased, or altered, connectivity in such networks might make people susceptible to paedophilia (Cantor et al., 2008).

Despite its devastating consequences, not more than a handful of VSS neuroimaging studies have tried to 'profile' paedophiles with functional neuroimaging (Poeppl et al., 2011; Ponseti et al., 2012; Sartorius et al., 2008; Schiffer et al., 2008a,b; Walter et al., 2007). The most important challenge in this type of studies is that for obvious legal, moral and ethical reasons, it is not feasible to employ pornographic photos or videos showing sexual activities involving children. Therefore, the kind of 'erotic' stimuli used in these studies is restricted to photos or drawings of nude or barely dressed children.

The evidence would seem to suggest that the brain responses to *child* stimuli in paedophilic participants are similar to the brain responses in non-paraphilic controls when they are presented with *adult* stimuli (Section 2.2). Recent evidence suggests that pedophiles and controls can be reliably classified on the basis of VSS-induced brain activity (Ponseti et al., 2012). Indeed, from the studies using direct comparisons between paedophiles and non-paraphilic controls, the data shows that male paedophiles have different brain responses to adult erotic stimuli. Such weaker responses have been identified in OFC, dorsolateral PFC, hypothalamus, dorsal midbrain, insula, and ventral premotor cortex (Walter et al., 2007), in aMCC, pACC, and visual cortical areas (Schiffer et al., 2008b), and in the caudate nucleus (Schiffer et al., 2008a). Moreover, the OFC was related to the expectation of nude adult images in non-paraphilic controls only (Walter et al., 2007), whereas the severity of pedophilic symptoms negatively predicted left dorsolateral PFC activity (Schiffer et al., 2008b; Walter et al., 2007). Other prefrontal areas whose activity was negatively associated with the severity of pedophilic characteristics were the OFC, vmPFC, and dmPFC (Schiffer et al., 2008b).

Due to the correlational nature of these findings, it is not possible to draw any strong conclusions about the neurobiology of

paedophilia. Nevertheless, the main difference is clearly in the kinds of sexual stimuli which will elicit a transfer to the sexual pleasure cycle. It is thus potentially important that heterosexual controls exhibit activity in OFC in response to images of adult nude women, while paedophilic men (and homosexual controls) do not. Together with structural variation in OFC volume (Schiffer et al., 2007) and white matter connectivity (Cantor et al., 2008) pointing in the same direction, it suggests that paedophilic men follow a similar sexual response cycle to normal men but that there is a difference in the impetus for changing through the various phases of the sexual response cycle. The relative poor responsivity of dorsal prefrontal areas to adult stimuli may also be related to the unfit object of desire, and is suggestive some kind of disturbance in cognitive or evaluative processing (Regestein and Reich, 1978). Still, these observations raise more questions than answers, and more research is needed to clarify these important issues.

6. Comparison of the human sexual response cycle to other reward cycles

Thus far we have reviewed the evidence from neuroimaging for identifying the main brain networks involved in initiating, sustaining and terminating the human sexual response cycle. The perhaps most striking finding is the similarity between the reward cycle involved in sex compared to food and social stimuli. At the same time, as indicated in the introductory sections of this review, sex not only critically shares characteristics with other pleasure cycles, combinations of the different pleasures can synergize and lead to amplification of sexual pleasure.

In the following sections, we compare the underlying brain networks for sex with those underlying the other pleasure cycles.

6.1. Comparison of sex and food cycles

From a systems neuroscience perspective it would be expected that there would be strong similarities between sex and food cycles given their critical role in survival. As such, it is likely that there could be 'innate' neural representations of survival-related stimuli, e.g. sweet taste or pheromone detection. Similarly, input to different primary sensory modalities can initiate and change the anticipation, consummation and satiety phases of the pleasure cycle.

Additionally, both the sex and food cycles are substantially modulated by internal state (e.g. blood levels of sex steroids or nutrients), external factors (e.g. availability), prior experiences or associations, and expectations and beliefs. In food research, all these features are being studied extensively (Veldhuizen et al., 2010), and, as shown in the previous sections, this evidence is highly relevant for understanding the functional neuroanatomy of sexual behavior. Yet, it should be noted that one of the main differences between food and sex is the role of social interactions.

6.1.1. Identification of food and sex in the brain

Identification of potential sources of pleasure such as food or sex is an important gateway to enter into a pleasure cycle. As described in Sections 2.1 and 2.2, all of the different sensory modalities can signal reproductive viability and serve to initiate the sexual interest cycle. The evidence (primarily from visual and odour stimuli) shows that this leads to activity in the posterior regions of the OFC (Oei et al., 2012; Platek and Singh, 2010; Schiffer et al., 2008b; Sescousse et al., 2010; Zhou and Chen, 2008).

These findings support the neuroimaging findings of other reward modalities showing that the posterior middle OFC has reward representations of the primary sensory modalities (Kringelbach, 2005). The identification processes of primary reinforcers such as smells, tastants, visual, and oral sensations associated with food recruit a very similar region of the OFC (Kringelbach and Stein, 2010).

Similarly, the multimodal fusion of some or all of these primary stimuli are also represented in the OFC (Kringelbach, 2005). This multimodal fusion of sensory input is a natural part of sex but interestingly has not yet been much investigated in neuroimaging studies, which have tended to concentrate on primarily unimodal visual studies.

The reward evaluation phase follows identification of reinforcers in order to allow for these reinforcers to have the appropriate behavioral consequences. Whereas the evidence shows that both attractive and aversive tastes and odours are represented in medial OFC (Rolls et al., 2003; Small et al., 2003), this hedonic dissociation has not yet been identified for positive and negative sexual stimuli.

Some studies have compared the brain responses in participants using erotic stimuli that are both similar and opposite to their stated sexual preferences (Paul et al., 2008; Ponseti et al., 2006; Stark et al., 2005). This, however, is not a particular sensitive approach to uncovering the hedonic monitoring of sexual stimuli and it would be important to use paradigms similar to those used in food research, e.g. comparing brain responses with subjective ratings of the sexual stimuli.

It would seem logical that the affective value of food or sex stimuli might be tightly coupled to their absolute survival value. In reality, however, it is important to realise that brain processing of the hedonic value of reinforcers is very complex and relies on both learned and anticipatory processes integrated with interoceptive signals and environmental factors.

For instance, the medial OFC was active when participants chose high- versus low-incentive menus, but this effect was much stronger when participants were hungry (Hinton et al., 2004). Similar flexibility is seen in sex reward representations in the OFC suggested by the finding that the activity in the OFC in women watching male faces increased near the time of ovulation, and that this activity correlated with perceived attractiveness (Rupp et al., 2009a).

In the following we review the similarities and differences between brain networks involved in sex and food for the three major phases of their cycles, anticipation, consummation and satiety.

6.1.2. Sex and food anticipation

In order to survive, it is important to be able to learn to predict when food or sex rewards become available. In the laboratory, this learning is often tested by using conditioning paradigms where researchers usually couple abstract (visual) cues to appealing food and sex stimuli, leading to conditioned responses. Fundamental brain mechanisms have been uncovered which help to control this vital ability which is not specific to a particular sensory modality (Blackburn et al., 1992). Thus, regardless of whether participants expected food (Gottfried et al., 2002, 2003; O'Doherty et al., 2002) or sex stimuli (Klucken et al., 2009; Sescousse et al., 2010), the conditioned stimulus was consistently processed by the ventral striatum, amygdala and OFC. The contingencies critically depend on homeostatic signals, exemplified by blunted responses in these areas, as well as anterior insula and ACC, to visual cues that predicted foods eaten to satiety (Gottfried et al., 2003), and by enhanced activity in large parts of this network during a hunger relative to a sated state (Del Parigi et al., 2002; Tataranni et al., 1999).

The finding that sexual conditioning is less effective in the postorgasmic period (Kantorowitz, 1978) strongly suggests that reward devaluation is not only present for foods but also for sexual stimuli. Additional evidence is provided by studies showing that the menstrual cycle significantly modulates reward (Ossewaarde

et al., 2010) and arousal (Goldstein et al., 2005) related brain activity, in particular in the amygdala, ventral striatum, and OFC.

So overall, the same fundamental brain network appears to be involved in the learning and prediction of sexual and food stimuli. Differences relate to the internal homeostatic signals that modulate this learning which are different for food and sex behaviors (but can interact).

6.1.3. Sex and food consummation

The neurobiological evidence of food reward in other animals has convincingly shown that there is a difference between 'wanting' and 'liking' a food, and that there are clear differences in their neurobiological substrates in terms of brain regions and neurotransmitters (Berridge, 1996).

Part of the pleasure of eating relates to ingesting the food which is a complex procedure that typically involves chewing which is a repeated motor pattern not unlike that found in sexual copulation. Yet, due to practical limitations, food brain imaging studies have a difficult time capturing the process of the chewing during eating. Instead, they focus on the effect of flavour after food ingestion. Flavour is the result of the multimodal integration of unimodal sensory input, which has been linked with a network of regions including the posterior parts of OFC, anteroventral insular cortex, anterodorsal insula–frontal operculum and aMCC (Small et al., 2004).

In sex research both the aMCC and the frontal operculum–anterodorsal insula were among the regions most strongly activated during sexual penis stimulation, and showed the most tight coupling with the degree of penile tumescence and reported sexual arousal (Georgiadis et al., 2010a). These regions overlap with those found to be involved in the multimodal percept of flavour and sexual genital stimulation, and may thus relate to proximity, interoception and multisensory integration.

Following this arousal phase, orgasm is perhaps most important and pleasurable part of the sexual consummatory phase. As shown above the mid-anterior and medial subregions of the OFC are strongly linked to the orgasm. This fits well with the existing literature implicating the OFC in pleasure and reward processing in food reward (Kringelbach, 2005).

The mid-anterior OFC activity clearly reflects subjective hedonic experience, when the reward value of one food was reduced by eating it to satiety (while remaining high to another food) (Kringelbach et al., 2003). This evidence from both sex, food and other reinforcers make the mid-anterior subregion of the OFC the most likely region coding of human subjective experience of pleasure (Kringelbach, 2005).

Similarly the responses in the medial OFC are interesting given the medial regions of the OFC show activity related to the valence of positive and negative events (Kringelbach and Rolls, 2004). Furthermore, as mentioned above, there is a medial-lateral hedonic gradient in medial OFC which interacts with an abstraction-concreteness gradient in the posterior–anterior dimension. It is important to realize that this medial region of OFC may not reflect the full dynamics of pleasure, since it does not appear to change its activity with reinforcer devaluation, as thus may serve primarily to monitor hedonics.

In addition to these cortical regions, recent theories of food reward have emphasized the role of the subcortical region ventral pallidum as a pivotal region in the generation of food liking and disliking (Smith and Berridge, 2005). Interestingly, the posterior part of the ventral pallidum showed increased activity during genital stimulation compared to the post-stimulatory period (Georgiadis et al., 2010a), supporting the idea that this part of the ventral pallidum processes food liking (Smith and Berridge, 2005).

Overall, it is clear that consummation invariably is linked to positive hedonic processing, since this provides the impetus for an animal to seek to transfer to this state. There are many similarities in the brain networks utilized during the pleasurable states of sexual and food consummation, the most pertinent those found in subregions of the OFC and in the ventral pallidum.

6.1.4. Sex and food satiety

Food intake is complex process which eventually leads to homeostatic changes e.g. distension of the stomach and other autonomic changes. This drives the learning that over time decreases the motivation to eat, i.e. drives the prediction that a certain amount of food ingested will provide the necessary amount of energy. Typically, over a time, this decrease in wanting is accompanied by a similar decrease in liking or hedonic appreciation of the food. Yet, it is also clear that there are mechanisms such as selective satiation that can selectively devalue one kind of food, e.g. the main course, while still leaving room for the dessert. Eating is primarily driven by expectation and the subjective feelings of hunger or thirst almost always set in long before actual metabolic changes (e.g. plasma glucose or sodium concentrations) (Egan et al., 2003).

Sexual consummation (e.g. coitus) also leads to homeostatic changes, but appears subjectively different from eating in that it tends to become increasingly more pleasant and arousing towards the orgasm. Orgasm is thus a strong clear signal of sexual satiation which is much more intense, and much less gradual, than the satiation process involved in food intake (at least in men). It is, however, also clear that sexual consummation without orgasm or even with multiple orgasms have much in common with the consummation related to food intake.

The difference between sexual and food consummation related to the orgasm is likely to be reflected in specific changes in brain networks. In particular, it would seem likely that the ventromedial PFC/OFC response patterns play a role. From onset to satiation, a gradual decrease in vmPFC activity characterizes both consummatory behaviors. However, while food intake eventually becomes aversive, genital pleasure becomes increasingly pleasant, leading to opposite correlations for food (Small et al., 2001) and sex (Georgiadis et al., 2006) between hedonic ratings and vmPFC activity. Interestingly, the vmPFC, along with sACC and anterior hypothalamus which also correlated with changing food hedonics, are most robustly active during the sharpest decline in penile tumescence after genital stimulation ceased (Georgiadis et al., 2010a). This could suggest that the activity of these areas may not reflect hedonia per se, but rather an effort to balance the dynamic equilibrium of the system (e.g. by changing the brain dynamics, restoring nutrient levels or down-regulating the system after high sympathetic arousal) (Kringelbach et al., 2011).

If the role of these areas is in rebalancing the brain networks, it may mean that pleasure interacts differently with the primary reinforcers of sex and food, which is also suggested by taking a closer look at their evolutionary origins. From an evolutionary perspective sex should be pleasurable for both sexes, but for males in particular it would be adaptive to reach the highest pleasure at and around ejaculation. Possibly as a consequence of this, most women may reach orgasm after a certain amount of clitoral stimulation (Lloyd, 2005).

In contrast, with regards to food, the first bite could be the most pleasurable, because it signals that in all likelihood homeostasis is going to be restored. It should be noted, however, that the first taste of food is also the most dangerous and important decisions have to be made regarding whether to ingest or reject (Kringelbach, 2004). The selective satiety principle also means that there can often be multiple pleasurable climaxes during a meal. Therefore, there is also much pleasure to be had during a meal

which is similar to that seen during sexual consummation and perhaps more like multiple orgasms.

In terms of what brain regions may drive the brain networks towards satiety, there are other prefrontal subregions that may also contribute to the termination of consummatory behavior. The lateral OFC has been shown to have increased activity related to increasing aversiveness when chocolate was eaten to (and beyond) satiety (Small et al., 2001). It was also active only when choosing items from a menu when participants were full (Hinton et al., 2004).

By contrast, during orgasm lateral OFC activity was very low as indexed by indirect neuroimaging measures, especially when compared to sexual genital stimulation (Georgiadis et al., 2006, 2007, 2009). According to one model of OFC function, the lateral OFC evaluates reward-related information leading to behavioral shifts (Kringelbach, 2005). This is supported by the food and sex experiments quoted, where the consummatory circumstances meant that the changes in lateral OFC may have been related to the ability to conform to the experimental design, as it meant that requested behavior was incongruent with perceived affect. In the case of food, eating to and beyond satiety, or choosing food while sated, represents such a situation. In the case of sex, a similar situation exists when participants want to achieve orgasm but are not allowed to (Georgiadis et al., 2006).

Recently, it was revealed how both OFC regions might affect behavior. When hungry, participants were fast to respond via button presses to visual food targets, which in turn correlated with medial OFC activity. However, when participants were sated, their food responses were slower correlating with lateral OFC activity (Mohanty et al., 2008).

Activity of dorsal PFC appears to characterize a sated relative to a hunger state, and has been proposed to reflect prefrontal inhibition of subcortical motivational mechanisms (Del Parigi et al., 2002; Tataranni et al., 1999). Likewise, dorsal PFC areas were active after the cessation of sexual activity (Georgiadis et al., 2010a), when participants were asked to inhibit their sexual arousal (Beauregard et al., 2001), and in hyposexual participants exposed to visual erotica (Redouté et al., 2005; Stoleru et al., 2003).

The lateral hypothalamus may be a subcortical target of considerable interest with respect to the shift towards satiety, not only because its activity decreases during food satiety (Smeets et al., 2005), but also because in male rats post-ejaculatory serotonin release in the lateral hypothalamus inhibits sexual motivation (Lorrain et al., 1999). Conversely, during sexual stimulation the lateral hypothalamus showed a strong association with sexual motivation and arousal (Brunetti et al., 2008; Ferretti et al., 2005; Georgiadis et al., 2010a). These observations fit with recent ideas that the lateral hypothalamus could be a critical link between arousal and reward (Harris et al., 2005).

Overall, satiety invariably follows consummation whether or not orgasm is achieved. This rebalancing of the brain networks is similar between food and sex but there are differences in the signalling of satiety. At least in males, orgasm is an important signal for the transition to the satiety phase. An equivalent signal is not found in food and thus there may be some minor differences in the exact pleasure time course related to food and sex. It should be noted, however, that the signalling of sexual satiety may be more similar to that of food satiety in women, where orgasm is either not always present – or potentially multiple.

6.2. Sex and social interaction

In social species such as humans, one of the most important pleasures is the social interaction with other conspecifics. This social pleasure is regarded by some researchers as a fundamental pleasure (Kringelbach and Berridge, 2010) and certainly one which interacts strongly with other basic pleasures such as food and sex.

Sexual reproduction by definition requires a male and a female specimen to interact, but the factors that influence this interaction are potentially numerous, especially in humans. Anecdotal evidence shows that interpersonal communication is perhaps the best predictor for the success of sexual attempts. In turn, intense social interaction during sexual activity is likely to amplify sexual pleasure, and also the meaning attributed.

Animal studies have convincingly demonstrated an interaction between sexual activity, the release of the anterior pituitary neuropeptides oxytocin and vasopressin, and pair bond formation (Young and Wang, 2004). This constitutes perhaps the most compelling neurobiological evidence of how sexual activity affects social behavior. However, human social behavior is inherently much more complex and while these neuropeptides may also be relevant, the effect they exert is likely to be more subtle than that found in rodents (Heckel and Fink, 2008; Walum et al., 2008).

In women, the stimulation of the vaginocervix and nipples are potent releasers of oxytocin, which may be particularly important in mother–infant bonding. Likewise, oxytocin, a powerful stimulant of uterine smooth muscle, is strongly associated with uterine contractions during labour. Uterine contractions are also assumed to occur during orgasm (Chayen et al., 1979), which fits with the finding of enhanced plasma oxytocin after orgasm (Carmichael et al., 1987, 1994). In turn, this oxytocin release is believed to strengthen the emotional tie between partners.

There is no convincing evidence from neuroimaging studies linking sex-induced hypothalamic function to release of these neuropeptides. Pharmacological studies in men have provided mixed results, showing elevated vasopressin and oxyocin during sexual arousal and orgasm, repectively (Murphy et al., 1987, 1990), but also failing to measure elevated oxytocin in cerebrospinal fluid during sexual activity and orgasm (Krüger et al., 2006). A nasal oxytocin spray did not significantly alter consciously reported sexual experience (Burri et al., 2008), but a single case study in an anorgasmic man found that oxytocin facilitated ejaculation (Ishak et al., 2008). Clearly, there must be many other factors that mediate the interaction between social behavior and sexual activity in humans.

Another way to approach this problem is to consider what human coitus entails. Even when human coital positions can be extremely versatile, the missionary position and other forms of face-to-face coitus are the most popular coital positions in a wide variety of human cultures (Dixson, 1998). Face-to-face coitus has been observed in other great apes such bonobos (Dixson, 1998), but the predominance of such coital positions in human beings could be taken to reflect the significance of social interaction for human sex.

There are various explanations for why humans evolved to have intercourse in this way. The vaginal opening in human females is relatively anterior and deep compared to their quadruped counterparts, and therefore less accessible from the rear. Another critical factor may be that human ovulations have evolved to be relatively 'concealed' in terms of overt behavior, which promotes the formation of long-lasting pair bonds and, therefore, male–female social interaction. In any case, it remains possible that during human evolution more sophisticated sexual behavioral strategies were selected for, that were enabled by – or perhaps even led to – major advances in brain complexity.

As shown above in Section 2.2.2, regions involved in sophisticated human behavioral strategies like mental action imitation (Caspers et al., 2010) and emotional empathy (Keysers and Gazzola, 2009) also readily respond to visual erotica, especially to film excerpts depicting multiple person sexual interactions. These regions (frontal operculum/ventral PMC, anterior insula,

intraparietal cortex, and vlOT) exhibit activity that correlate with penile tumescence and sexual arousal (see e.g. Ferretti et al., 2005; Redouté et al., 2000). Remarkably, these areas were also active when participants with eyes closed underwent sexual penis stimulation from another person (Georgiadis et al., 2010a). Thus, it seems that there is a tight connection between social behavior (understanding other people) and sexual arousal at the brain level, insofar that they share a common neuroanatomy.

If observing the sexual arousal perceived by others somehow connects to own perceived sexual arousal, this constitutes a tangible link between sex and social behavior. This idea is related to mirror neuron theory: All of the regions discussed in this section are known to contain neurons that become active both during action execution of observation of that same task (see e.g. Rizzolatti and Craighero, 2004).

The existence of 'sexual mirror neurons' has been suggested (Moulier et al., 2006; Mouras et al., 2008; Ponseti et al., 2006), but never proven directly. Nevertheless, findings in favour of this proposition can be identified. Foremost, regions with such properties would need to active both when undergoing sexual genital stimulation (action execution) and when viewing people engaged in similar activity. Potential candidates for such regions are found in the vPMC and vlOT where activity has been shown to predict the magnitude of the penile response recorded 20 s later (Moulier et al., 2006; Mouras et al., 2008). Further regions include the the IPC, vPMC and vlOT where sight of other people being touched changes the brain activity (Blakemore et al., 2005; Ebisch et al., 2008). Note, however, that activity in these areas may vary across individuals, both in terms of their vicarious activity (Blakemore et al., 2005), and in the functional connectivity between them (Borg et al., 2012; Zaki et al., 2010). Note also that there is nothing specifically sexual about any of these brain regions.

This line of reasoning has important theoretical implications. It means that sexual activity is facilitated and synergized when we are able to understand or recognize the bodily and non-bodily sexual message conveyed by others. Further, it is potentially important that the functionality of this network may vary between individuals, because it may explain why people differ in the degree they are captured by e.g. pornography, or maybe even the prospect of intimate sexual contact.

The development of brain systems related to social interaction is one which starts with the early parent–infant relationship, then shifts to the peer groups and grows progressively more complex during development. In the context of the synergy between sex and social interaction, it is clear that in normal development, the ability to understand and relate to sexuality needs to develop, as children do not seem to recognize sexual interactions as erotic. Puberty is likely to be a vital stage in this respect, suggesting that gonadal hormones mediate the development of this ability (see Fig. 2).

6.3. Sex, drugs, and rock 'n roll: pleasure, euphoria and arousal

Sexual encounters can be very costly in terms of energy expenditure, and generally engage very high arousal levels. Interestingly, arousal and mood seem to interact closely (Pfaff et al., 2008), though this is not true for all pleasure cycles. Could it be that all this hard work in the end serves to enhance the sexual experience?

Recent theories stress the importance of arousal in behavioral activation, giving specific reference to the facilitating role of general arousal for sexual activity (Weil et al., 2010). From a functional perspective, and focusing on males, sufficient sympathetic arousal seems key to reaching ejaculation. This is exemplified by markedly elevated norepinephrine levels measured in cerebrospinal fluid during masturbation-induced sexual arousal and ejaculation (Krüger et al., 2006).

Neuroimaging studies that have measured peripheral indices of general arousal (e.g. heart rate, skin conductance) have consistently shown that the aMCC and anterior insula are linked to autonomic arousal accompanying a variety of tasks and processes that typically require effort and behavioral engagement. In particular, activity in these areas correlates with increasing sympathetic tone (Critchley et al., 2003, 2011). Conversely, the cognitive part of the default mode network (sACC, vmPFC) correlates negatively with sympathetic arousal, or positively with parasympathetic tone (Nagai et al., 2004). Decreased vmPFC and amygdala activity is associated with feelings of relief (Hariri et al., 2000), pointing to possible contributions of the default mode network functionality to the pleasure system. Of note, time courses of aMCC and sACC activity track penile tumescence and detumescence, respectively (Georgiadis et al., 2010a), suggesting that penile responses are closely coupled to general indices of bodily arousal, and that this may be orchestrated by similar networks at the central level.

Music is an interesting example which may help both to make sex happen and to make it more pleasurable. As suggested above, sympathetic arousal is strongly coupled with pleasure (Salimpoor et al., 2009), explaining why arousing activities like exercise/sports, dancing and music are so ubiquitous in human culture. The link between autonomic responses and pleasure has been studied mainly for music (Salimpoor et al., 2009). Many individuals experience a particularly euphoric response to music, sometimes described as "shivers-down-the-spine" or "chills", which perhaps is not unrelated to the orgasm phase of the sexual pleasure cycle.

In one study, music lovers listened to music which included their favourite music and rated the intensity of perceived chills afterwards (Blood and Zatorre, 2001). Areas strongly implicated in sympathetic arousal, like the aMCC and insula (Critchley et al., 2003, 2011), tracked increasing ratings of chills, and these areas also showed a strong association with sexual genital stimulation and arousal. In a more recent study, the aMCC, insula, and frontal operculum/vPMC were active when judging liked versus non-liked rhythms (Kornysheva et al., 2010), suggesting a congruency between arousal, pleasure, and motor output in these areas that may also apply to sexual activity.

Perhaps even more interesting is the finding that activity in VS/NAcc, medial and mid-anterior OFC strongly correlated with the intensity of chills related to musical pleasure (Blood and Zatorre, 2001). Further studies showed that VS/NAcc dopamine release were specifically linked to the peak of perceived chills and not to their anticipation (Salimpoor et al., 2011), and there was an absence of activity in VS/NAcc and OFC when exposed to a novel, but liked, pop song (Berns et al., 2010). The peaks in the medial and mid-anterior OFC are very similar to those found during orgasms or during hedonic processing of foods. Similarly, the nucleus accumbens has been strongly implicated in the generation of liking response.

Yet, as shown above, VS/NAcc and medial OFC have also been shown to be involved in the anticipation primary rewards like food and sex (Section 6.1.2). This dual role of these regions fits well with the evidence from reward-processing. Both the coding and prediction of rewards have been found in subregions of OFC (Kringelbach, 2005; Sescousse et al., 2010). Yet, due to the problems with low temporal resolution of current neuroimaging techniques such as fMRI and PET, we do not yet fully understand the temporal coupling between the networks involved in prediction and receipt of rewards. Other neuroimaging techniques such as magnetoencephalography may help to unravel these links.

In terms of linking music and sex, it is also of interest that negative correlations with chills intensity were found in vmPFC, amygdala, and hippocampus (Blood and Zatorre, 2001), which can be linked to their negative association with sympathetic arousal

(Nagai et al., 2004) and sexual pleasure (Georgiadis et al., 2006, 2009, 2010a). The potential underlying neuroanatomical overlap is helpful, and suggests that one of the reasons that music may synergize with to sex is related to the elicited arousal, which may – often quite literally – "move" people. Or, as Mae West put it: "sex is emotion in motion".

Drugs of abuse that enhance sympathetic arousal also typically induce euphoria, which is described as intensely pleasurable, especially in drug naïve participants (Vollm et al., 2004). In one fMRI study, participants rated feelings of high, low, rush, and craving after cocaine infusion (Breiter et al., 1997). Rush and high both peaked within 3 min after the volunteers received cocaine, after which these feelings dissipated (though rush more quickly than high). Because of the strong overlap in rush and high ratings, only rush was used as regressors in the brain activity analysis. Thus, areas correlating with rush are not only likely to reflect general arousal effects (e.g. elevated heart rate, sweating), but also the euphoria associated with high. The overlap between areas related to cocaine rush/high and sexual arousal (genital stimulation) is striking, and includes aMCC, anterior and posterior insula, ventral pallidum/basal forebrain, and frontal operculum/vPMC. In addition, the amygdala showed prolonged decreased activity after cocaine infusion, similar to decreased activity during sexual genital stimulation (Georgiadis et al., 2009, 2010a).

The VS/NAcc showed a predominant association with ratings of craving, but also active during peak rush (Breiter et al., 1997). Moreover, both VS/NAcc and OFC was active during a saline retest, which is suggestive of expectancy effects in these areas similar to those observed for sexual stimuli (Klucken et al., 2009; Sescousse et al., 2010).

In a larger perspective still, brain regions like the aMCC, insula, mid-anterior OFC and frontal operculum are rich in mu-opioid receptors (Petrovic et al., 2002; Willoch et al., 2004), respond to placebo treatments (Petrovic et al., 2002), and show anticipatory activity to a painful stimulus (Wager et al., 2007). This is interesting in the context of the substantial overlap between the brain regions involved in pleasure and pain (Leknes and Tracey, 2008). Some of the most important components of this network include the aMCC and insula (Leknes and Tracey, 2008).

Interestingly, Naloxone, a mu-opioid anatagonist, is known to inhibit orgasmic pleasure and sexual arousal (Murphy et al., 1990), suggesting that this network focusing on the aMCC might be key in regulating hedonic impact, possibly by regulating arousal levels in relation to cognitive state and required behavior. Opioid-mediated sexual pleasure is critical for functional sexual behavior: Animal studies have shown that naloxone, when given during first sexual experiences, will lead to a state of sexual non-reward and greatly reduced sexual behavior reminiscent of hyposexual desire (Pfaus et al., 2012).

Overall, it is clear that the sexual response cycle shares many commonalities to that of other reward cycles including those involved in music and drugs, hence the popular conception of a close link between them. We have highlighted some of the important links, focussing here mostly on the role of arousal as a common driver for change between the different phases of the reward cycles.

6.4. Life-time evolution of sex in relation to other pleasure cycles

Sex is a natural activity in consenting adults and as such a source of much pleasure. Similar to many other animals, sex is necessary for reproduction, but in humans, sex also serves a large recreational role. The object of sexual desire is typically other of the opposite sex, although as mentioned above there can be considerable individual variations, including same sex preference as well as objects.

While there are many similarities between sex and other rewards such as food, there are also significant differences. One very important difference during an individual's lifetime is when certain rewards come to be able to initiate the pleasure cycle. The sight of a food source (such as lactating breast) will invariably allow for the food pleasure cycle to be initiated even in newborn babies. Similarly, the sight of the caregiver, typically the mother, may initiate the social reward cycle in babies but unlike food, social stimuli rely strongly on learning and an infant only gradually learns to direct attention to other conspecifics.

Sex only becomes important much later in development (Fig. 2). Pre-puberty children generally do not show any interest in sexual stimuli. While it may be possible, if highly controversial, for pre-adolescent children to seek sexual gratification (Nechay et al., 2004), this is an unusual manifestation and taboo in most human societies.

We know very little about the development of the brain networks related to sex in adolescents. A better understanding of these developmental brain changes may help to understand not only the normal human sexual response cycle but also to understand maladaptive variations such as paedophilia, as well as potential treatments. While it may be impossible for ethical reasons to conduct this kind of sexual research in humans, it may be helpful to consider similarities to other the developmental trajectory of other pleasures such as food.

7. Conclusion

In this review, we have carefully synthesized the existing literature on the human sexual brain to describe the brain networks involved in sustaining and switching between the different phases of the sexual pleasure cycle. Special brain networks have developed to help prioritize and solve the difficult resource allocation problem of how to best select between competing wants and likes (Lou et al., 2011). The human sexual pleasure cycle typically involves different phases related to expectation, consummation and satiety (Fig. 1). As part of this cycle, the brain processes sensory stimuli which give rise sexual interest, excitement, genital arousal and orgasm.

The scientific evidence clearly shows that the brain networks involved in the sexual response cycle are remarkably similar to the pleasure cycles involved in other pleasures such as food (Kringelbach et al., 2012). There are, however, differences over a life time since both food and social pleasures are likely to elicit pleasure almost from birth while sex normally only becomes interesting around puberty as a gateway to the sexual response cycle (Fig. 2).

Much of our current knowledge comes mainly from neuroimaging studies investigating the early interest and arousal phases of the sexual response cycle (Fig. 3). Most of these studies have used visual stimuli in populations of mainly healthy young men, and as such are limited in what they tell us about the human brain in general. This opens up for ample opportunities to expand on our current knowledge (Box 3), including the use of other uni- and multimodal stimuli (e.g. smell and auditory) in complementary populations (e.g. women).

When it comes to the later phases of the cycle, related to the consummatory aspects of sexual behavior, much research remains to be done. Some insights have been gained from careful experimentation using self-limited partnered stimulation protocols in men (Fig. 4) and comparing partner-induced orgasms and subjective sexual pleasure measurements in women (Fig. 5).

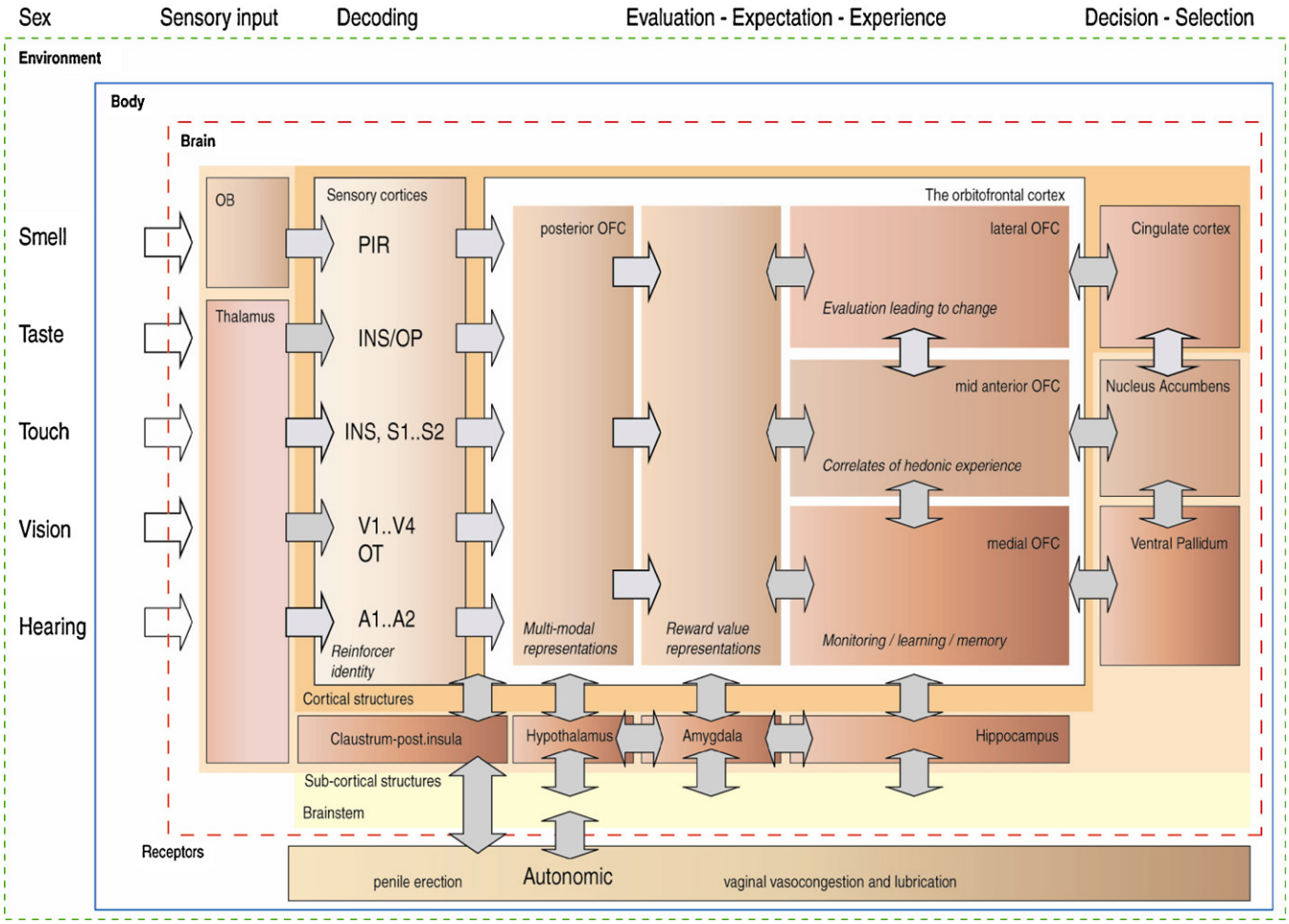

Fig. 7. Model of brain regions identifying and evaluating sexual stimuli. The brain processing of sexual stimuli is complex and bears more than a passing resemblance to that involved in other pleasures such as food (see text). The figure provides a summary of the brain processing of sexual stimuli with a special focus on the role of the orbitofrontal cortex. Potential sources of sexual stimuli in the environment are identified on the basis of the sensory input to the appropriate receptors, processed in the primary sensory cortices via the thalamus (except for olfaction) and made available for pattern-association between primary (e.g. odor) and secondary (e.g. visual) reinforcers. Stimulus sensory identities are then processed for multimodal perceptual integration in the posterior orbitofrontal cortex (evaluation, expectation, experience as well as decision and selection). Hedonic reward value is represented in more anterior parts of orbitofrontal cortex, from where it can then be used to influence subsequent behavior (in lateral parts of the anterior orbitofrontal cortex with connections to anterior cingulate cortex), stored for valence learning/memory (in medial parts of the anterior orbitofrontal cortex) and made available for subjective hedonic experience (in mid-anterior orbitofrontal cortex). There are multiple modulatory brain-loops with other important structures such as the nucleus accumbens, ventral pallidum, hippocampus, amygdala and hypothalamus, as well as modulation with autonomic input from the genitals. Abbreviations: V1, V2, V4, primary and secondary visual areas; SS, somatosensory cortex (3,1,2); A1...A2, auditory cortex; INS/OP, insular cortex/frontal operculum; IT, inferior temporal visual cortex; PIR, piriform cortex; OB, olfactory bulb; OFC, orbitofrontal cortex.

Behavioral measurements have even allowed for comparison of the differences in brain networks involved in faked and real orgasms in women. Yet, almost nothing is known about the brain networks involved in the satiety period.

We have summarized our existing knowledge of the changes over the sexual response cycle in the important brain network hubs and nodes mediating the state changes (Fig. 6, Table 1). From this complex figure, it is clear that the networks involved in human sexual behavior are remarkably similar to the networks involved in processing other rewards.

We have also summarized the findings from the neuroimaging literature on the significant variations in the normal human sexual cycle coming from studies investigating homosexual orientation, hyposexual desire and paedophilia.

Overall, this review has clearly shown that the brain processing of sex is very similar to that involved in other pleasures such as food and other conspecifics. We have synthesized the available information in a model with a special focus on the role of the orbitofrontal cortex (Fig. 7). Potential sources of sexual stimuli in the environment are identified and processed in the primary sensory cortices. The information is made available for pattern-association between primary and secondary reinforcers, and processed for multimodal perceptual integration in the orbitofrontal cortex with regards to evaluation, expectation, experience, as well as decision and selection. Hedonic reward value is represented in anterior parts of the orbitofrontal cortex, from where it can then be used to influence subsequent behavior (in lateral parts of the anterior orbitofrontal cortex with connections to anterior cingulate cortex), stored for valence learning/memory (in medial parts of the anterior orbitofrontal cortex) and made available for subjective hedonic experience (in mid-anterior orbitofrontal cortex). This can in turn be modulated by brain-loops with other important structures such as the nucleus accumbens, ventral pallidum, hippocampus, amygdala and hypothalamus, as well by somatosensory and visceral input from the genitals.

Table 1
Functional neuroanatomy of the human sexual response cycle.

Sex cycle		Desire	Excit./Plateau		Orgasm	Refraction
Stimulation		VSS brief (photo)	VSS long (video)	Penis stim.	Penis/clit. stim.	Post-stim. de-arousal
Brain areas						
Subcortical	HT	▲	▲	▲		▲
	VS	▲				
	VP			▲		▼
	Amy	▲	▼	▼	▼	▲
Insula	Ant. (FO/Ins)	▲	▲	▲		
	Pos. (ins/Clau)		▲	▲		
Cingulate	sACC					▲
	pACC	▲				▲
	aMCC		▲	▲		
Prefrontal	OFC	▲			▼	▲
	vmPFC		▼	▼	▼	▲
	dlPFC/dmPFC			▼	▼	
Frontal	Pelvic MI			▲		
Parietal	SPL	▲				
	IPC/SII		▲	▲		
	Genital SI			▲		
Occipital	vlOT	▲	▲	▲		▼
Temporal	Med-temp		▼	▼	▼	▲
Cerebellum	Vermis (cb)				▲	
Behavioral state		Expectation	Consummation			Satiety
Pleasure cycle		Wanting	Liking			Learning

This table lists brain areas that dominate the different phases of the sexual response cycle, as indicated by a thorough review of the neuroimaging literature. The symbols ▲ and ▼ refer to increased and decreased activity, respectively, relative to either a baseline state or a control condition. Note how involvement of these areas also falls within more general frameworks of motivated behavior and pleasure cycles. Most areas are involved in more than one sex phase, but it was not always possible to determine whether this was due to activity in the same or in different subregions. An exception is the hypothalamus (HT), where distinct subregions support sexual arousal (lateral hypothalamus) and de-arousal after genital stimulation (anteroventral hypothalamus). Likewise for the orbitofrontal cortex (OFC), the posterior subdivision seems important for sexual salience identification whereas more anterior and lateral portions are involved in orgasm. The posterior insula regularly showed co-activation with the claustrum (Ins/Claus), whereas anterior insula activity was nearly always paired with activity in the overlying frontal operculum (FO/Ins), which is the reason these areas are listed together. Note that this table summarizes the information depicted graphically in Fig. 6. aMCC, anterior part of middle cingulate cortex; Amy, amygdala; dlPFC/dmPFC, dorsolateral prefrontal cortex/dorsomedial prefrontal cortex; genital S1, penis/clitoris primary somatosensory cortex; IPC/SII, intraparietal cortex/secondary somatosensory cortex; pACC, pregenual anterior cingulate cortex; sACC, subgenual anterior cingulate cortex; SPL, superior parietal lobule; vlOT, ventrolateral occipitotemporal cortex; vmPFC, ventromedial prefrontal cortex; VP, ventral pallidum; VS, ventral striatum; pelvic M1, pelvic floor primary motor cortex;

Box 3. Future directions

The exploration of the functional neuroanatomy of the human sexual response cycle is still in its infancy. As demonstrated in this review, we have made some progress which has demonstrated that sex is not that different from other rewards. Thanks to the progress made for these other rewards, we should be able to make swift progress in advancing our understanding of the brain mechanisms involved in the various parts of the sexual response cycle.

Here, in no particular order, we list a set of important sex questions that could be pursued in the future using neuroimaging. For further details the reader is invited to read the relevant parts of our review.

Multisensory identification: While there have been many studies in the visual domain, there is currently a dearth of studies using the other primary reinforcers: somatosensory, auditory, olfactory and gustatory. This is surprising given their importance for sex and is thus a fertile ground for novel research.

Sexual learning: New paradigms should be developed to study how the human brain deals with sexual novelty, expectancy, conditioning, and maybe even operant conditioning. In particular, it would be important to study how learning affects and is affected by the state of human sexual cycle.

Social learning: Following pioneering animal research, it would seem important to develop novel paradigms that can elucidate the role of social learning in sex, and the role of social interactions in shaping of sexual preference.

Sexual inhibition: The control of initiating, sustaining and terminating the various parts of the human sexual cycle relies on a number of mechanisms of which sexual inhibition is currently underexplored. In particular, it would be of interest to understand the role of the prefrontal cortex in promoting sexual inhibition.

Sexual preference: Novel paradigms could be developed to show how the brain flexibly adapts to available sexual preferences and potentially, under certain circumstances, to cross orientations. It would be significant to explore the driving role of sexual desire or satiety in this processing.

Moral aspects: Sexual arousal induction could potentially be used to study the moral affiliations of sex such as investigating if our moral sexual judgments vary as a function of arousal.

Improved sexual paradigms: It would be essential to improve the kinds of sex studied with neuroimaging and thus improve the partnered stimulation protocols. Ideally, sex in the scanner should be as close as possible to the real thing. Failing that, it might be possible to find ways to include stimulation akin the mechanical properties of an aroused vagina.

Satiety: Our understanding of the functional neuroanatomy of the satiety state following orgasm is severely lacking in many aspects. A better understanding is likely to help understand and potentially treat many sexual disorders.

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