# The role of incentive learning and cognitive regulation in sexual arousal

Brom, Mirte

**SECTION 1**

**Chapter 2**

# The Role of Conditioning, Learning and Dopamine in Sexual Behaviour:

# A Narrative Review of Animal and Human Studies

Mirte Brom

Stephanie Both

Ellen Laan

Walter Everaerd

Philip Spinhoven

**Neuroscience & Biobehavioral Reviews, 2014, 38, 38-59.**

**Abstract**

Many theories of human sexual behaviour assume that sexual stimuli obtain arousing properties through associative learning processes. It is widely accepted that classical conditioning contributes to the aetiology of both normal and maladaptive human behaviours. Despite the hypothesized importance of basic learning processes in sexual behaviour, research on classical conditioning of the sexual response in humans is scarce. In the present paper, animal studies and studies in humans on the role of Pavlovian conditioning on sexual responses are reviewed. Animal research shows robust, direct effects of conditioning processes on partner- and place preference. On the contrast, the empirical research with humans in this area is limited and earlier studies within this field are plagued by methodological confounds. Although recent experimental demonstrations of human sexual conditioning are neither numerous nor robust, sexual arousal showed to be conditionable in both men and women. The present paper serves to highlight the major empirical findings and to renew the insight in how stimuli can acquire sexually arousing value. Hereby also related neurobiological processes in reward learning are discussed. Finally, the connections between animal and human research on the conditionability of sexual responses are discussed, and suggestions for future directions in human research are given.

## 2.1. Introduction

It is widely accepted that associative learning contributes to the aetiology of both normal and maladaptive human behaviours (Day & Carelli, 2007). Psychopathology and deviant sexual preferences and behaviours are also thought to develop through conditioning processes (Letourneau & O'Donohue, 1997; Ågmo et al., 2004; Martin-Soelch et al., 2007; Pfaus, 1999a,b; Singer & Toates, 1987; Toates, 2009). Knowledge about basic learning processes involved in sexual behaviours, can help foster potentially critical insights in the aetiology of extreme forms of sexual behaviour. This may help in the development of clinical treatments for those behaviours, including paraphilias, or deviant sexual preferences, that manifest perturbed motivation, but also for the more prevalent sexual desire and arousal disorders. Because much sexual behaviour is thought to be acquired through learning, and given the specific hypothesis that classical conditioning plays an etiological role in the development of sexual dysfunction, research in the area of classical conditioning of human sexual arousal is warranted. Despite the hypothesized importance of basic learning processes in sexual behaviour, research of classical conditioning of sexual response in humans is scarce (Akins, 2004; Pfaus et al., 2001). Sexual conditioning studies with women are even scarcer in the literature. In the present paper, we will discuss the studies that provide evidence for basic sexual learning and conditioning processes in sexual arousal, desire and behaviour, and focus especially on how stimuli can acquire sexually arousing properties.

According to incentive motivation models, sexual motivation is the result of the interplay of a sensitive internal sexual system with external motivational stimuli. External stimuli that can promote motivation are called incentive stimuli (Ågmo, 1999; Bindra, 1968, 1974; Both et al., 2007; Singer & Toates, 1987). Sexual incentives are generally positive, and likely to illicit approach behaviour. The motivational valence can be unconditioned (primary)

or conditioned (secondary) as a result of associative leaning (Di Chiara, 1995). Some stimuli, e.g. stroking or kissing may be innately sexually competent, but many sexual stimuli are not intrinsically sexually competent. The attractiveness of those stimuli depends on their history of positive or negative consequences and the resulting meaning that is stored in memory. Specific cues of sexually competent stimuli may gain learned incentive value through their association with the stimulus. While conditioned learning is not the only way in which humans acquire certain sexual behaviours, these processes represent an essential link between stimulus and response (Toates, 1998), and can be point of intervention in the treatment of disorders in sexual behaviour. Therefore, it seems highly valuable to gain insight in the processes through which stimuli may acquire sexual motivational value. Despite the overall consensus that learning plays an essential role in sexual development and the expression of sexual activity, sexual learning has only recently been tied into a more general framework of incentive motivation theory. Over the last decade, clinical and empirical support for the incentive-motivation model of desire has accumulated and the model is now incorporated into the current operational definition of sexual desire disorder in the DSM-5 (Brotto, 2010). This, combined with the fact that the model of incentive motivation was developed primarily with reference to research in nonhumans (Toates, 2009; Pfaus et al., 2001) makes clear that there is a need for an overview of the integration and extension of this theory with a focus on recent human sex research. Thereby, an attempt is made to form links between the processes described in the incentive motivation model and the proposed human brain regions involved.

First, we briefly discuss the different forms of conditioning and the associated neural systems. Further insights in associative learning by looking closely at the neural pathways involved in these processes have identified different brain regions and neurotransmitter systems involved in conditioned learning. Especially, dopaminergic terminations in the basal forebrain foster

sexual arousal and sexual motivation and seem to play a major role in reward learning (Di Chiara, 1999; Dominguez & Hull, 2005; Hull et al., 2004). Gaining knowledge about the functional neurobiology underlying human sexual behaviour is important, as this may lead to understanding of functions that apply to the most primitive aspects of human mental functioning. Thereby, it may also offer an opportunity for intervention. Although the involvement of other neurotransmitter systems such as the serotonergic, endorphin, and glutamate system in sexual behaviour have been reported, the current article primarily focuses on the dopaminergic system. Further on, we briefly review the literature on appetitive and aversive conditioning of the sexual response in animal studies. Mainly results from rat studies will be discussed, but when relevant, studies with other rodents, avian species, nonhuman primates and even fish will be discussed. Subsequently, the literature of sexual conditioning in humans is reviewed. In that section we will first discuss literature on the conditioning of the male sexual response, after which we will discuss the research conducted so far on the conditioning of the female sexual response. We will conclude with a discussion and suggestions for future directions. But first, for a thorough understanding, we will outline the different forms of conditioning and the related basic learning phenomena in the following section.

### 2.2. Basic learning processes

Why include basic learning mechanisms in an understanding of the neurobiology of sexual behaviour? From an evolutionary perspective, the development of sexual learning mechanisms is thought to offer some reproductive advantage and modulate reproductive fitness. This has indeed been shown by several animal studies. For instance, classical-conditioned male quail subjects released greater volume of semen and greater numbers of spermatozoa than control subjects (Domjan et al., 1998). Second, in blue gourami fish, classical conditioning provides the means to enhance territorial

defence and yields large reproductive benefits (Hollis et al., 1997). Classical-conditioned males are able to spawn with females sooner and produce more young than males that do not have the benefit of a signal. These examples demonstrated that animals can learn to associate environmental cues with the appearance of biologically important events. More important, the ability to anticipate the appearance of such different biologically important events suggests that learning principles may play a significant role in the behavioural ecology of all kinds of animals.

### 2.2.1. Habituation, sensitization, generalization and discrimination

Habituation is a systematic decrease in the magnitude of a response upon repeated presentations of an eliciting stimulus. This decrement is not due to fatigue or receptor adaption (Thompson & Spencer, 1966). Sensitization, in contrast, is the progressive amplification of a response after repeated administrations of a stimulus. An important characteristic of habituation is that it is stimulus-specific. For example, a habituated response can occur for the sound of a barking dog, without affecting the magnitude of the response to the sound of a slamming door. Yet, a transfer of habituation from one stimulus to a new, but equivalent stimulus is possible. This transfer and other transfers of the effects of conditioning to similar stimuli in general are covered by the term generalization. The amount of generalization depends on the degree of similarity between the stimuli (Mazur, 2002). The opposite of generalization is discrimination, in which it is learned only to respond to one stimulus but not to a similar stimulus. The degree of habituation depends on multiple factors such as frequency of stimulation, stimulus duration, stimulus intensity and the number of previous habituation trials (O'Donohue & Geer, 1985). In male animal subjects, a habituation-like phenomenon is detected when repeated copulations reduce sexual interest in a familiar female partner, but introduction of a novel receptive female sometimes results in recovery of the sexual

behaviour (Domjan & Hollis, 1988). Second, several researchers have reported findings that support short-term habituation of sexual arousal in humans (Koukounas & Over, 1993; Meuwissen & Over, 1990). Habituation effects can both be temporary as they can be retained for very short periods of time and be of a long term character. Recovery of the initial response can be observed after a longer time course. We will discuss this phenomenon of recovery in more detail later.

### 2.2.2. Classical conditioning

Classical conditioning or also called Pavlovian conditioning is one of the most studied paradigms in behavioural psychology and has a long and distinguished history dating back to pioneers in this field like Pavlov, Thorndike and Skinner. This form of associative learning has been demonstrated in a wide range of species and response systems (Hollis, 1997; Turkkan, 1989). Pavlovian responses, mainly involving approach and withdrawal, are elicited by the appetitive or aversive valence associated with predictive stimuli (Bouton, 2006). Biological relevant outcomes such as food can be labelled as unconditioned stimuli (US), because they are able to evoke innate or unconditioned responses (UR), such as salvation, approach and consumption (Pavlov, 1927). Through the repeated associating of a neutral stimulus (NS) with an US, the NS will eventually trigger the same reaction as the US (Pavlov, 1927; Bindra, 1974; Mazur, 2002; Pfaus et al., 2001). For instance, research has shown that in a 'triad mating paradigm' with two sexually receptive females, male rats trained previously to associate a neutral odour (almond or lemon) with sexual activity ejaculated preferentially with females bearing that odour (Pfaus, 1999a,b). The NS is now called the conditioned stimulus (CS) and the reaction to the CS is called the conditioned response (CR). According to classical models of learning, CS-US pairing causes the CS to become an 'emotional substitute' for the US.

Subsequently, the CS ultimately elicits similar emotional responses as the US does (Blair et al., 2005).

### 2.2.3. Basic principles of classical conditioning

Contiguity, contingency and prediction error are three factors that govern classical conditioning (Mazur, 2002; for a review see Schultz, 2006). Contiguity refers to the requirement of near simultaneity, which means that a US needs to follow a CS or response by an optimal interval of time. Contingency refers to the requirement that a US needs to occur more frequently in the presence of a stimulus as compared with its absence. Furthermore, conditioning will only occur when the CS is predictive of something important, such as an upcoming reward or shock. Prediction error postulates that even when it occurs in a contiguous and contingent manner, a reward that is fully predicted does not contribute to the process of learning. This means that learning advances only to the extent to which a reinforcer is unpredicted and the process of learning slows as the reinforcer becomes more predicted. Furthermore in extinction learning, the CS is no longer paired with the US, so conditioned behaviour diminishes (Delamater, 2004; Mazur, 2002; Schultz, 2006). As a result, the ability of the CS to evoke the CR is decreased. However, extinction does not result in complete unlearning of the CS-US association (Bouton, 2004; Delamater, 2004; Mazur, 2002; Rescorla, 2001). Phenomena like reinstatement, spontaneous recovery and renewal of conditioned responding can occur following a context shift out of the extinction context. Reinstatement is the restoration of CR in the context where extinction training occurred but not in a different context after an US is presented again. Renewal is the restoration of the CR in context A but not in context B when learning occurred in context A and extinction in context B, and spontaneous recovery can be described as the restoration of the CR when the retention test occurs after a long but not a short delay after extinction training. Extrapolating to clinical practice, someone who

acquired a craving for internet-sex at home (context A) is successfully extinguished by cue exposure therapy in a therapeutic setting (Context B), may experience strong craving upon changing context such as sitting behind the computer at home (Context A) or a different computer in a new situation (Context C). So it appears that specific CS-US associations are preserved after an extinction treatment. Moreover, extinction procedures seem to result in new learning that is especially context-dependent (Bouton, 2004) and this can be formulated in terms of the formation of an inhibitory association between the CS and the former CR (Delamater, 2004).

Furthermore, not all stimuli will result in equally rapid learning. This brings us to the phenomenon of preparedness. The fundament for the assumption of preparedness comes from Seligman (1970), who in the context of fear learning suggested that primates are predisposed to condition fear more readily to stimuli related to recurrent survival threats than to stimuli that never have threatened survival or to fear-relevant stimuli that emerged only recently in our evolutionary history. As with prepared associations for the module of fear, one can postulate that this principle also accounts for appetitive modules, like that of sexual arousal. It has been hypothesized that humans indeed are born with sensitivity to what we call sexual stimuli (Everaerd et al., 2000; Janssen et al., 2000) and may be prepared to form particular associations between stimuli and sexual arousal (Laws & Marshall, 1990). For example, an abdomen of the opposite sex has more sexual relevance than a penny jar for instance, and should therefore become more easily associated with sexual arousal. The theory further proposes that prepared associations should be easy to acquire and also obey different laws of learning than do nonprepared associations. Prepared associations will be more resistant to extinction relative to nonprepared associations and are less influenced by rational or cognitive input (Seligman & Hager, 1972; Öhman & Mineka, 2001). Although an extensive and critical discussion of the literature on preparedness is beyond the

scope of this article, it is worth mentioning that alternative theories to explain resistance to extinction have arisen. Lovibond et al. (1993) proposed an alternative theory of selective sensitization, where a pre-existing response tendency is activated by a perceived threat. The interpretation of the studies by Mineka and colleagues has also been questioned by Davey (1995), who suggests that the readiness with which some stimuli become associated with aversive outcomes arises from biases in the processing of information about threatening stimuli rather than from phylogenetically based associative predispositions. Nevertheless, despite these critiques, the preparedness theory is still widely accepted as a valid account of the aetiology of fears and phobias. Concerning sexual learning, the theory would imply sexual relevant cues to become more easily associated with sexual arousal, and thereby prepared sexual associations will be more resistant to extinction.

### 2.2.4. Operant conditioning

The learning processes in classical conditioning are centred on the contingency between two stimuli, whereas those involved in operant conditioning are centred on the contingency between a stimulus and a response. However, despite these differences, it is not always easy to distinguish whether classical or operant responses are being observed in an experimental situation. The central mechanism underlying the mechanism of operant conditioning, also referred to as instrumental conditioning, is reinforcement, and was introduced by Skinner (1937). In operant conditioning an organism learns a new motor response in order to obtain a positive outcome (e.g. food, mating opportunities or the avoidance of pain). For instance, male rats can be taught to run from level to level in bilevel chambers in anticipation of receiving access to a receptive female (Pfaus et al., 1990). Operant conditioning focuses on changes in the frequency of (goal-directed) behaviour, resulting from its association with reinforcing or punishing consequences. Reinforcing stimuli, such as rewards,

have the power to enhance the probability of occurrence of a response. This means that rewarding stimuli or events can reinforce behaviours by strengthening associations between stimuli and behavioural responses and Thorndike (1911) described this as 'Law of Effect': the greater the satisfaction or discomfort, the greater the strengthening or weakening of the association.

### 2.2.5. Rewards and reinforcers

Although the terms reward and reinforcement are frequently used interchangeably, it should be mentioned that both are clearly different. Something that is reinforcing is not necessarily rewarding (Di Chiara, 1995, 1999). From a purely behaviourist point of view, and as described before, reinforcement refers to an increase in the probability of a response (Paredes, 2009). This increase can be associated with the introduction of an appetitive stimulus or with removal of an aversive one. Secondly, it can be measured as the strength of a behavioural response (Berridge & Robinson, 1998). Punishers act as reinforcers by increasing behaviour that result in decreasing the aversive outcome. In general, reinforcers are stimuli that strengthen the association of events to which they are contingent. In contrast, reward refers to the ability to elicit an approach behaviour, similar to incentive motivation. And to be complete, an incentive can be defined as any stimulus that activates approach behaviour (Schultz et al., 1997). Aversive environmental stimuli, such as loud noises or painful shocks, have opposite valence to reward and induce withdrawal behaviour (Schultz, 2006). They act as reinforcers by increasing and maintaining avoidance behaviour on repeated presentation, thereby reducing the level of danger or impact of damaging events. Furthermore, aversive stimuli or events induce emotional states of anger, fear and panic. Food, water and certain kinds of sexual stimulation are called primary rewards, because they do not require associative learning processes as they can reinforce behaviour (Di

Chiara, 1999; Schultz, 2006; Wise, 2002). On the contrary stimuli like money gain their reward value by learned associations with primary rewards.

### 2.2.6. Incentive motivation and associative learning in sexual behaviour

Within the incentive motivational framework (Bindra, 1974; Robinson & Berridge, 2003; Toates, 2009), incentives that predict sexual reward can elicit a conditioned appetitive motivational state, reflected in sexual arousal and sexual desire. Common to most theories on sexual functioning is the assumption that sexual behaviour is intrinsically rewarding or reinforcing (Ågmo, 1999; O'Donohue & Plaud, 1994; Woodson, 2002). Especially ejaculation or orgasm, can be seen as primary rewards, and therefore can reinforce learning processes (Ågmo et al., 2004; Tenk et al., 2009). The positive affect produced by sexual encounters can become associated to environmental stimuli, and consequently, these stimuli can become conditioned sexual incentives and thereby come to elicit sexually relevant responses. The strength of the conditioning will be enhanced by repeated exposure to the specific stimuli while experiencing sexual reward. However, when expected rewards are absent this may have aversive consequences, which may become associated to environmental stimuli resulting in a decrease in responding or approach behaviour (Ågmo et al., 2004). Consequently, the quantity and quality of incentives that are able to activate the sexual system depend on the individual's sexual learning history and varies between individuals. For instance, some individuals may never form associations between sexually rewarding experiences and stimuli or only to a limited amount, in which case there will be a limited number of incentives that can activate sexual arousal and desire. Under other conditions, there may be a history of strong and frequent associations, resulting in a large number of stimuli that can elicit sexual arousal and desire. Also, associations may occur in conjunction with deviant stimuli and lead to a paraphilia (Geer et al., 1993; Toates, 2009).

## 2.3. Neurobiological processes in reward

### 2.3.1. The reward system

The first authors to describe brain reward pathways were Olds and Milner (1954). They observed that when they placed electrodes in certain brain areas of rats, these rats proceeded to active self-stimulation of these brain areas. Since then, a substantial amount of research has found a common pattern of activation in brain areas that respond to diverse rewarding stimuli. Both animal studies and human studies have shown that rewards like food, sex and drugs, have the ability to stimulate the mesoaccumbens dopamine projection within different brain areas and increase extracellular concentrations of mesolimbic dopamine (DA) (Arana et al., 2003; Di Chiara, 1998; Di Chiara, 1999; Giuliano & Allard, 2001; Hyman et al., 2006; Kalivas & Nakamura, 1999; Pierce & Kumaresan, 2006; Schultz et al., 1997, 2000; Schultz, 2006; Volkow et al., 2002; Damsma et al., 1992; Richard et al., 2012). Whereas DA responses distinguish rewards from non-rewards, DA neurons apparently do not discriminate between different sorts of reward like objects, food or liquid reward (Schultz, 2002). Although it is interesting to note that they do distinguish between a less-than-expected punishment and a greater-than-expected reward (Fiorillo, 2013). The observation that DA neurons are activated by all sorts of rewards has led to the hypothesis that the brain may process rewards along a single final common pathway in the form of a kind of common neural currency (Fields et al., 2007; McClure et al., 2004). The circuits involved in this process have been called the brain reward system. It is suggested that the reward pathway can be divided into two parts, i.e. the opioid ('liking') system and the dopaminergic ('wanting') system (Berridge, 1996; Di Chiara, 1995, 1998; Zhang & Kelley, 1997, 2000). Whereas the opioid system is associated with satisfying consummatory aspects of reward (e.g. blissfulness, sedation), the dopaminergic system is associated with the incentive and acquisition aspect of reward

(Berridge, 2007a,b; Di Chiara & North, 1992; Wightman & Robinson, 2002; Wise, 2002). The human brain has an exquisite sensitivity to signals for reward, by activation of this mesolimbic and mesocortical reward circuitry (Adinoff, 2004; Di Chiara, 1995, 1999; Koob, 2000; Schultz, 2000). The dopaminergic mesolimbic and mesocortical pathways originate with dopaminergic cell bodies in the ventral tegmental area (VTA) (Fields et al., 2007; Koob, 2000; Tanaka et al., 2004; Robbins & Everitt, 1996). This dopamine-rich nucleus is located in the midbrain, medial to the dopamine-rich substantia nigra and ventral to the red nucleus. The dopaminergic axons most extensively project to the nucleus accumbens (NAc), but also extend to other brain structures, like the septum, amygdale, prefrontal cortex (PFC), hippocampus and certain parts of the thalamus (Adinoff, 2004; Berke & Hymann, 2000; Di Chiara, 1995; Fields et al., 2007; Koob, 2000; McClure et al., 2004). The projection from the VTA to the NAc is the richest in DA neurons and is 65–85% dopaminergic (Fields et al., 2007). The DA system assigns incentive salience to percepts and representations (Berridge, 1996). In this way DA causes an event or environmental stimulus to become attractive and 'wanted', which can subsequently mediate approach behaviour.

Whereas DA in the NAc enhances motivation, DA in the lateral hypothalamus (LH) inhibits motivated behaviours (Parada et al., 1995; Hull, 2011). Research with rats with excitotoxic lesions of the lateral hypothalamic area and NAc revealed that the LH plays an inhibitory role in the regulation of sexual arousal and an excitatory role in the regulation of ejaculation. The NAc was found to play an excitatory role in the regulation of sexual arousal (Kippin et al., 2004). Research with female rats has shown that mesolimbic DA neurons that terminate in the NAc can be modulated in vivo by estrogen and that this modulation may be mediated by both genomic (long term) and nongenomic (short term) mechanisms (Thompson & Moss, 1994). Moreover, testosterone facilitates copulation in male rats by increasing neuronal nitric oxide synthase

immunoreactivity in the medial preoptic area (mPOA) of the hypothalamus, which in turn increases both basal and female stimulated DA release (Hull et al., 1995; Hull et al., 1997; Putnam et al., 2003). Glutamate is also released in the mPOA during copulation, and glutamate, acting via NMDA receptors and calcium inflow, may increase nitric oxide, and thereby DA release (Hull, 2011). In addition, research has demonstrated interactions between glutamate and gonadal steroids in the regulation of limbic and hypothalamic functions (Diano et al., 1997). This mechanism seems to be gender and site specific, suggesting that excitatory neurotransmission and related physiological mechanisms also may be distinctly different in males and females (Diano et al., 1997; Orsini, 1985).

Despite little is known about hormonal influence on the DA reward system in humans, research has demonstrated sex differences in striatal DA release in healthy men and women (Munro et al., 2006; Riccardi et al., 2006, 2011). For instance, Munro et al. (2006) demonstrated greater DA release in men compared to women after amphetamine administration in the ventral striatum, anterior putamen, and anterior and posterior caudate nuclei, whereas other researchers found greater DA release in extrastriatal areas in a similar study (Riccardi et al., 2006). Variations in dopamine-related genes and in hormone levels affect the physiological properties of the DA system in nonhuman primates and modulate the processing of reward and social information in humans (Caldú & Dreher, 2007). For instance, it is suggested that testosterone regulates incentive sensitivity through interactions with mesolimbic DA pathways (Wood, 2008; Hermans et al., 2010). And second, some observed sex differences in response to stimulants are in large part due to the fluctuations in estrogen and progesterone that occur over the female reproductive cycle. For example, several of the positive subjective effects of amphetamine (e.g. euphoria and increased energy) are potentiated during the follicular phase relative to the luteal phase (Justice & de Wit, 1999). These

findings help in the understanding of the biological mechanisms underpinning addictive behaviours and how these differentially affect vulnerability to drug abuse or the development of sexual dysfunctions in men and women.

### 2.3.2. The reward system in sexual behaviour

A number of investigations in humans using fMRI technique have consistently shown that sexual stimuli evoke neuronal activity in the reward system (Garavan et al., 2000; Park et al., 2001; Karama et al., 2002; Hamann et al., 2004). Using different techniques, studies have detected overlapping activation patterns across multiple brain regions (Fonteille & Stoleru, 2010), including ventral striatal regions involved in reward in both men and women in reaction to visual sexual stimuli (Hamann et al., 2004; Park et al., 2001; Ponseti et al., 2006; Stóleru et al., 1999; for a review see Rupp & Wallen, 2008) or during ejaculation or feelings of orgasm (Georgiadis et al., 2009; Holstege et al., 2003; Komisaruk et al., 2004; Komisaruk & Whipple, 2005; McClure et al., 2004). In the imaging study by Walter and colleagues (Walter et al., 2008) patterns of differential activation between several regions related to a brain network of sexual arousal were compared. They demonstrated that activations in the ventral striatum and hypothalamus were related to stimulus specific sexual intensity, and independent of induced general emotional arousal or valence. Activations in the anterior cingulate cortex were associated with an interaction between sexual intensity and emotional valence. Recent studies using high resolution fMRI indicated extension of this network to thalamic nuclei (Metzger et al., 2013). Studies on brain activation during orgasm (Georgiadis et al., 2009; Hamann et al., 2004; Karama et al., 2002; Holstege et al., 2003) show activation in the region of the VTA and NAc, suggesting they have a role in mediating orgasmic pleasure in humans. These findings presumably represent an anatomical substrate for the strongly reinforcing nature of sexual activity in humans. The ability of sexual behaviour, especially orgasm and ejaculation, to

increase the concentration of DA in the NAc is considered to be crucial to their reinforcing effects (for reviews see Berke & Hymann, 2000; Di Chiara, 1999; Volkow et al., 2002).

Furthermore, results from a study in our laboratory support the view that DA is involved in the energetic aspects of appetitive sexual behaviour, at least in men (Both et al., 2005). It was found that levodopa facilitates early motor preparation – as measured with reflex modulation – in response to sexual stimuli. And a more recent fMRI-study from our lab (Oei et al., 2012) provides compelling evidence for a mediating role of DA in processing of subconscious perceived sexual stimuli. It was found in healthy young men that levodopa significantly enhanced the activation in the NAc and dorsal anterior cingulate cortex in response to subliminal sexual stimuli, whereas haloperidol (a DA antagonist) decreased activations in those areas. This first evidence for pharmacological modulation of implicit sexual reward processing, points at the possibility for DA to affect sexual motivation at its earliest onset, that is, outside awareness. But as these results only apply for men, further studies are warranted to investigate the role of DA in female sexual behaviour.

There is agreement in the literature that androgens play a conditional role in sexual responsiveness (Bancroft, 2009), and from studies in rats there is evidence for an interaction between sex steroids and DA in the control of sexual behaviour (Hull et al., 1999). Gonadal steroids regulate dopaminergic innervation in both hypothalamic and extra-hypothalamic structures at various developmental stages in male rats (Hull et al., 2004). Moreover, there is a remarkable consistency across species in the role that the mPOA plays in the orchestration of consummatory sexual responses (Bancroft, 1999). In female rats, estradiol increases oxytocin levels and release in the mPOA stimulating the lordosis reflex (Caldwell and Moe, 1999). Moreover, research supports the hypothesis that a rise in DA in the mPOA is specifically related to sexual motivation in males as compared to copulatory behaviour per se (Hull et al.,

1995; Kleitz-Nelson et al., 2010a,b). Although, it appears that testosterone is necessary for mPOA DA release during male copulatory behaviour and for mating itself, testosterone alone does not elicit DA in mPOA (Wood & Swann, 1999). Research suggests that testosterone creates a permissive environment that allows external sensory stimuli to induce mPOA DA release during copulation (Dominguez et al., 2001; Dominguez & Hull, 2001). In line with this, studies in humans have shown that high levels of testosterone are associated with reward sensitivity, and it is suggested that testosterone regulates incentive sensitivity through interactions with mesolimbic DA pathways (Wood, 2008; Hermans et al., 2010).

**2.4. Associative learning and DA**

Considerable evidence exists regarding the role of DA in memory and learning (Berke & Hymann, 2000; Di Chiara, 1995, 1999). Research has shown that DA activity is associated with responses to novel stimuli; encoding reward function; error detection signalling during the acquisition of new learning; and approach behaviour and incentive motivation (Schultz, 1998; Schultz et al., 1997; Montague et al., 2004; Schultz, 2002). There is substantial evidence suggesting that mesolimbic DA plays a critical role in the interpretation of stimuli and the acquisition of behaviours reinforced by rewarding stimuli (Adinoff, 2004; Kirsch et al., 2003; Di Chiara, 1995, 1999; Koob & Bloom, 1988; Schultz, 1998). For instance, neurons in the VTA contribute to both positive reinforcement and to the acquisition and expression of learned appetitive behaviours (Everitt & Robbins, 2005; Fields et al., 2007; Kalivas & Volkow, 2005; Schultz, 2002; Wise, 2002). Also, conditioning of an otherwise neutral stimulus by repeated association with a certain stimulus can be reinforced by stimulation of DA transmission (Di Chiara, 1995; Schultz, 2002).

As mentioned before, incentive salience transforms the neural representations of conditioned stimuli, converting an event or stimulus from a

neutral representation into an attractive and 'wanted' incentive (Berridge & Robinson, 1998; Berridge, 2007a,b). Subsequently, learning hypotheses posit that DA neurons mediate associative learning and expectations based on previous experience with a stimulus. In order to connect the learned predictive significance of a cue with appropriate responses, storage of specific patterns of information within the brain is required. As a result, internal representations of the reward-related stimulus and series of cue-related action sequences are stored in memory. Furthermore, behavioural responses can increase with repeated exposure to a rewarding stimulus (Kalivas & Stewart, 1991), because strengthening of stimulus-response and stimulus-reward associations sensitize the mesolimbic pathways (Di Chiara, 1999). This sensitization has been proposed as a central neural mechanism underlying addiction disorders (Robinson & Berridge, 2003; Hyman et al., 2006). When drugs or natural rewards evoke an increased DA release from the VTA into the NAc, this further alters the responsiveness to glutamate. The VTA and NAc receive extensive glutamatergic inputs from the prefrontal cortex and other brain areas. These excitatory inputs are considered crucial for establishing addictive and other motivated behaviours (Chen et al., 2010). CREB (cAMP response element-binding protein) is a nuclear transcription factor, involved in the development of addictive behaviours (Wise & Morales, 2010; Nestler, 2001). In response to ingestion of drugs or in response to natural rewards, the DA levels especially in the NAc rise. This stimulates DA-responsive cells to enhance cyclic AMP (cAMP) concentrations, thereby activating CREB. CREB generates a specific gene expression that codes proteins. One of these CREB-dependent proteins is dynorphin. Dynorphin is synthesized in the NAc and is a natural molecule with opium-like effects. It triggers a negative feedback loop, exerting inhibitory effects on VTA neurons. But since CREB is switched off only shortly after drug consumption has ended, this transcription factor may not be responsible for relapse in chronic substance abuse or other addictive behaviour

(Esch & Stefano, 2004). Delta FosB is another transcription factor that exerts its functions in response to chronic drug abuse and is also released in NAc. Interestingly, delta FosB is also induced in response to repetitious non-drug rewards. For this reason, it is suggested that delta FosB represent a more general mechanism participating in reward-associated behaviour change. Delta FosB remains active for a very long period following drug ingestion or following natural rewards and therefore delta FosB may cause sensitization to drugs or natural rewards (Kelz et al., 1999; Nestler, 2001). Delta FosB exerts its effects on behaviour through the AMPA (-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) glutamate receptor subunit GluR2 in the NAc. In addition, research has demonstrated that the LH facilitates glutamate-mediated responses, and regulates the glutamate-dependent long-term potentiation in VTA DA neurons. Orexins (or hypocretins) are neuropeptides made exclusively in the hypothalamus. Research has shown that a subset of these cells in the LH is involved in reward processing and addictive behaviours. Orexin-containing neurons from the LH project densely to the VTA (Borgland et al., 2008). Orexin facilitates activation of VTA DA neurons by stimulus-reward associations. This LH-VTA orexin pathway was found to be necessary for learning a morphine place preference. These findings are consistent with results showing that orexin facilitates glutamate-mediated responses, and is necessary for glutamate-dependent long-term potentiation in VTA DA neurons. Since LH orexin cells are an important input to VTA for behavioural effects associated with reward-paired stimuli, LH orexin neurons are thought to play an important role in reward processing and the development of addictive behaviours (Aston-Jones et al., 2010; Harris & Aston-Jones, 2006; Harris et al., 2005). In addition, gonadal steroids possibly differentially regulate pituitary orexin receptors and adrenal orexin receptors in male and female rats and may therefore contribute to specific sex-dependent neuroendocrine and endocrine actions of orexins (Jöhren et al., 2003). Hull and co-workers (Muschkamp et al.,

2007) suggest a model for the regulation of the orexin system by gonadal steroids, and VTA DA by the orexin system. It is suggested that estradiol, synthesized from gonadal testosterone by aromatase, acts on estrogen receptors containing neurons in the bed nucleus of the stria terminalis, mPOA, and LH. These structures project to hypothalamic orexin neurons. Orexin projections to VTA enhance midbrain DA neuronal activity during male sexual behaviour. This effect may be blocked by intra-LH infusions of serotonin that inhibit orexin activity, impairing sexual behaviour and NAc DA release.

## 2.5. The role of learning in the sexual behaviour of animals

### 2.5.1. Male studies

*CS-characteristics:* Early studies on sexual learning employed arbitrary auditory and visual stimuli as CSs. When these cues are paired with the presentation of a member of the opposite sex or with the opportunity to copulate, a rapid acquisition of conditioned approach to the stimuli is found in male animal subjects (Farris, 1967; Hollis et al., 1989; Ågmo, 1999; Akins et al., 1994; Burns & Domjan, 1996; Domjan et al., 1986). For instance, Farris (1967) used a buzzer as CS and access to a live female quail as US to classically condition strutting (i.e. courting behaviour) in male quail. And in a study by Domjan et al. (1986) conditioned approach behaviour was observed using a red light bulb as CS prior to access to a female quail. Conditioned males approached and remained near the CS and had shorter copulatory latencies than control subjects.

Next to auditory or visual stimuli, odours can also serve as CS. A substantial amount of research has demonstrated that when neutral odours like almond or lemon, are paired with copulation, male rats develop a conditioned ejaculatory preference (CEP) for females bearing the olfactory cue associated with copulatory training (Ismail et al., 2009a,b; Kippin & Pfaus, 2001a,b;

Kippin et al., 1998, 2001). Also in nonhuman primates, conditioning of sexual arousal has been established making use of olfactory cues. Snowdon and colleagues (2011) successfully conditioned male marmosets to copulation with a sexually receptive female using an arbitrary olfactory cue (lemon odour) as CS. Post-conditioning, males showed sexual responses (erections, and increased exploration of the location where they previously experienced a receptive female, increased scratching) to the olfactory cue in absence of any cues from a female. The CRs were demonstrated even up to a week after the end of the conditioning trials.

Furthermore, research has demonstrated that places can also become associated with sexual encounters and may influence CRs in animals. Both male rats and quails develop a conditioned place preference (CPP) for an environment associated with copulation with a receptive female (Ågmo & Berenfeld, 1990; Paredes & Alonso, 1997; Akins, 1998; Everitt, 1990; Pfaus et al., 2001; Tenk et al., 2009). Furthermore, Sachs & Garinello (1978) demonstrated that when male rats were placed into the same chamber in which copulation had previously occurred, the latency to display penile erections was reduced dramatically. Another remarkable study was conducted by Pfaus et al. (2013), in which it was found that somatosensory stimuli can also be used to condition sexual arousal in male rats. Males displayed faster intromission and ejaculation latencies when they were tested with a harness jacket on, which they wore during prior sexual experience.

Pfaus and colleagues have demonstrated that the association with reward can also reduce the impact of aversive stimuli (Pfaus et al., 2001). They gave rats their first nine sexual experiences with either cadaverine-scented females, or unscented control females. Cadaverine is an aversive odour, which is produced in decaying flesh. Therefore, cadaverine is considered unconditionally aversive. A third group of males were habituated to the cadaverine odour in their home cages and copulation trials with unscented

females. During the 10th trial all males from the three groups were allowed to copulate freely with two receptive females: one scented with cadaverine and one unscented. Both males in the control group and from the habituation-group pursued the unscented females selectively and ejaculated exclusively with them. In contrast, males that had copulated previously with cadaverine-scented females pursued, copulated, and ejaculated with both females. This indicates that the aversive properties of cadaverine had been diminished after pairing with sexual reward. This study demonstrated that an unconditionally aversive odour can be made less aversive and even conditionally appetitive by pairing with sexual reward.

*CS-US similarity:* Research has suggested that although arbitrary CSs such as auditory and visual stimuli appear to be effective CSs, more female-like CSs appear to elicit different CRs in male animals. In a study by Domjan et al. (1988) male quail acquired conditioned approach behaviour to both a yellow stuffed toy, and a female quail whose appearance had been altered by attaching bright feathers to her shoulders. However, only the female elicited conditioned copulatory responses. Furthermore, a CS that included species-typical cues affected the acquisition and extinction of conditioned sexual responses in male quail. Results suggest that conditioned responses toward sexually relevant CSs, in contrast to results obtained with arbitrary CSs, might be highly resistant to extinction in male quail. In line with former theories (Rescorla & Furrow, 1977), Krause et al. (2003) suggested that CS-US similarity is an important factor in conditioning.

*CS-US intervals*: Zamble et al. (1986) demonstrated delay learning in a sexual conditioning paradigm. Rats were placed for different time spans in a plastic tub that served as CS. A female rat served as US and was separated from the male rat by a divider. The duration of CS-US intervals was manipulated. After conditioning, male rats demonstrated a longer ejaculatory latency irrespective of the duration of the CS-US interval, in comparison with

ejaculation latency prior to conditioning. Thus, sexual learning occurred at varying and relatively long CS-US intervals. In an attempt to replicate the study of Zamble and colleagues in an avian species, Akins et al. (1994) separated male quail subjects from the female's smaller cage and used a grey foam block with bilaterally-attached orange feathers as CS. Quails receiving 0.5, 5 and 10 min CS-US intervals showed an increase in the percent time they spent near the CS. The results from this study were interpreted as evidence that also in avian species, sexually conditioned approach behaviour can occur with long CS-US intervals. Another noteworthy study by Villarreal and Domjan (1998) showed that even inconsistent pairing of a CS with sexual reward was able to elicit conditioned approach behaviour in male gerbils. In sum, even long CS-US intervals or inconsistent pairing of the CS with the US can result in sexual learning.

*US Factors:* Research has suggested that sexual learning can take place without permitting subjects to complete copulation (Hollis et al., 1989). Zamble et al. (1985) demonstrated conditioning in male rats that were permitted to intromit but not ejaculate. Second, they also found conditioning effects in male subjects when both intromission and ejaculation were precluded. Kippin and Pfaus (2001a,b) examined the copulatory components that comprised the US for the development of CEP. Male rats were allowed either multiple intromissions without ejaculation, single ejaculation, or multiple ejaculations with almond-scented females. Subsequently, copulatory preferences for an almond scented female or an unscented female were assessed. It was demonstrated that the development of CEP is dependent upon ejaculation with a scented female during the conditioning sessions. When male rats were not allowed to ejaculate during conditioning sessions, they did not demonstrate a preference. Moreover, the researchers demonstrated that the presence of the scented female following ejaculation is critical to the development of CEP in male rats. Moreover, they postulate that because the USs for CEP and USs for

conditioned sexual excitement are different, not all conditioning effects on sexual behaviour may involve the same US. Holloway and Domjan (1993) determined that completed copulation with a female quail was more effective than exposure to a female without copulation, but the latter also produced conditioned approach responding to the CS. Hilliard et al. (1998) devaluated the US by sexually satiating male quail. They found that consummatory responses (e.g. mount and cloacal contact) showed a stronger decline with sexual satiation, compared to appetitive responses (e.g. approach responses).

#### 2.5.1.1. Aversive conditioning studies

Some studies have demonstrated that aversive conditioning can also influence sexual behaviour in animals. By the administration of lithium chloride (LiCl), copulation-illness associations can be induced. Reduced sexual motivation and longer intromission latencies are found when male rats and hamsters are injected with LiCl following copulation, or after exposure to estrous females (Ågmo, 2002; Peters, 1983; Johnston et al., 1978; Koch & Peters, 1987). Another study demonstrated that when domestic pony stallions are exposed to erection-contingent aversive conditioning with electric shocks, erection responses and attention to stimulus mares was suppressed (McDonnell et al., 1985). On the contrary, other research has shown that the pairing of a CS with a painful shock can induce copulation in noncopulating male rats (Crowley et al., 1973). The researchers conditioned sexually inactive male rats to associate tones with electric shock to the flanks. Eventually, the tones were presented when males were in the presence of an estrous female. The tones induced copulation with extreme regularity and the authors attributed this finding to an arousal augmentation by the anticipation of pain. Earlier research already suggested that the sexual drive of male rats seemed to be augmented by the nonspecific arousal reaction associated with the shock. Barfield and Sachs (1968) administered electric shocks to the back of sexually experienced males

that were in the presence of an estrous female. The administration of a shock, compared against a control condition in which no shock was delivered, could facilitate sexual activity. Other research by Caggiula and Eibergen (1969) with sexually naïve rats revealed that shocks induced copulatory behaviour toward estrous females in nearly four times as many animals as in a no-shock control condition. Shocks could also induce copulatory behaviour toward other male rats or toward stuffed toy animals. Interestingly, other behaviours like feeding or drinking were not influenced by tail shocks. It seemed therefore that the facilitative effect of pain-induced arousal is limited to certain behaviour like sexual activity that is associated with high levels of activation.

#### 2.5.1.2. Reward system and dopamine receptor antagonism

Animal studies support involvement of the mesolimbic dopaminergic systems in sexual conditioning. West et al. (1992) trained one group of male rats to associate novel odours with a sexually receptive female, and one group with an unreceptive female and another group of rats received no training. They found that pairing odours with the presentation of sexually receptive females enhanced the responsiveness of NAc neurons to those odours. This was even more pronounced in those animals that were allowed to ejaculate during training than in animals that were not. Kippin et al. (2003) examined the pattern of neural activation in rats as revealed by Fos immunoreactivity (Fos-IR) after exposure to either the neutral odour of almond, which was paired previously with copulation with a receptive female, estrous odours, or no odour. It was demonstrated that estrous and sexually conditioned odours were processed by distinct neural pathways, which both included the NAc core. The authors postulate this structure has a unique role in processing sexual stimuli.

The effect of DA in the expression of conditioned level changing in rats in bilevel chambers has been investigated by Pfaus and Phillips (1991). In a bilevel box procedure, the number of level changes of a male rat in anticipation

of a female is thought to reflect sexual motivation. Male rats in bilevel chambers normally display an increase in level changing in anticipation of the arrival of a sexually receptive female (Pfaus et al., 1990), but administration of a D1 or D2 receptor antagonist produces a decrease in frequency of conditioned level changing in male rats. Also infusions of Haloperidol in the NAc, anteriodorsal striatum and mPOA were investigated and only infusions into the NAc and medial preoptic area decreased conditioned level changing. Furthermore, López and Ettenberg (2002) investigated the role of DA in mediating the positive value and behaviourally activating effects of a sexually conditioned cue. They conditioned male rats to associate two neutral olfactory cues with copulation and social isolation respectively. The rats' approach behaviour toward the scent was taken as an objective measure of its motivational value. Conditioned subjects were treated with different doses (0.0, 0.075, 0.15 or 0.30 mg/kg) of haloperidol 45 minutes prior testing their motivation to approach either the CS+ or CS− scents. Their data revealed that an olfactory cue associated with sexual reward can become a conditioned incentive that is capable of eliciting approach behaviour. Secondly, they found evidence for a dopaminergic role in mediating these motivational effects, as control subjects given vehicle injections took significantly less time to approach the CS+ than an unscented goalbox. This decrease in run latency was not observed in subjects within the 0.075 and 0.15 mg/kg haloperidol groups. These results support the notion that sexual reward is a powerful mediator of incentive formation and enhancement, and such associations are mediated by DA functioning.

### 2.5.2. Female studies

In contrast to the large number of male studies on sexual behaviour, the number of studies on conditioning of female sexual arousal and sexual behaviour are less abundant. To the best of our knowledge, no empirical

research on aversive conditioning of the sexual response of female animals has been conducted, but several studies have addressed appetitive conditioning.

Gutiérrez and Domjan (1997) have shown that when a visual stimulus is consistently preceding the arrival of a male quail, females approach and remain near the CS. Research has shown that CPP also develops in female rats and hamsters, although more robust preferences are seen in males (Oldenburger et al., 1992; Paredes & Alonso, 1997; Paredes & Vasquez, 1999; Arzate et al., 2011). Research suggests that CPP in female rats may be stronger associated with paced, than with nonpaced mating (Paredes & Alonso, 1997). Female paced mating behaviour is the pattern of approach and withdrawal during sexual encounters or the opportunity for the female to escape. In nonpaced mating environments the male controls the tempo of sexual interactions and the female cannot escape from the testing environment (Erskine, 1989). Research has shown that paced copulation induces greater DA release in NAc and striatum in female rats compared with nonpaced copulation (Mermelstein & Becker, 1995). This increase in DA does not depend on the amount of vaginocervical stimulation received from the male, but on the amount of paced vaginocervical stimulation (Becker et al., 2001). Pacing is the critical factor for sexual rewards in the female rat, and only in paced-mating studies the willingness of a female rat to initiate and engage in sexual interaction is reflected, whereas this is not the case in non-paced studies. A study by Pfaus and colleagues (Coria-Avila et al., 2005) demonstrated conditioned partner preference in female rats for males scented with an arbitrary odour that had been paired with paced copulation. This study demonstrated that also in female rats, neutral odours can acquire sexual incentive value and modulate partner preference when paired with the rewarding effects of paced copulation. Subsequent studies by Pfaus and colleagues (Coria-Avila et al., 2006) demonstrated that even though female rats have an unconditioned preference to copulate with males of the same strain, this preference can be switched

toward males of a different strain if that male is associated with the sexual reward induced by paced copulation.

Meerts and Clark (2009) tested the hypothesis that both vaginocervical stimulation and social interaction (placing a male rat into the arena with the experimental rat) can induce a CPP in female rats. Their study showed that female rats expressed a CPP for the context paired with nonpaced mating or artificial vaginocervical stimulation. These findings provide support for the notion that not only pacing or control per se is necessarily the rewarding element in copulation, but rather that vaginocervical stimulation is also an important aspect of the reinforcing effect of mating. Pfaus and colleagues (Parada et al., 2010) studied the ability of clitoral stimulation to induce CPP. They concluded that a form of stimulation is able to induce CPP, similar to the studies by Meerts and Clark (2009) that used vaginocervical stimulation. They also demonstrated that compared to no stimulation, clitoral stimulation induced Fos in hypothalamic and limbic structures, including the NAc. The authors suggest that clitoral stimulation induces a reward state in female rats. In a subsequent study by Pfaus and colleagues (Parada et al., 2011) it was investigated if clitoral stimulation could also induce a conditioned partner preference. In this study they paired a neutral odour with clitoral stimulation. Results suggest that clitoral stimulation of female rats indeed can induce partner preference. In a more recent study (Parada et al., 2013) it was demonstrated that sexual experience prior to conditioning presumably generates a US pre-exposure effect, which makes female rats less responsive to external clitoral stimulation alone. In this experiment female rats remained sexually naïve or received 1 or 5 copulatory sessions prior to conditioning. The female rats were able to pace the copulatory stimulation. Females that received 5 copulations did not develop a significant CPP to external clitoral stimulation, whereas females with either the no prior copulatory experience, or those who received 1 copulation, developed significant CPP to external clitoral stimulation. Thus,

external clitoral stimulation can be devalued as a reward by copulatory experiences.

Furthermore, two studies by Pfaus and colleagues (Coria-Avila et al., 2008a,b) examined the neurochemical basis of conditioned partner preference in female rats. The authors demonstrated that sexual reward in the form of paced copulation in female rats involves the activation of brain opioid systems. In their study, one group of female rats were conditioned to associate scented and unscented males with paced and nonpaced conditioning. The other group of females was conditioned to associate albino or pigmented males with paced or nonpaced copulation. Before each conditioning trail naloxone (an opioid antagonist) or saline was administered. The authors found that the naloxone-trained female rats showed no preference to copulate with either a pacing related or nonpaced related male rat. They concluded that opioids mediate the conditioned partner preference induced by paced copulation. In the second study, with a similar procedure as the first, they concluded that DA transmission is implicated in odour conditioning but is not necessary for the conditioning of strain cues of sexual reward. The administration of flupenthixol, a D1 and D2 receptor antagonist, disrupted odour conditioning but not strain conditioning. This suggests that in conditioned partner preference, the role DA plays depends on the type of stimuli to be learned. The authors suggest some cues may be more potent in terms of activating mesolimbic DA unconditionally. This could explain why it appears to be easier to condition strain cues to sexual reward. They speculate that it is possible that the necessary DA release to induce a significant increase of Fos in the NAc is simply not activated once strain cues have been conditioned. The authors suggest that it could be that strain cues alone produce more DA release than neutral olfactory cues before their association with sexual reward. This makes some associations more easy to learn and possibly less sensitive to disruption by DA antagonists (Coria-Avila et al., 2008a,b).

A more recent study by Arzate et al. (2011) allowed female rats to pace sexual interaction. This study was also designed to compare the rewarding properties of paced mating and morphine (opioids) injections. One group of females was allowed to paced mating before being placed in a non-preferred compartment. Later, they intraperitoneally received a morphine injection before being placed in the nonpreferred compartment and in alternate sessions they received a morphine injection before being placed in the preferred compartment. In the other group, treatments were reversed. Only females placed in the originally non-preferred compartment after paced mating changed their original preference. These results suggest that paced mating induces a positive reward of higher intensity than the intraperitoneally given morphine injection of 1 mg/kg.

Taken together, sexual behaviour can be modified by positive sexual and negative experiences in a wide range of taxa. Data from studies with male rats suggests that experience with ejaculation activates the reward system and sensitizes mesolimbic systems associated with incentive motivation. In female rats, the experience with paced copulation appears to activate the same reward and incentive systems. In quail species, a similar effect may underlie the copulatory reward in both males and females. To conclude, results from animal studies support the notion that sexual reward is a powerful mediator of incentive formation and enhancement, and such associations are mediated by DA functioning. Although in recent years a few very interesting studies have been published by Pfaus and co-workers, in animals the role of learning in sexual arousal and sexual behaviour has been studied less extensively in females than in males. Unfortunately, this is not only the case within animal studies, but also in human studies as the next sections will illustrate. Before discussing the research on conditioning of the human sexual response, we first briefly discuss used methods within this field of research.

## 2.6. Conditioning studies on human sexual response

In human research, the US is a sexually arousing stimulus rather than copulation with a receptive mate. As seen in animal studies, humans can show CRs to the CS, and secondly, humans are able to detect the nature of the contingency between CS and US. Evaluation of states of sexual arousal in human studies are usually measured by self-reports, rating tasks or questionnaires that ask subjects about their level of sexual arousal or other feelings. The CRs are measured by objective procedures such as physiological responding or behavioural recording (Lovibond & Shanks, 2002). The physiological components of sexual arousal include changes in genital response: erection in men and vaginal vasocongestion in women (Janssen et al., 2000; Laan et al., 1995a,b). Erectile responsiveness in men can be recorded by genital measurement devices on penile volume, circumference, and rigidity (Janssen et al., 2006). In laboratory use, penile strain gauges that measure circumference are most widely used. Female physiological sexual arousal can be measured by vaginal photoplethysmography. In this technique, a photometer detects increases in blood volume in the vaginal wall and yield vaginal pulse amplitude (VPA). In the following sections we first will discuss literature available on the classical conditioning of the sexual response in men, after which we will discuss the studies conducted in women. We will focus on the more recent literature, although we will refer to former studies, where they were of particular significance. Before discussing the studies on classical conditioning, we will first briefly consider studies on habituation of sexual arousal.

### 2.6.1. Male studies

#### 2.6.1.1. Habituation of male sexual arousal

O'Donohue and colleagues demonstrated habituation of erectile responses with repeated exposure to the same erotic slides (O'Donohue & Geer, 1985) and to

erotic audiotapes (O'Donohue & Plaud, 1991). In contrast, a study by Smith and Over (1987) demonstrated no habituation in erectile responses or self-reported sexual arousal, while male subjects engaged in structured sexual fantasy over different trials. Since the subjects of this study had earlier participated in another study to employ strategies designed to maintain consistency in sexual arousal over trials, these results should be interpreted with caution. In a later study by Koukounas and Over (1993), sexual arousal habituated with repeated erotic stimulation through both fantasy as well as film material. They also found for both modes that when the repetitive stimulus was replaced by novel content, sexual arousal recovered. The authors pointed out that a change in absorption could have caused the habituation effects in the film condition, because attention to the film fragment had shifted from a participant perspective to a spectator perspective. In a subsequent study, Koukounas and Over (2001) addressed whether sexual arousal fails to habituate when participants maintain a constantly high level of absorption across repeated episodes of erotic stimulation. For this, they used two instructional sets that differed in their manipulation of absorption (i.e. emotion-based attention vs. stimulus-directed attention). The researchers found that under each instructional set, there was a reduction in sexual arousal during repeated erotic stimulation. After controlling for the changes in attentional focus, sexual arousal remained relatively stable over trials. Koukounas and Over suggested that sexual arousal is less likely to habituate if attentional focus remains constant during repeated erotic stimulation. Given the different methodologies used in the studies discussed above, there are indications that male sexual arousal is prone to habituation, but it seems that attentional processes such as the involvement in the erotic stimulus mediate habituation effects.

In a more recent study, Dawson et al. (2013) used erotic film clips with explicit sexual content to investigate habituation in both men and women. Subjects were presented with nine presentations of the same erotic clip,

followed by two presentations of different erotic clips and two presentations of the original erotic clip, while measuring genital responses by mercury-in-rubber strain gauges or vaginal photoplethysmography. Following each stimulus, participants rated their sexual and genital arousal as well as their level of attention during the stimulus using a nine-point scale. The researchers found that repeated exposure to the same erotic stimulus caused a reduction of genital responses in both men and women. Furthermore, subjective reports of sexual arousal showed a similar decline. Also neither sex showed dishabituated responses when re-exposed to the habituated stimulus. The researchers only found a sex difference in the initial response to sexual stimuli. Compared to women, men reported greater initial arousal to the habituation stimulus and their subjective sexual arousal followed a more marked decline with repeated exposure. Taken together, as the discussed studies have shown, male sexual arousal is prone to habituation.

#### 2.6.1.2. Classical conditioning of the sexual response in human males

The most recent reviews on the conditioning of human sexual arousal have been provided by Akins (2004) and Hoffmann (2007). In an earlier review by O'Donohue and Plaud (1994), the authors concluded that the evidence for a relationship between classical conditioning and sexual behaviour was thin. Nevertheless, results from studies since then show that human studies may link more closely with animal studies with regard to the role of the nature of the CS or stimulus relevance in eliciting sexual arousal than perhaps thought (Akins, 2004).

As early as the work of Krafft-Ebing (1929), accidental pairing of an abnormal stimulus with sexual arousal or ejaculation is thought to be 'at base' of the development of sexual deviations. Interpretation of the results from earlier studies on sexual conditioning is complicated by methodological problems. Nevertheless, we will discuss some noteworthy studies. One of the

first studies on the conditioning of sexual arousal is that of Lovibond (1963). In this study it was demonstrated that the galvanic skin response can be conditioned in heterosexual males by using film presentation with graphic symbols as CS and pictures of nude females as US. Also, Rachman (1966) demonstrated sexual arousal in three adult male participants to a pair of black boots, using penile plethysmography. As US, a slide of an attractive nude woman was used. A conditioned response was defined as five successive penile responses to the CS. However, a minimum size of penile responding was not defined in advance. More important, the experiment did not rule out the possibility that it could have been the US itself that has led to sexual responding to the CS. To eliminate methodological criticism, Rachman and Hodgson (1968) replicated their study. In the experimental condition, the CS was contingently paired with the US. But this time, to control for the possibility of pseudo-conditioning, in the control condition the US was presented prior to the CS. The study was successful in reproducing the findings of the earlier study, but under a backward conditioning procedure no sexual responses to the boots were evoked. Subsequently, in a variant of the experiment by Lovibond (1963), McConaghy (1967, 1970) modified the film as used in the Lovibond experiment, by including pictures of male nudes, allowing for the study of classical conditioning in heterosexual as well as homosexual subjects. Film fragments of young adult women and men were shown alternately. Films of the women were preceded by photographs of a red circle, those of the men by photographs of a green triangle. Conditioned penile volume increases occurred for the CS paired with the US of the preferred sex and detumescence for the CS paired with the US of the nonpreferred sex. An important comment on this study made by Langevin and Martin (1975) was that the found detumescence for the CS paired with the US of the non-preferred sex, might have been due to natural detumescence following a period of arousal, and not to conditioned responses. Besides, as with the Rachman studies, no random control procedure

was utilized. Kantorowitz (1978) further examined the nature of association between the US and conditioned arousal induced by erotic slides in eight heterosexual male volunteers. During eight conditioning sessions, for each subject, three different slides of nude women were paired with the plateau, refractory, and resolution stages of masturbation. Stimuli paired with the plateau phase produced an increase in penile erection and stimuli paired with the refractory phase produced a decrease in erection. Not only may classical conditioning have been responsible for the increase in penile response to the stimuli paired with the plateau phase, the orgasm may have conditioned the sexual response in an operant manner as well (Dekker & Everaerd, 1989).

Inspired by the results of the experimental studies by Rachman and McConaghy and colleagues, theories arose about the aetiology of what was then called sexual deviant behaviour (McGuire et al., 1965). The application of behavioural techniques for the reorientation of sexual desires in an attempt to 'treat' these sexual behaviours increased exponentially during the following years. In most cases aversion techniques were applied in attempts to alter sexual behaviours (Solyom & Miller, 1965; McConaghy & Barr, 1973; McConaghy, 1975; Laws et al., 1978). Most, if not all of these studies lacked proper control procedures and often described single case studies. Nevertheless, these studies all suggested that sexual arousal can be classically conditioned.

Since then a number of well controlled studies have demonstrated that classical conditioning can augment sexual arousal in men. Two studies using nonclinical samples have shown convincing evidence for conditioning of male sexual arousal. In an experiment by Lalumière and Quinsey (1998) 10 male participants were exposed to a slide of a nude women and a highly arousing film clip of heterosexual sexual interactions. The other 10 participants were only exposed to a slide depicting a nude woman. Participants exposed to the slide plus the film clip showed increased penile responses to this slide of a nude woman, relative to other responses to other test stimuli (other slides of semi-

clothed women, two neutral slides that depicted trees and flowers). Participants exposed to only the slides depicting a nude woman, showed a reverse pattern: they showed a decrease in sexual arousal to the slide. The authors proposed that the finding of increased penile responses to the original slide with a nude woman, relative to the responses to other test stimuli (other slides of nude women) in the group that was also presented with the film clip, could be produced by inhibition to stimuli that were not associated with the US. The inhibition to the stimulus (slide of the nude woman) in the group that was not presented with the erotic film clip may have been the result of habituation, because the participants were exposed 11 times to the slide. The authors concluded that because the group difference was due to a relative increase in arousal to the stimulus of a nude woman when paired with an arousing sexual stimulus, and a relative decrease in arousal to the stimulus of a nude woman when presented alone, any attempts to increase sexual arousal using classical conditioning may be hindered by the male tendency to habituate to stimuli when presented repeatedly.

Plaud and Martini (1999) conditioned male sexual arousal in 9 subjects, using sexually explicit slides as US. As CS they used a slide of a penny jar. In the conditioning procedure, the CS was presented for 15 s, followed by the US for 30 s. The second procedure was identical to the first conditioning procedure, except that the US was presented before the CS. In the third procedure, the presentation of the CS and US was determined randomly. The results of this study indicated that subjects showed increases in penile tumescence from baseline in the first mentioned condition procedure, but not during the other control conditions.

A more recent study by Hoffmann et al. (2004) found sexual conditioning effects in men, but these effects only approached a conventional level of statistical significance. In their study both male and female subjects received subliminal or conscious presentations of a photograph of either a

sexually relevant or irrelevant CS, which was followed by an erotic film clip. Both men and women showed greater conditioned sexual responding when a subliminal CS was more sexually relevant (the abdomen of an individual of the opposite gender) than when it was less relevant (a gun). This supports the notion of stimulus relevance in humans. However, when consciously perceived CSs were used, gender differences came into view. Women showed conditioned arousal to the sexually irrelevant rather than the relevant CS, whereas men receiving conscious presentations of the CS showed more evidence of conditioned sexual arousal to the abdomen than to the gun.

In contrast to the study of Hoffmann et al., results from a fMRI study of Klucken et al. (2009) provide stronger evidence for conditioning in men than in women. Klucken and colleagues investigated neural activation during sexual conditioning. They presented a geometric shape (a rhomb) as CS+. This figure was followed by highly sexually arousing pictures (US). Another geometric figure (a square) served as CS− and was followed by neutral pictures. Arousal ratings were significantly higher for the CS+ than for the CS−. Second, greater activations in response to the CS+ were seen in reward related structures (e.g. OFC, VTA and ventral striatum) compared to the CS−. Furthermore, subjects who were aware of the contingency of the CS and US as compared to unaware subjects showed greater hemodynamic responses in the ventral striatum, medial OFC, occipital cortex, and VTA in response to the CS+ compared with the CS−. And also interesting, compared to women, men showed stronger conditioned activation in the amygdala, thalamus and occipital cortex. The researchers considered the results to be in line with other findings (Pfaus et al., 2001; Gutiérrez & Domjan, 1997), suggesting that men are more receptive to conditioning of sexual arousal than women.

More recent, Hoffmann et al. (2012) used a field study design to explore the conditioning of male sexual arousal in a real-world setting. The experiment was divided into a baseline and testing session in the laboratory and

intervening conditioning sessions in the field (e.g. participant or partner residence). They instructed seven heterosexual couples to include a novel, neutrally preferred scent as a CS+ during sexual interaction and another scent during non-sexual coupled-interaction like watching a movie together. Hereto, females were given two white cotton tops, two aroma fans and vials with geranium and basil essential oils. In a control group seven couples used both scents during non-sexual interaction. Over a 2-week period both experimental and control couples had three sexual interactions. Furthermore, experimental couples had three non-sexual interactions, while controls had six non-sexual interactions. The female partner was responsible for orchestrating 'conditioning' and was instructed to alternate activities (sexual and non-sexual) and to spread them out for more than 12 h apart. During the baseline session and the testing session in the lab, men placed electromechanical strain gauges on their penis and positioned an oxygen cannula for odour presentation. Subsequently, they were exposed to presentations of basil and geranium odours, while listening to relaxing music accompanied by media player visuals on a computer monitor. This procedure was repeated with two different odours, but now participants were exposed to short fragments of a non-sexual film and a sexual film. The final testing session was similar to the baseline session except that odorants were presented in a different order. In the experimental group, an increased genital responding to the CS+ was observed relative to the control group. In addition, males in the experimental group also showed a trend for decreased preference for the CS− odour. Somewhat contrary to what the authors expected, the genital CRs were not stronger than those obtained during laboratory-based sexual conditioning. Nonetheless, participants retained the CR for at least several days (since participants, although instructed did not return straight to the laboratory for testing after completion of the conditioning phase). This study does show a longer-retention of conditioned sexual responses than has typically documented in humans. This

study also provides evidence for evaluative sexual conditioning in men, as they found an increase in preference for the partner-paired odour in the control group and the sexually paired odour in the experimental group.

In summary, studies providing empirical evidence for conditioning in human male sexual arousal are scarce. As a result of procedural problems and confounds, the interpretation of results from former studies within this field is limited. Nevertheless, latter studies contribute to the growing evidence that classical conditioning procedures can condition the male sexual response. The next section will focus on empirical evidence for operant conditioning in male sexual arousal.

#### 2.6.1.3. Operant conditioning of the sexual response in human males

There are several studies on the regulation of genital responses as a function of instrumental contingencies. Rosen and colleagues (Rosen, 1973; Rosen et al., 1975) conducted two studies to investigate the possible modification of penile tumescence by instrumental conditioning. In the first study (Rosen, 1973) as a result of contingent feedback highly significant suppression of tumescence relative to the flaccid state was obtained. In order to elicit penile tumescence, a series of erotic tape-recordings were presented. A red light was presented to male volunteers whenever their erection exceeded a criterion increase, and in this way they learned to significantly inhibit tumescence over the course of three experimental sessions. In their second study, Rosen and colleagues gave subjects in the experimental group analogue visual feedback and monetary rewards for increases in penile tumescence in the absence of external erotic stimuli. Rosen and co-workers concluded that instrumental conditioning is effective in modifying sexual arousal. However, they did not test for sexual fantasizing.

Inspired by the results obtained in classical conditioning procedures on the treatment of particular sexual behaviours, several case studies have reported

pairing sexual arousal produced by masturbation with heterosexual stimuli in the treatment of homosexuality or undesired sexual behaviour. But in order to 'treat' these forms of sexual behaviour, many case studies describe aversive conditioning (Bancroft, 1969, 1970; Feldman, 1966; Freeman & Meyer, 1975; Herman et al., 1974a,b; Josiassen et al., 1980; Gold & Neufeld, 1965; Quinn et al., 1970; Beech et al., 1971; Rosen & Kopel, 1977). For example, MacCulloch and Feldman (1967a,b) used aversion therapy in homosexual subjects. Subjects could avoid a shock after seeing a male picture by turning off the slide by pressing a switch. Thereby, the introduction of female slides was made contiguous with the removal of the male slides. Over half of these subjects reported a change in sexual orientation during this experiment, but no follow-up was conducted. In their second study a follow-up study was conducted. Eventually a substantial number of participants were said to have shown a change in sexual orientation that was still present at one-year follow-up. However, the reliability of self-report as a treatment outcome measure may be questioned. Also other types of clinical conditioning techniques like that of orgasmic reconditioning (guided fantasy in masturbation) or covert sensitization were applied in order to shape sexual behaviour (Abel et al., 1970; Abel & Blanchard, 1974; Alford et al., 1987; Jackson, 1969; MacCulloch et al., 1971; Brownell et al., 1977; Schaefer & Colgan, 1977). The evidence in support of these procedures used alone is mixed (Conrad & Wincze, 1976; Lande, 1980; VanDeventer & Laws, 1978) and again, most of these studies concern uncontrolled (case) studies (Conrad & Wincze, 1976; Keller & Goldstein, 1978). The study of Marquis (1970) is a good example of an orgasmic reconditioning study. Subjects with 'perversions' were instructed to masturbate to the point of orgasm (using a preferred fantasy), at which time the subject was instructed to switch to more 'appropriate' fantasies. Almost all subjects were reported to be cured, or to be improved. Because of the lack of objective measures, again these results cannot be interpreted straightforwardly. Although

there has been some empirical evidence that learning plays a role in the development of partner preferences, and partner preferences appear to be influenced by experiences both early in life and in adulthood, the general assumption is that the orientation-preference is at least in part determined by sexual imprinting (Pfaus et al., 2001; Woodson, 2002).

Even though no firm conclusions can be drawn from most of those uncontrolled operant conditioning studies because possible evidence does not go beyond the case study level, combined with the results from classical conditioning studies, they do point to the conclusion that conditioning procedures can affect the human sexual response. Although it is unlikely that conditioning procedures can alter sexual orientation, conditioning can influence the (motivational) valence of an incentive. Although it may be expected that the same effects should occur in women, literature on this topic is scarce. First we will discuss the studies of habituation of female sexual arousal and continue with studies on classical conditioning.

### 2.6.2. Female studies

#### 2.6.2.1. Habituation of female sexual arousal

Parallel to the habituation effects that O'Donohue and Geer (1985) established for men, Meuwissen and Over (1990) demonstrated decreased levels of genital and subjective sexual arousal in women, after repeated exposure to erotic fantasy as well as erotic film fragments. There was recovery of arousal to the original response level, when a new erotic stimulus, i.e. a new fantasy or film fragment was introduced. A later study to assess the occurrence of habituation in female subjects after repeated stimulus exposure could however not draw reliable conclusions considering habituation of female sexual arousal (Laan & Everaerd, 1995a,b). After 21 trials of sexual stimulus presentation, female subjects continued to show both genital and subjective arousal. In a more

recent study from our laboratory a habituation design with 'hot vs. cool' attentional strategies was used to investigate the regulation of sexual arousal (Both et al., 2011b). Manipulation of a hot and a cool attentional focus was done by instructing participants to either imagine that they were engaged in the sexual activities depicted in the erotic film stimulus and to focus on their physiological and emotional reactions that they felt during film viewing (hot focus), or to realize that they were "just looking at a film" and to focus on characteristics of the physical setting of the erotic film (cool focus). Under the hot focus stronger sexual feelings were observed than under the cool focus. Furthermore, habituation and novelty effects were found: during repeated erotic stimulation genital responses and sexual feelings diminished and with the introduction of a novel stimulation they increased. Interestingly, the hot attentional focus did not preclude habituation of sexual arousal. As earlier mentioned, the study by Dawson, Suschinsky and Lalumière (2013) showed that men and women showed statistically similar patterns of genital responding to repeated stimulation. Women showed diminution of both genital responses and subjective reports of sexual arousal. The authors concluded that there is a possibility that sexual responses of men and women are similarly malleable and equally subject to learning processes. Despite, there seems to be some evidence for female sexual arousal to habituate, more research is needed on this topic and it is too early to draw firm conclusions.

#### 2.6.2.2. Conditioning studies on female sexual arousal

To the best of our knowledge, in contrast to the numerous comparable reports on men, only one case of a conditioning procedure in an attempt to alter female homosexuality was published. Blitch and Haynes (1972) described a case study of treating a female homosexual by systematic desensitization and manipulation of masturbation fantasies. The participant was instructed to make image switches when her masturbation image was initially homosexual. After the

termination of the therapy, an increase in heterosexual images of masturbation were said to have taken place. A follow-up study stated that no overt homosexual behaviour had occurred since the therapy. Since this study was solely based on self-report measures, no further conclusions can be made.

The first controlled conditioning study on female sexual arousal study was that of Letourneau and O'Donohue (1997). The authors tried to condition subjective sexual arousal and vaginal blood flow. They used film fragments showing heterosexual oral or coital sex and as a neutral stimulus they used amber light. A significant conditioning effect was not detected. They attributed these results to an ineffective US. Opposing to this study, Hoffmann et al. (2004) found statistically significant evidence for conditioned genital arousal in women, as discussed earlier. When the CS was presented subliminally, men and women showed more conditioned arousal to the sexually relevant CS than the sexually irrelevant CS (gun). When the CS was consciously perceived, women showed stronger conditioned arousal to the sexually irrelevant CS compared with the relevant one. It was suggested the latter finding was due to an increase in automatic nervous system responding such that women showed greater general arousal to the nonsexually relevant CS than to the sexually relevant CS. This pleads in favour of the assumption that there is an independent role for automatic processing in human sexual response mechanisms. Their findings are consistent with Öhman and Soares (1994) in demonstrating that associative learning in humans can occur without awareness of the CS-US contingency. In a comparable study, in our lab unconscious classical conditioning of sexual arousal in women was investigated (Both et al., 2008a). Clitoral vibrostimulation served as US and two subliminally presented erotic pictures served as CS+ or CS−. With a forced choice recognition task, conscious perception was tested. Results from this task revealed that participants were not able to perceive the CSs during masked presentation. Thus, evidence was found for a conditioned genital response following repeated pairing of masked erotic pictures with

genital vibrostimulation and these findings add to the increasing evidence for associative emotional learning without awareness of the CS-US contingency (Öhman & Soares, 1993, 1994, 1998; Wong et al., 2004; Hoffmann et al., 2004).

A later study in our lab (Both et al., 2008b) was the first that provided evidence for a conditioned genital response to an initially neutral CS in human females. Again a differential conditioning procedure was used with genital vibrostimulation as US. Two neutral pictures of cartoon male faces served as the CS stimuli. A conditioned genital arousal response to the neutral picture that was paired with genital vibrostimulation was found. Secondly, a relation was observed between the strength of the conditioned genital arousal response and sexual functioning and sexual arousability as measured by questionnaires. It was suggested that a person who is more easily sexually conditionable may associate several stimuli with rewarding sexual experience and subsequently, this may result in sexual arousal and desire when confronted with these cues. In a following study, a few changes were made compared to the earlier study (Both et al., 2011a). Skin conductance level (SCL) and subjective affective value was measured as well as genital and subjective sexual arousal in response to the CSs. Again they observed a conditioned sexual arousal response, as genital arousal was higher in response to the CS+ than in response to the CS−. Also, a marginally significant difference was found for affective value ratings between the CS+ and CS−, indicating a more positive evaluation of the CS that was followed by genital vibrostimulation.

In addition, a differential conditioning study on aversive conditioning was conducted (Both et al., 2008b). In this study evidence was found for attenuation of female genital response through aversive conditioning. This time two erotic pictures served as CS and a painful stimulus at the wrist as US. After conditioning VPA was lower in response to the CS+. Moreover, the CS+ was rated more negative compared to the CS−. Although this is the only study on aversive sexual conditioning in women to date, these results support the view

that in women, as a result of classical conditioning, aversive sexual experiences may result in decreased sexual arousal.

The results obtained by Hoffmann and colleagues, and Both and colleagues, oppose the study by Letourneau and O'Donohue (1997) in which no evidence was found for female conditioned genital response. As stated before, Letourneau and O'Donohue suggested that the failure to demonstrate conditioned sexual arousal may have been because of an ineffective US. However, in the studies in our laboratory genital responses to the US were also weak, suggesting that a strong responding to the US is not a prerequisite to demonstrate conditioned genital arousal in women. More interesting is the fact that Letourneau and O'Donohue used a coloured light as CS, whereas in the studies by Hoffmann et al. (2004) and our studies (Both et al., 2008a,b, 2011a) more sexually relevant CSs were used (i.e. a picture of a male abdomen and a picture of a male face). Possibly the conditioning of female sexual arousal may be facilitated by the use of those more sexually relevant CSs. Also interesting to note is the finding in our studies that conditioned genital response as well as conditioned affective value did not clearly diminish during the extinction phase. This suggests resistance to extinction of conditioned sexual responses. However, since the number of extinction trials in these studies was small, firm conclusions regarding the presence or absence of extinction of conditioned responses cannot be made.

Concluding, despite the limited amount of research, there is growing support that female sexual arousal can be conditioned as well. But evidence is scarce and efforts to replicate these studies are encouraged.

### 2.7. Discussion

Sexual behaviour of animals can be modified by positive sexual and negative experiences in a wide range of taxa. Arbitrary CSs such as auditory, visual and olfactory stimuli appear to be effective CSs in both male and female animals,

but even more intriguing, greater CS-US similarity appears to elicit different CRs, at least in male animals. In contrast to results obtained with arbitrary CSs, conditioned responses toward sexually relevant CSs might be highly resistant to extinction, at least in male quail. Therefore, CS-US similarity seems to be an important factor in conditioning (Rescorla & Furrow, 1977; Krause et al., 2003). Furthermore, it seems that even long CS-US intervals or inconsistent pairing of the CS with the US can result in sexual learning in animals. Moreover, this sexual learning can take place without permitting subjects to complete copulation (Hollis et al., 1989; Zamble et al., 1985; Holloway & Domjan, 1993). But Kippin and Pfaus (2001a,b) demonstrated that the development of CEP in male rats is dependent upon ejaculation. And because the USs for CEP and USs for conditioned sexual excitement are different, not all conditioning effects on sexual behaviour may involve the same US. Furthermore, results from animal studies support the notion that a state of sexual reward, by for instance ejaculation in male rats or paced mating or vaginocervical/clitoral stimulation in female rats, is a powerful mediator of incentive formation and enhancement, and such associations are mediated by DA functioning.

Research on human sexual conditioning has lagged substantially behind that of animal sexual functioning. Nevertheless, studies in humans have demonstrated that classical conditioning can augment or diminish subjective and genital sexual arousal in both male and female subjects. Human studies may link more closely with animal studies with regard to the role of the nature of the CS or stimulus relevance in eliciting sexual arousal than perhaps thought (Akins, 2004). We will discuss the most prominent overlaps.

The mechanism of preparedness may cause some events or stimuli to become more easily associated than others. First, the results of both the study by Hoffmann and colleagues and Letourneau and O'Donohue support the notion of stimulus relevance in humans as well as animals. As we have

mentioned before, Hoffmann et al. (2004) found no clear evidence of conditioning in human males as their effects in men only approached a conventional level of statistical significance, but both men and women showed greater sexual responding when a subliminal CS was more sexually relevant than when it was less relevant. The lack of a significant conditioning effect in the Letourneau and O'Donohue (1997) study in women may have been due to their use of a sexually irrelevant CS. It is possible that the conditioning of female sexual arousal may be facilitated by the use of sexually more relevant CSs.

The results of the study by Hoffmann and colleagues do not entirely support this hypothesis of preparedness. In their study they used a picture of an abdomen of an individual of the opposite gender as 'relevant' CS. Interestingly, experimental eye-tracking studies on viewing patterns of sexual stimuli have shown that when men and women are presented with the same sexual stimuli, they do not view them in the same manner (Rupp & Wallen, 2008). Both men and women spent less time looking at a male body look zone than would be expected based on the average proportion of picture area it occupied. This may mean that heterosexual female participants are not interested in the male bodies, unless genitalia are depicted. A study by Lykins et al. (2006) revealed that nude male bodies are relevant for heterosexual women. When the genitals are included in the male body look zone, women do preferentially view nude male bodies. Possibly, this reflects a female preference for looking at male genitalia. It could be that a picture of an abdomen of an individual of the opposite gender, as used by Hoffmann and co-workers, was not the evident relevant CS after all, at least for women. It would be interesting to use explicit pictures of genitals of the opposite sex as CSs in future sexual conditioning studies in women. Future studies should therefore focus on sexually relevant and sexually irrelevant CSs. It would be very interesting to further investigate if some aspects of sexual stimulus processing in humans do indeed involve

preferential rapid learning to certain classes of innately 'prepared' stimuli (Seligman, 1971; Öhman, 1986; Öhman & Mineka, 2001). But as mentioned before, the preparedness theory is not incontrovertible. Therefore, the rapid learning to certain classes of stimuli can also be explained by experience with certain stimuli (Davey, 1995). For instance, Masataka (1993) demonstrated that experiences with certain stimuli that are not snakes (e.g., live insects) can differentially sensitize a fear of snakes in laboratory-bred monkeys, suggesting that experiences with selected non snake stimuli can influence subsequent fearful reactions to snakes in some direct or indirect way. In a similar way, possible rapid learning to sexual relevant stimuli could also be explained by past experiences and the cognitive ability to infer that there are important functional differences between CSs. Nevertheless, conditioned responses to sexually relevant CSs seem highly resistant to extinction in animals and findings in humans point to the same direction. Results from the sexual conditioning studies by Both and colleagues (Both et al., 2008a,b, 2011a,b) showed that conditioned subjective affect does not extinguish significantly during the extinction phase. This suggests a resistance to extinction. This finding is in line with evaluative conditioning research (Vansteenwegen et al., 2006). Acquired subjective likes and dislikes are seemingly quite resistant to extinction. Such a resistance to extinction may have important clinical implications. When conditioned valence is indeed relatively resistant to extinction, in treatment of hypersexuality and paraphilia a combination of extinction therapy with counter conditioning, thus learning new opposite responses, would be more effective than extinction therapy alone. But more research should be conducted within this field to be conclusive. Second, future studies could also investigate this possible resistance to extinction with an implicit measurement, like an approach and avoidance task (Chen & Bargh, 1999; Wiers et al., 2011). Self-report measures assess mental processes or representations that are consciously accessible. In contrast, implicit measures assess automatic processes that often

operate outside awareness. As subjective measures are prone to socially desirable bias, it would be interesting for future studies to include an implicit measure.

Moreover, in animals, sexual conditioning experiments indicate involvement of limbic reward circuitry, including the NAc. To date, only one fMRI study on human sexual conditioning has been reported, using erotic pictures as US (Klucken et al., 2009). Nevertheless, also conditioned activation was seen in reward structures. Since vibrostimulation has proven to be an effective US in women, it would be interesting to conduct a similar study using a tactile US instead of a visual US. A tactile US may yield stronger conditioning effects.

To conclude, how do stimuli acquire sexually arousing properties? The ability of sexual behaviour, especially orgasm and ejaculation, to increase the concentration of DA in the NAc is considered to be crucial for the acquisition of new sexual learning in humans (Berke & Hymann, 2000; Di Chiara, 1999; Robinson & Berridge, 2003). Stimuli that resemble some innate sexual US more closely, are thought to become more easily associated with a state of sexual reward. But by the means of powerful mediating DA functioning, also sexual irrelevant stimuli can become associated with sexual reward. The brain stores an internal representation of experiential sexual events, and DA neurons mediate associative learning and expectations based on previous experience with a stimulus. Furthermore, repeated exposure to a sexual rewarding stimulus causes strengthening of stimulus-response and stimulus-reward associations, and sensitizes the mesolimbic pathways (Di Chiara, 1999). Subsequently, sexual rewards evoke an increased DA release into the NAc. Repetitive sexual rewards result in releasing Delta FosB in the NAc. Delta FosB may cause sensitization to sexual rewards (Nestler, 2001). In addition, since orexin is thought to facilitate glutamate-mediated responses, and to be necessary for glutamate-dependent long-term potentiation in VTA DA neurons, it is suggested that the

altered glutamate sensitivity by exposure to sexual rewards strengthens the neural pathways that link memories of the sexual stimulus event and related cues with high reward (Esch & Stefano, 2004; Hyman et al., 2006; Chen et al., 2010; Wise & Morales, 2010; Kelz et al., 1999; Aston-Jones et al., 2010; Fields et al., 2007).

Bancroft and Janssen (2000) proposed a theoretical model of dual control of sexual arousal and associated behaviours in which the net expression of sexual behaviour is based on the influence of excitatory and inhibitory mechanisms in the brain. As in Gray's biopsychological theory about behavioural activation and inhibition systems (Gray, 1982) this model stresses the adaptive nature of both excitatory and inhibitory processes. The dual model by Bancroft en Janssen can be described as a theory of approach and avoidance and the associated concepts of reward and punishment. The authors assume that sexual inhibition and excitation are both adaptive, serving a number of biological functions. Although they suggest that learning possibly plays a role in determining individual variabilities in response tendencies, they assume that individual variation in sexual inhibition and excitation is a stable trait, which is possibly genetically determined (Janssen & Bancrtoft, 2007). Individuals with an unusually high propensity for excitation or a low propensity for inhibition are more likely to engage in high-risk sexual behaviour. In contrast, individuals with a low propensity for sexual excitation or a high propensity for sexual inhibition are more likely to experience problems with impairment of sexual response (Bancroft et al., 2009). The model of dual control of sexual arousal allows the sexual response systems to be flexible. Flexibility in sexual responding possibly results in a sexual system that can exist under a variety of optimal and even unoptimal internal and external conditions. As Pfaus et al. (2001) state it "Flexibility in responding gives different species an enormous amount of chance to recombine in different ways, yielding a higher degree of diversity." Nevertheless, learning processes constrain the individual's attention to sets of

stimuli and patterns of behaviour that result in the proximal goal of sexual reward (in other words: stimuli that are known to "work"). Such stimuli are likely to differ from person to person based on every individual's sexual history, and this also accounts for the related behaviours. This means that how excited or how aroused an individual becomes by a certain stimulus is determined by the counterbalancing of experience and conditioning on one hand and instinctual responses to unconditionally arousing stimuli (both internal secretions and external cues) on the other. Pfaus (2009) presented an overview of neurochemical and neuroanatomical systems involved in sexual inhibition and excitation. During sexual inhibition the opioid, endocannabinoid, and serotonin systems are activated. In contrast, the DA systems, melanocortin, oxytocin, and norepinephrine systems are activated during sexual excitation. The core of sexual excitation pathway includes the mPOA and its outputs to the VTA. Brain pathways for sexual inhibition involve the activation of inhibitory opioid, endocannabinoid, and serotonergic feedback to various levels of the excitatory pathway. The inhibitory pathway is activated by sexual stimulation that reaches critical thresholds for sexual reward, sedation, and satiety. Since the excitatory pathway is stimulated both hormonally and conditionally by the expectancy of sexual rewards, external incentive stimuli can act as occasion setting for the excitatory system.

Despite the observed convergence between animal studies and human studies, there are many topics that need further exploration in the study of human sexual conditioning. Results from a study by Both and colleagues (Both et al., 2005) support the view that DA is involved in the energetic aspects of appetitive sexual behaviour, at least in men. And a more recent fMRI-study from our lab (Oei et al., 2012) provides compelling evidence for a mediating role of DA in processing of subconscious perceived sexual stimuli. In healthy young men, levodopa significantly enhanced the activation in the NAc and dorsal anterior cingulate cortex in response to subliminal sexual stimuli,

whereas haloperidol (a DA blocker) decreased activations in those areas. This first evidence for pharmacological modulation of implicit sexual reward processing, points at the possibility for DA to affect sexual motivation at its earliest onset, that is, outside awareness. But as these results only apply for men, further studies are warranted to investigate the role of DA in female sexual behaviour. Moreover, as enhancing effects of testosterone administration on neural activity related to appetitive goal attainment in mesolimbic incentive processing circuits has been demonstrated (Hermans et al., 2010), these findings may have implications for the understanding of why relatively more men are prone to develop hypersexuality or paraphilia (Krueger & Kaplan, 2001; Kafka & Hennen, 2003).

Moreover, no human research has been done on the role of dopamine in sexual reward learning, while facilitation as well as impairment of sexual reward learning is relevant in the context of treatment of hypo- and hypersexual desire disorder. Future studies on sexual behaviour also need to investigate how DA affects the incentive reward of neutral stimuli paired with rewarding ones. Presumably, the combination of individual differences in DA sensitivity in combination with frequent exposure to sexual cues and reinforcement processes might explain the initiation of aberrant sexual desires. The use of an implicit task in future studies would also be interesting because, as stated before, according to the incentive-salience hypothesis the dopaminergic pathway of the reward system attributes incentive salience to representations of stimuli or events that were associated with appetitive reward. As Berridge (1996) underlines that both wanting and liking can exist without subjective awareness, reward processing and learning can occur without conscious experience (Damasio & Carvalho, 2013). On the contrast of implicit emotion as a corresponding label for unconscious affective reactions, explicit emotion refers to the person's conscious awareness of an emotion, state or feeling (Berridge & Winkielman, 2003). Although emotions can occur unconscious and

people are not able to report their emotional reaction at the moment it is caused, this emotional reaction can be visible in their behaviour, physiological responses or subjective impressions of an-affect laden event. In this way, sexual stimuli can activate bodily responses (and implicit memory) before conscious appraisal. For this reason it would be very interesting to study dopaminergic effects on implicit sexual reward learning in human beings. Although there is evidence for enhanced tendencies to approach sexual stimuli following DA increased activation (Both et al., 2005) no study to date investigated whether DA-dependent increased activations by for instance conditioned sexual stimuli are related to increases in approach behaviour.

What can be said about possible gender differences in sexual conditioning at the moment? As little research has been done within the field of conditioning of the sexual response in humans, and most of this conducted research is limited to one of the sexes, exploration of possible sex differences is not straightforward. Nevertheless, we will discuss the most remarkable possible sex differences. First, as the research with male rats by Pfaus and co-workers has shown, sexual reward is a powerful mediator of incentive formation and enhancement, and those associations are mediated by DA functioning. But as the studies by Pfaus (Coria-Avila et al., 2008a,b) have shown, the administration of a D1 and D2 receptor antagonist disrupted odour conditioning but not strain conditioning in female rats. This suggests that in conditioned partner preference, the role DA plays in female rats depends on the type of stimuli to be learned. In humans, little research has looked into the role of DA in sexual motivation and sexual reward processing. Moreover, no studies to date have addressed the role DA plays in mediating associative sexual learning in both men and women. Therefore, future research is warranted to explore possible gender differences. Second, as studies in rats have shown, tones paired with electric shocks in an aversive conditioning procedure, can induce copulation in noncopulating male rats. And this finding was attributed to an arousal

augmentation by the anticipation of pain. Unfortunately, to the best of our knowledge, to date no empirical research on aversive sexual conditioning in female animals has been conducted. Therefore, we do not know whether such a finding would be observed in female rats. But in women, we found attenuation of sexual response by aversive conditioning (Both et al., 2008b). Research on pain-related fear on sexual arousal in women revealed that the threat of a painful shock to the wrist impeded genital arousal and positive affect, whereas it amplified negative affect (Brauer et al., 2007). Therefore, one might conclude that expected pain is likely to reduce sexual arousal in women. Furthermore, it would be interesting to investigate if electric shocks during a conditioning procedure could facilitate sexual arousal in human males. Third, results from the fMRI study by Klucken et al. (2009) revealed stronger conditioned activation in the amygdala, thalamus and occipital cortex in men compared to women. The researchers considered the results to be in line with other findings (Pfaus et al., 2001; Gutiérrez & Domjan, 1997), and subsequently suggested that men are more receptive to conditioning of sexual arousal than women. But since there is so little literature within this field it is too early to suggest such a difference in conditionability between men and women. Gender differences in the number of DA neurons are influenced by several factors, including sex chromosome complement (Lombardo et al., 2012), the presence of the sry gene (Dewing et al., 2006) and as discussed in more detail before, gonadal hormones. Therefore it is conceivable that that gender differences in conditionability do exist. But since research on conditionability and related neuromodulatory systems in humans is in its infancy, we can only speculate if similar processes can be proven to account for any gender differences that may be found in future human studies. We can only conclude that not only more research is needed in bridging the gap between animal studies and human studies, but also future replication studies in both men and women are needed before we can say anything about possible gender differences in sexual conditioning.

As has been shown, much empirical evidence from both animal and human studies fits the assumptions of the incentive motivation theory. According to the model, individual differences in sensitivity for certain sexual stimuli can predict which incentives are preferred, and which are not. Interestingly, research has demonstrated that sexual arousal is preference-specific in men, whereas women have a nonspecific pattern of sexual arousal (Chivers et al., 2004). Heterosexual men are more aroused by female than by male sexual stimuli and homosexual men show the opposite pattern. In contrast, the genital responses of women are only modestly related to their preferred category. Thereby, genital arousal in women is not per se accompanied by subjective desire or arousal (Laan & Everaerd, 1995a,b; Laan et al., 1995a,b). In relation to the incentive motivation theory, that states that sexual motivation is the result of the interplay of a sensitive internal sexual system with external motivational stimuli, this implies that for homosexual men for example, a picture of an attractive nude man may be innately sexually competent, but for heterosexual men this is likely not the case. As mentioned, research does confirm such a mechanism, at least for men. But with respect to women, genital responses are not very informative about sexual preference. Only subjective arousal reflects their preference. Notwithstanding the importance of incentives, individuals are not simply passive until triggered by the matching preferred external incentives or the cues associated with them. Cognitive processes like conscious awareness, goals and social restrictions can influence this process. Although men and women do not differ with respect to basic sexual learning, it is speculated that women are more sensitive to variations in social and cultural factors (i.e., exhibit more erotic plasticity") compared to men (Baumeister, 2000; Toates, 2009). In women, a sexual stimulus tends to trigger a wider range of cognitions as compared to men (Laan & Janssen, 2007). Therefore it is suggested that women's sexual motivation and arousal might be more strongly controlled by cognitive factors, whereas men's

sexual motivation tends to be more strongly controlled by stimulus factors. The above mentioned findings make clear that the theory of incentive motivation captures in a simplified form only some of the processes that underlie human sexual motivation and behaviour (Toates, 2009). Further insights require looking more closely at the pathway of information between stimulus and response and considering how the processes captured by the original incentive motivation model are embedded within other (higher-level) processes.

As DA is not the only neurotransmitter involved in the sexual system, future studies should also look at the serotonin system. Pharmacological manipulations of the central serotonin neurotransmitter system alter functioning of the hypothalamicpituitary- adrenal (HPA) axis. Such HPA changes play important roles in behavioural modulation and may contribute to the alteration of sexual and social behaviour (Aubert et al., 2012). For example, serotonin has sexual side effects such as decreased sexual desire (Meston & Frohlich, 2000), and serotonin reuptake inhibitors seem to have efficacy in treating hypersexuality (Bradford, 2001). Flibanserin, a postsynaptic 5-HT1A agonist/5-HT2A antagonist, has been shown to increase sexual desire and reduce sexual distress in women with Hypoactive Sexual Desire Disorder (HSDD) (Kennedy, 2010; Thorp et al., 2012). Therefore, it would be worthwhile to examine how serotonin possibly inhibits the reward system activity during processing of sexual stimuli, and study the role of serotonin in associative sexual reward learning in general.

In addition to DA, opioids are also differentially involved in conditioned and unconditioned sexual behaviours (Holloway, 2012). The brain opioid system is involved in sexual reward in the form of ejaculation in male rats, or paced copulation in female rats (Pfaus & Gorzalka, 1987; Pfaus et al., 2013) and is believed to be the main modulator of sexual reward (Ågmo & Berenfeld, 1990; Coria- Avila et al., 2008a,b). In the distinction made by Berridge, 'wanting' has been characterized as the value of incentive motivation

held by a stimulus without any hedonic component, and mediated by DA functioning. On contrast, 'liking' encompasses the hedonic aspect of a stimulus presentation, the positive sensory component that accompanies reward delivery (Berridge, 2004) and is thought to be mediated by the opioid system. Research has revealed two different domains in which endogenous opioids, present in separate and distinct brain regions, are involved (van Ree et al., 2000). One is related to incentive motivation, in which opioid systems in the VTA and the mesolimbic DA system are involved, and may relate to sexual motivation. The other is the performance of certain behaviours involving endogenous opioids, like sexual performance. In general, opioids and opioid drugs are found to have an inhibitory role in both male and female sexual behaviour (Pfaus & Gorzalka, 1987; Holloway, 2012). Research has demonstrated that opioid actions in the VTA potentiate mesolimbic DA activation, whereas opioid actions in the mPOA inhibit sexual behaviour in rodents (van Furth et al., 1995; Holloway, 2012; van Ree et al., 2000). Administration of opioid antagonists (e.g. naloxone) in sexual conditioning experiments has shown to disrupt the incentive motivation for and/or hedonic value of a CS predicting sexual opportunity or of the sexual stimulus itself (Holloway, 2012). Moreover, opioids have been implicated in mediating 'wanting' through their activity in the amygdala. The central nucleus of the amygdala is involved in the translation of learning into motivation. Mahler et al. (2009) demonstrated that opioid stimulation of the central nucleus of the amygdala in rats magnified and focused learned incentive salience onto a specific reward cue (CS). This motivation enhancement made the CS more attractive, resulting in more appetitive and consummatory behaviours. The authors concluded that opioid neurotransmission in the central nucleus of the amygdala is involved in the process of making one reward cue more "wanted" than others. Unfortunately, to date no studies on the role of opioids in human sexual conditioning have been conducted (for an overview on the role of opioids in learned sexual behaviour in animal see Holloway, 2012).

Seen the importance of the opioid system in mediating sexual reward, future research is needed.

As the aversion conditioning studies that attempted to alter certain sexual behaviours have demonstrated, there has been some empirical evidence that learning possibly can play a role in the shaping of partner preferences via conditioning. But since no robust or long lasting changes in sexual orientation in humans have been reported, the general assumption to date is that the orientation-preference is, at least in part, determined by sexual imprinting (Woodson, 2002; Swaab, 2008). In animal models, there are documented effects of conditioning on sexual arousal, approach behaviour, sexual performance and strength of sexual preference toward opposite-sex targets, but also no robust and long-lasting demonstrations of learning in the organization of same-sex preferences among males could be found (Nash & Domjan, 1991; Pfaus et al., 2001). Although some studies with rats have shown that as a result of repeated cohabitation under the effects of a D2-type receptor agonist, rewarding associations with same-sex individuals can facilitate socio-sexual partner preference in male rats (Coria-Avila, 2012; Cibrian-Llanderal et al., 2012; Triana-Del Rio et al., 2011), this result could also be interpreted as not solely a homosexual preference, but rather as a same sex social preference over receptive females. Moreover, the observed preference could also be a preference for a familiar social partner over a novel unfamiliar one, rather than a preference for male rats over receptive females.

In comparison to the substantial amount of research on anxiety and aversive conditioning in animals and humans, and despite its relevance for extinction-based treatments, little attention has been devoted to the phenomenon of renewal in appetitive conditioning. In treatments using cue exposure, for example in addiction disorders or anxiety disorders, people are exposed to conditioned stimuli while preventing their learned response, to extinguish cue-activated responses. However, many people relapse after being

'cured'. An important question is how to explain the return of responses following extinction procedures. Although CS-alone presentations may extinguish conditioned responses, the extinction procedure does not erase the originally learned association. It seems that this original association is retained (Bouton & Moody, 2004). This retention of the original association has been shown by renewal. This suggests that extinction is especially dependent on context. To the best of our knowledge human studies on extinction and renewal in the sexual domain are completely lacking. Translating the renewal phenomenon to the sexual domain, as noted before, a patient who is craving for internet-sex may be successfully extinguished by cue exposure therapy in a specific context, but may experience strong craving upon changing context such as sitting behind a different computer. Therefore, because of their clinical relevance, future studies on renewal of conditioned sexual responses should be given attention. As conditioning of subjective sexual arousal and genital arousal in humans can occur without awareness of the CS-US contingency, another prominent research question for future research within this field would be which brain systems are involved in conscious and unconscious sexual reward learning and in the regulation of sexual emotion. The investigation of brain responses during conscious and unconscious sexual learning will lead to new basic knowledge, and will underscore the importance of implicit processes. The level of detail that has been achieved in humans pales in comparison to the animal studies on neural circuits involved in conditioned learning. The amygdala contributes to both appetitive and aversive states. Studies in primates have shown that appetitive and aversive signals are processed by distinct neuronal populations of cells in the lateral/basal amygdale (LeDoux, 2012). LeDoux's (1996, 2012) work on the role of the amygdala is of great influence on thinking about unconscious activation of emotions. LeDoux discovered parallel transmission to the amygdala from the thalamus and the cortex (1996, 2000). The thalamo-amygdala projections appear to be involved in the

processing of the affective significance of relatively simple sensory features and this is the fast, direct route. The thalamo-corticoamygdala projections are necessary when more complex aspects of stimuli are processed. As LeDoux has shown, relative simple sensory processing by subcortical areas can provide the requisite inputs to structures such as the amygdale, bypassing or short-circuiting cortical areas (LeDoux, 1996). For example, humans can recognize certain emotions by the eyes alone and do not need to process the face as a whole (Whalen et al., 2004). Research has shown that this processing occurs subcortically (see LeDoux, 2012). Although there is an ongoing debate in visual attention research about what information is exactly transmitted from the thalamus to the amygdala (i.e. likely no geometric information due to the receptive-field properties of the superior colliculus, but more likely only gross luminance changes; Redgrave et al., 2008), it is possible that this same principle accounts for the processing of sexual stimuli too. In a world flooded with sexual stimuli, subconscious processes, as Oei et al. (2012) have shown, might play a role in compulsive reward-seeking behaviours such as hypersexuality. Cognitive behavioural therapy more and more incorporates treatments that target implicit processes. For example, attentional bias training in abstinent alcoholic patients (Schoenmakers et al., 2010), cognitive bias modification in depression (Holmes et al., 2009), and retraining automatic action tendencies in hazardous alcohol drinkers (Wiers et al., 2010) have been shown to be promising treatment possibilities. These interventions can also be promising for the treatment of sexual arousal disorders. In the case of hypersexuality, retraining automatic action tendencies with an approach/avoidance-task or attentional bias training could be fruitful interventions, whereas in the case of decreased sexual arousal not only retraining automatic action tendencies, but also cognitive bias modification using mental imagery can be a possible form of clinical intervention.

There are many topics that need future investigation in the study of sexual associative learning and the brain. The described list of possible future research directions is only meant to point out some of the obvious examples that need further attention. Taken together, the suggested future research may strongly influence ideas about disordered sexual motivation, and will hopefully contribute to the development of treatments for hypoactive and hyperactive sexual desire.

**References**


Abel, G.G., & Blanchard, E.E. (1974). The role of fantasy in the treatment of sexual deviation. *Archives of General Psychiatry, 30*, 467–475.

Abel, G.G., Levis, D., & Clancy, J. (1970). Aversion therapy applied to taped sequences of deviant behavior in exhibitionism and other sexual deviations: a preliminary report. *Journal of Behavior Therapy and Experimental Psychiatry, 1*, 58–66.

Adinoff, B. (2004). Neurobiologic processes in drug reward and addiction. *Harvard Review of Psychiatry, 12*, 305–320.

Ågmo, A. (1999). Sexual motivation – an inquiry into events determining the occurrence of sexual behaviour. *Behavioural Brain Research, 105*, 129–150.

Ågmo, A. (2002). Copulation-contingent aversive conditioning and sexual incentive motivation in male rats: evidence for a two-stage process of sexual behavior. *Physiology & Behavior, 77*, 425–435.

Ågmo, A., & Berenfeld, R. (1990). Reinforcing properties of ejaculation in the male rat: role of opioids and dopamine. *Behavioral Neuroscience, 104*, 177–182.

Ågmo, A., Turi, A.L., Ellingsen, E., & Kaspersen, H. (2004). Preclinical models of sexual desire: conceptual and behavioral analyses. *Pharmacology Biochemistry and Behavior, 78*, 379–404.

Akins, C.K. (1998). Conditioned excitation and modulation of sexual conditioning in male Japanese quail. *Animal Learning & Behavior, 26*, 416–426.

Akins, C.K. (2004). The role of Pavlovian conditioning in sexual behavior: a comparative analysis of human and nonhuman animals. *International Journal of Comparative Psychology,* 17, 241–262.

Akins, C.K., Domjan, M., & Gutiérrez, G. (1994). Topography of sexually conditioned behavior in male Japanese quail (Coturnix japonica) depends on the CS-US interval. *Journal of Experimental Psychology: Animal Behavior Process*es, *20*, 199–209.

Alford, G.S., Morin, C., Atkins, M., & Schoen, L. (1987). Masturbatory extinction of deviant sexual arousal. *Journal of Behavior Therapy and Experimental Psychiatry, 1*, 59–66.

Aston-Jones, G., Smith, R.J., Sartor, G.C., Moorman, D.E., Massi, L., Tahsili-Fahadan, P., & Richardson, K.A. (2010). Lateral hypothalamic orexin/hypocretin neurons: a role in reward- seeking and addiction. *Brain Research, 1314C*, 74.

Arana, F.S., Parkinson, J.A., Hinton, E., Holland, A.J., Owen, A.M., & Roberts, A.C., (2003). Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. *Journal of Neuroscience, 23*, 9632–9638.

Arzate, D.M., Portillo, W., Rodríguez, C., Corona, R., Paredes, R.G. (2011). Extended paced mating tests induces conditioned place preference without affecting sexual arousal. *Hormones and Behavior, 59*, 674–680.

Aubert, Y., Gustison, M.L., Gardner, L.A., Bohl, M.A., Lange, J.R., Allers, K.A., Sommer, B., Datson, N.A., Abbott, D.H. (2012). Flibanserin and 8-OH-DPAT implicate serotonin in association between female marmoset monkey sexual behavior and changes in pair-bond quality. *Journal of Sexual Medicine, 9*, 694–707.

Bancroft, J. (1969). Aversion therapy of homosexuality. *British Journal of Psychiatry*, *115*, 1417–1431.

Bancroft, J. (1970). A comparative study of aversion and desensitisation in the treatment of homosexuality. In: Burns, L.E., Worsley, J.E. (Eds.), Behaviour Therapy in the 1970's. Wright, Bristol.

Bancroft, J. (1999). Central inhibition of sexual response in the male: a theoretical perspective. *Neuroscience & Biobehavioral Reviews, 23*, 763–784.
Bancroft, J. (2009). Human Sexuality and Its Problems, 3rd ed. Elsevier Health Sciences, Churchill Livingstone.
Bancroft, J., Graham, C.A., Janssen, E., & Sanders, S.A. (2009). The dual control model: current status and future directions. *Journal of Sex Research, 46*, 121–142.
Bancroft, J., & Janssen, E. (2000). The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunctions. *Neuroscience & Biobehavioral Reviews, 24*, 571–579.
Barfield, R.J., & Sachs, B.D. (1968). Sexual behavior: stimulation by painful electrical shock to skin in male rats. *Science*, *161*, 392–395.
Baumeister, R.F. (2000). Gender differences in erotic plasticity: the female sex drive as socially flexible and responsive. *Psychological Bulletin*, *126*, 347–374.
Beech, H.R., Watts, F., & Poole, A.D. (1971). Classical conditioning of a sexual deviation: a preliminary note. *Behavior Therapy, 2*, 400–402.
Becker, J.B., Rudick, C.N., & Jenkins, W.J. (2001). The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. *Journal of Neuroscience, 21*, 3236–3241.
Berke, J.D., & Hymann, S.D. (2000). Addiction, dopamine, and the molecular mechanisms of memory. *Neuron, 25*, 515–532.
Berridge, K.C. (1996). Food reward: brain substrates of wanting and liking. *Neuroscience & Biobehavioral Reviews, 20*, 1–25.
Berridge, K.C. (2004). Motivation concepts in behavioral neuroscience. *Physiology & Behavior, 81*, 179–209.
Berridge, K.C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191, 391–431.
Berridge, K.C., & Robinson, T.E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews, 28*, 309–369.
Berridge, K.C., & Winkielman, P. (2003). What is an unconscious emotion? The case for unconscious 'liking'. *Cognition and Emotion, 17*, 181–211.
Bindra, D. (1968). Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behaviour. *Psychological Review*, *75*, 1–22.
Bindra, D. (1974). A motivational view of learning, performance, and behavior modification. *Psychological Review, 81*, 199–213.
Blair, H.T., Sotres-Bayon, F., Moita, M.A.P., & LeDoux, J.E. (2005). The lateral amygdala processes the value of conditioned and unconditioned aversive stimuli. *Neuroscience, 133*, 561–569.
Blitch, J., & Haynes, S. (1972). Multiple behavioral techniques in a case of female homosexuality. *Journal of Behavior Therapy and Experimental Psychiatry, 3*, 319–322.
Borgland, S.L., Storm, E., & Bonci, A. (2008). Orexin B/hypocretin 2 increases glutamatergic transmission to ventral tegmental area neurons. *European Journal of Neuroscience, 28*, 1545–1556.
Both, S., Brauer, M., & Laan, E. (2011a). Classical conditioning of sexual response in women: a replication study. *Journal of Sexual Medicine, 8*, 3116–3131.

Both, S., Everaerd, W., & Laan, E. (2007). Desire emerges from excitement: a psychophysiological perspective on sexual motivation. In: Janssen, E. (Ed.), The Psychophysiology of Sex. Indiana University Press, Bloomington, pp. 327–339.
Both, S., Everaerd, W., Laan, E., & Gooren, L. (2005). Effect of a single dose of levodopa on sexual response in men and women. *Neuropsychopharmacology*, *30*, 173–183.
Both, S., Laan, E., Everaerd, W. (2011b). Focusing "hot" or focusing "cool": attentional mechanisms in sexual arousal in men and women. *Journal of Sexual Medicine, 8*, 167–179.
Both, S., Laan, E., Spiering, M., Nilsson, T., Oomens, S., & Everaerd, W. (2008a). Appetitive and aversive classical conditioning of female sexual response. *Journal of Sexual Medicine, 5*, 1386–1401.
Both, S., Spiering, M., Laan, E., Belcome, S., van den Heuvel, B., & Everaerd, W. (2008b). Unconscious classical conditioning of sexual arousal: evidence for the conditioning of female genital arousal to subliminally presented sexual stimuli. *Journal of Sexual Medicine, 5*, 100–109.
Bouton, M.E. (2004). Context and behavioral processes in extinction. *Learning & Memory*, *11*, 485–494.
Bouton, M.E. (2006). Learning and Behavior: A Contemporary Synthesis. Sinauer Associates, Inc., Sunderland, MA.
Bouton, M.E., & Moody, E.W. (2004). Memory processes in classical conditioning. *Neuroscience & Biobehavioral Reviews, 28*, 663–674.
Bradford, J.M.W. (2001). The neurobiology, neuropharmacology, and pharmacological treatment of the paraphilias and compulsive sexual behaviour. *Canadian Journal of Psychiatry, 46*, 26–34.
Brauer, M., ter Kuile, M.M., Janssen, S.A., & Laan, E. (2007). The effect of pain-related fear on sexual arousal in women with superficial dyspareunia. *European Journal of Pain, 11*, 788–798.
Brotto, L.A. (2010). The DSM diagnostic criteria for hypoactive sexual desire disorder in women. *Archives of Sexual Behaviour, 39*, 221–239.
Brownell, K.D., Hayes, S.C., & Barlow, D.H. (1977). Patterns of appropriate and deviant sexual arousal: the behavioral treatment of multiple sexual deviations. *Journal of Consulting and Clinical Psychology, 45*, 1144–1155.
Burns, M., & Domjan, M. (1996). Sign tracking versus goal tracking in the sexual conditioning of male Japanese quail (Coturnix japonica). *Journal of Experimental Psychology: Animal Behavior Processes, 22*, 297–306.
Caggiula, A.R., & Eibergen, R. (1969). Copulation of virgin male rats evoked by painful peripheral stimulation. *Journal of Comparative & Physiological Psychology, 69*, 414–419.
Caldú, X., & Dreher, J.C. (2007). Hormonal and genetic influences on processing reward and social information. *Annals of the New York Academy of Sciences*, *1118*, 43–73.
Caldwell, J.D., & Moe, B.D. (1999). Conjugated estradiol increases female sexual receptivity in response to oxytocin infused into the medial preoptic area and medial basal hypothalamus. *Hormones and Behavior, 35*, 38–46.
Chen, B.T., Hopf, F.W., & Bonci, A. (2010). Synaptic plasticity in the mesolimbic system: herapeutic implications for substance abuse. *Annals of the New York Academy of Sciences, 1187*, 129–139.

Chen, M., & Bargh, J.A. (1999). Nonconscious approach and avoidance behavioral consequences of the automatic evaluation effect. *Personality and Social Psychology Bulletin*, *25*, 215–224.
Chivers, M.L., Rieger, G., Latty, E., & Bailey, J.M. (2004). A sex difference in specificity of sexual arousal. *Psychological Science*, *15*, 736–744.
Cibrian-Llanderal, T., Rosas-Aguilar, V., Triana-Del Rio, R., Perez, C.A., Manzo, J., Garcia, L.I., & Coria-Avila, G.A. (2012). Enhanced D2-type receptor activity facilitates the development of conditioned same-sex partner preference in male rats. *Pharmacology, Biochemistry and Behavior*, *102*, 177–183.
Conrad, S., & Wincze, J. (1976). Orgasmic reconditioning: a controlled study of its effects upon the sexual arousal and behavior of adult male homosexuals. *Behavior Therapy, 7*, 155–166.
Coria-Avila, G.A. (2012). The role of conditioning on heterosexual and homosexual partner preferences in rats. *Socioaffective Neuroscience & Psychology*, *2*, 17340.
Coria-Avila, G.A., Jones, S.L., Solomon, C.E., Gavrila, A.M., Jordan, G.J., & Pfaus, J.G. (2006). Conditioned partner preference in female rats for strain of male. *Physiology & Behavior, 88*, 529–537.
Coria-Avila, G.A., Gavrila, A.M., Boulard, B., Charron, N., Stanley, G., & Pfaus, J.G. (2008a). Neurochemical basis of conditioned partner preference in the female rat: II. Disruption by flupenthixol. *Behavioral Neuroscience, 122*, 396–406.
Coria-Avila, G.A., Ouimet, A.J., Pacheco, P., Manzo, J., & Pfaus, J.G. (2005). Olfactory conditioned partner preference in the female rat. *Behavioral Neuroscience*, *119*, 716–725.
Coria-Avila, G.A., Solomon, C.E., Vargas, E.B., Lemme, I., Ryan, R., Menard, S., Gavrila, A.M., & Pfaus, J.G. (2008b). Neurochemical basis of conditioned partner preference in the female rat: I. Disruption by naloxone. *Behavioral Neuroscience, 122*, 385–395.
Crowley, W.R., Popolow, H.B., & Ward Jr., O.B. (1973). From dud to stud: copulatory behavior elicited through conditioned arousal in sexually inactive male rats. *Physiology & Behavior, 10*, 391–394.
Damasio, A., & Carvalho, G.B. (2013). The nature of feelings: evolutionary and neurobiological origins. *Nature Reviews Neuroscience*, *14*, 143–152.
Damsma, G., Pfaus, J.G., Wenkstern, D., Phillips, A.G., & Fibiger, H.C. (1992). Sexual behaviour increases dopamine transmission in the Nucleus Accumbens and Striatum of male rats: comparison with novelty and locomotion. *Behavioral Neuroscience, 106*, 181–191.
Davey, G.C.L. (1995). The merits of an experimentally testable model of phobias. *Behavioral and Brain Sciences*, *20*, 363–364.
Dawson, S.J., Suschinsky, K.D., & Lalumière, M.L. (2013). Habituation of sexual responses in men and women: a test of the preparation hypothesis of women's genital responses. *Journal of Sexual Medicine, 10*, 990–1000.
Day, J.J., & Carelli, R.M. (2007). Nucleus accumbens and Pavlovian reward learning. *Neuroscientist, 13*, 148–159.
Dekker, J., & Everaerd, W. (1989). Psychological determinants of sexual arousal: a review. *Behaviour Research and Therapy, 27*, 353–364.
Delamater, A.R. (2004). Experimental extinction in Pavlovian conditioning: behavioural and neuroscience perspectives. *Quarterly Journal of Experimental Psychology: Comparative and Physiological Psychology, 57*, 97–132.

Dewing, P., Chiang, C.W.K., Sinchak, K., Sim, H., Fernagut, P.O., Kelly, S., Chesselet, M.F., Micevych, P.E., Albrech, K.H., Harley, V.R., & Vilain, E. (2006). Direct regulation of adult brain function by the male-specific factor SRY. *Current Biology, 16*, 415–420.
Diano, S., Naftolin, F., & Horvath, T. (1997). Gonadal steroids target AMPA glutamate receptor containing Neurons in the rat hypothalamus, septum and amygdala: a morphological and biochemical study. *Endocrinology, 138*, 778–789.
Di Chiara, G. (1995). The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug and Alcohol Dependenc,e 38*, 95–137.
Di Chiara, G. (1998). A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *Journal of Psychopharmacology 12*, 54–67.
Di Chiara, G. (1999). Drug addiction as dopamine-dependent associative learning disorder. *European Journal of Pharmacology 375*, 13–30.
Di Chiara, G., & North, R.A. (1992). Neurobiology of opiate abuse. *Trends in Pharmacological Sciences 13*, 185–193.
Dominguez, J.M., & Hull, E.M. (2001). Stimulation of the medial amygdala enhances medial preoptic dopamine release: implications for male rat sexual behavior. *Brain Research 917*, 225–229.
Dominguez, J.M., & Hull, E.M. (2005). Dopamine, the medial preoptic area, and male sexual behavior. *Physiological Behavior 86*, 356–368.
Dominguez, J., Riolo, J.V., Xu, Z., & Hull, E.M. (2001). Regulation by the medial amygdala of copulation and medial preoptic dopamine release. *Journal of Neuroscience 21*, 349–355.
Domjan, M., Blesbois, E., & Williams, J. (1998). The adaptive significance of sexual conditioning: Pavlovian control of sperm release. *Psychological Science 9*, 411–415.
Domjan, M., & Hollis, K.L. (1988). Reproductive behavior: a potential model system for adaptive specializations in learning. In: Bolles, R.C., Beecher, M.D. (Eds.), Evolution and Learning, Hillsdale, NJ.
Domjan, M., Lyons, R., North, N.C., & Bruell, J. (1986). Sexual Pavlovian conditioned approach behavior in male Japanese quail (Coturnix coturnix japonica). *Journal of Comparative Psych*ology *100*, 413–421.
Domjan, M., O'Vary, D., & Greene, P. (1988). Conditioning of appetitive and consummatory sexual behavior in male Japanese quail. *Journal of the Experimental Analysis of Behavior, 50*, 505–519.
Esch, T., & Stefano, G.G. (2004). The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters, 25*, 235– 251.
Erskine, M.S. (1989). Solicitation behavior in the estrous female rat: a review. *Hormones and Behavior 23*, 473–502.
Everaerd, W., Laan, E., & Spiering, M. (2000). Male sexuality. In: Szuchman, L., Muscarella, F. (Eds.), Psychological Perspectives on Human Sexuality. Wiley, New York, pp. 60–100.
Everitt, B.J. (1990). Sexual motivation: a neural and behavioural analysis of the mechanisms underlying appetitive and copulatory responses of male rats. *Neuroscience & Biobehavioral Reviews 14*, 217–232.
Everitt, B.J., & Robbins, T.W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience 8*, 1481–1489.

Farris, H.E. (1967). Classical conditioning of courting behavior in the Japanese quail, coturnix coturnix japonica. *Journal of the Experimental Analysis of Behavior 10*, 213–217.
Feldman, M.P. (1966). Aversion therapy for sexual deviations: a critical review. *Psychological Bulleti*n *65*, 65–67.
Fields, H.L., Hjelmstad, G.O., Margolis, E.B., & Nicola, S.M. (2007). Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. *Annual Review of Neuroscience 30*, 289–316.
Fiorillo, C.D. (2013). Two dimensions of value: dopamine neurons represent reward but not aversiveness. *Science 341*, 546–549.
Fonteille, V., & Stoleru, S. (2010). The cerebral correlates of sexual desire: functional neuroimaging approach. *Sexologies 20*, 142–148.
Freeman, W., & Meyer, R.G. (1975). A behavioral alteration of sexual preferences in the human male. *Behavior Therapy 6*, 206–212.
Garavan, H., Pankiewicz, J., Bloom, A., Cho, J., Sperry, L., Ross, T., Salmeron, B., Risinger, R., Kelley, D., & Stein, E. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *American Journal of Psychiatry 157*, 1789–1798.
Geer, J.H., Lapour, K.J., & Jackson, S.R. (1993). *The information processing approach to human sexuality*. In: Birbaumer, N., Ohman, A. (Eds.), The structure of Emotion: Psychophysiological, Cognitive, and Clinical Aspects. Hogrefe-Huber, Toronto, pp. 139–155.
Georgiadis, J.R., Farrell, M.J., Boessen, R., Denton, D.A., Gavrilescu, M., Kortekaas, R., Renken, R.J., Hoogduin, J.M., & Egan, G.F. (2009). Dynamic subcortical blood flow during male sexual activity with ecological validity: a perfusion fMRI study. *Neuroimage 50*, 208–216.
Giuliano, F., & Allard, J. (2001). Dopamine and sexual function. *International Journal of Impotence Research 13*, 18–28.
Gold, S., & Neufeld, I. (1965). A learning theory approach to the treatment of homosexuality. *Behaviour Research and Therapy 2*, 201–204.
Gray, J.A. (1982). The Neurophysiology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System. Oxford University Press, Oxford.
Gutiérrez, G., & Domjan, M. (1997). Differences in the sexual conditioned behavior of male and female Japanese quail (Coturnix japonica). *Journal of Comparative Psychology 111*, 135–142.
Hamann, S., Herman, R.A., Nolan, C.L., & Wallen, K. (2004). Men and women differ in amygdala response to visual sexual stimuli. *Nature Neuroscience 7*, 411–416.
Harris, G.C., Aston-Jones, G. (2006). Arousal and reward: a dichotomy in orexin function. *Trends in neuroscience* 29, 571–577.
Harris, G.C., Wimmer, M., Aston-Jones, G. (2005). A role for lateral hypothalamic orexin neurons in reward seeking. *Nature 437*, 556–559.
Herman, S.H., Barlow, D.H., & Agras, W.S. (1974a). An experimental analysis of classical conditioning as a method of increasing heterosexual arousal in homosexuals. *Behavior Therapy 5*, 33–47.
Herman, S.H., Barlow, D.H., & Agras, W.S. (1974b). An experimental analysis of exposure to explicit heterosexual stimuli as an effective variable in changing arousal patterns of homosexuals. *Behaviour Research and Therapy 12*, 335–345.

Hermans, E.J., Bos, P.A., Ossewaarde, L., Ramsey, N.F., Fernández, G., & van Honk, J. (2010). Effects of exogenous testosterone on the ventral striatal BOLD responseduring reward anticipation in healthy women. *Neuroimage 52*, 277–283.
Hilliard, S., Domjan, M., Nguyen, M., & Cusato, B. (1998). Dissociation of conditioned appetitive and consummatory sexual behavior: satiation and extinction tests. *Animal Learning & Behavior 26*, 20–33.
Hoffmann, H. (2007). The role of classical conditioning in sexual arousal. In: Janssen, E. (Ed.), The Psychophysiology of Sex. Indiana University Press, Bloomington, IN.
Hoffmann, H., Janssen, E., & Turner, S.L. (2004). Classical conditioning of sexual arousal in women and men: effects of varying awareness and biological relevance of the conditioned stimulus. *Archives of Sexual Behavior 33*, 43–53.
Hoffmann, H., Peterson, K., & Garner, H. (2012). Field conditioning of sexual arousal in humans. *Socioaffective Neuroscience and Psychology 2*, 17336.
Hollis, K.L. (1997). Contemporary research on Pavlovian conditioning: a 'new' functional analysis. *American Psychologist 52*, 956–965.
Hollis, K.L., Cadieux, E.L., & Colbert, M.M. (1989). The biological function of Pavlovian conditioning: a mechanism for mating success in the blue gourami. *Journal of Comparative Psychology 103*, 115–121.
Hollis, K.L., Pharr, V.L., Dumas, M.J., Britton, G.B., & Field, J. (1997). Classical conditioning provides paternity advantage for territorial male blue gouramis (Trichogaster trichopterus). *Journal of comparative psychology 111*, 219–225.
Holloway, K.S. (2012). Opioid mediation of learned sexual behaviour. *Socioaffective Neuroscience & Psychology 2*, 14874.
Holloway, K.S., & Domjan, M. (1993). Sexual Approach conditioning: unconditioned stimulus factors. *Journal of Experimental Psychology: Animal Behavior Processes 19*, 38–46.
Holmes, E.A., Lang, T.J., & Shah, D.M. (2009). Developing interpretation bias modification as a 'cognitive vaccine' for depressed mood – imagining positive events makes you feel better than thinking about them verbally. *Journal of Abnormal Psychology 118*, 76–88.
Holstege, G., Georgiadis, J.R., Paans, A.M.J., Meiners, L.C., Van der Graaf, F.H.C.E., & Reinders, A.A.A.T.S. (2003). Brain activation during human male ejaculation. *Journal of Neuroscience 23*, 9185–9193.
Hull, E.M., 2011. Sex, drugs and gluttony: how the brain controls motivated behaviors. *Physiology & Behavior* 104, 173–177.
Hull, E.M., Lorrain, D.S., Du, J., Matuszewich, L., Lumley, L.A., Putnam, S.K., Moses, J. (1999). Hormone-neurotransmitter interactions in the control of sexual behavior. *Behavioural Brain Research 105*, 105–116.
Hull, E.M., Du, J., Lorrain, D.S., & Matuszewich, L. (1995). Extracellular dopamine in the medial preoptic area: implications for sexual motivation and hormonal control of copulation. *Journal of Neuroscience 15*, 7465–7471.
Hull, E.M., Du, J., Lorrain, D.S., & Matuszewich, L. (1997). Testosterone, preoptic dopamine, and copulation in male rats. *Brain Research Bulletin 44*, 327– 333.
Hull, E.M., Muschkamp, J.W., & Sato, S., (2004). Dopamine and serotonin: influences on male sexual behaviour. *Physiology & Behavior, 83*, 291–307.
Hyman, S.E., Malenka, R.C., & Nestler, E.J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Review of Neuroscience 29*, 565–598.

Ismail, N., Gelez, H., Lachapelle, I., & Pfaus, J.G. (2009a). Pacing conditions contribute to the conditioned ejaculatory preference for a familiar female in the male rat. *Physiology & Behavior 96*, 201–208.
Ismail, N., Girard-Bériault, F., Nakanishi, S., & Pfaus, J.G. (2009b). Naloxone, but not flupenthixol, disrupts the development of conditioned ejaculatory preference in the male rat. *Behavioral Neuroscience 123*, 992–999.
Jackson, B. (1969). A case of voyeurism treated by counter conditioning. *Behaviour Research and Therapy 7*, 133–134.
Janssen, E., & Bancroft, J. (2007). *The dual control model: the role of sexual inhibition & excitation in sexual arousal and behavior*. In: Janssen, E. (Ed.), The Psychophysiology of Sex Bloomington. Indiana University Press.
Janssen, E., Everaerd, W., Spiering, M., & Janssen, J. (2000). Automatic processes and the appraisal of sexual stimuli: toward an information processing model of sexual arousal. *Journal of Sex Research 37*, 8–23.
Janssen, E., Prause, N., & Geer, J. (2006). The sexual response system. In: Cacioppo, J.T., Tassinary, L.G., Berntson, G.G. (Eds.), Handbook of Psychophysiology, 3rd ed. Cambridge University Press, New York.
Johnston, R.E., Zahorik, D.M., Immler, K., Zakon, H. (1978). Alterations of male sexual behavior by learned aversions to hamster vaginal secretion. *Journal of Comparative and Physiological Psychology 92*, 85–93.
Jöhren, O., Brüggemann, N., Dendorfer, A., & Dominiak, P. (2003). Gonadal steroids differentially regulate the messenger ribonucleic acid expression of pituitary orexin type 1 receptors and adrenal orexin type 2 receptors. *Endocrinology 144*, 1219–1225.
Josiassen, R., Fantuzzo, J., & Rosen, A. (1980). Treatment of pedophilia using multistage aversion therapy and social skills training. *Journal of Behavior Therapy and Experimental Psychiatry 11*, 55–61.
Justice, A.J., & de Wit, H. (1999). Acute effects of d-amphetamine during the follicular and luteal phases of the menstrual cycle in women. *Psychopharmacology 145*, 67–75.
Kafka, M.P., & Hennen, J. (2003). Hypersexual desire in males: are males with paraphilias different from males with paraphilia-related disorders? *Sexual Abuse 15*, 307–321.
Kalivas, P.W., & Nakamura, M. (1999). Neural systems for behavioral activation and reward. *Current Opinion in Neurobiology 9*, 223–227.
Kalivas, P.W., & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Research Reviews 16*, 223–244.
Kalivas, P.W., & Volkow, N.D. (2005). The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry 162*, 1403–1413.
Kantorowitz, D.A. (1978). An experimental investigation of preorgasmic reconditioning and postorgasmic deconditioning. *Journal of Applied Behavioral Analysis 11*, 23–24.
Karama, S., Lecours, A.R., Leroux, J.M., Bourgouin, P., Beaudoin, G., Joubert, S., & Beauregard, M. (2002). Areas of brain activation in males and females during viewing of erotic film excerpts. *Human Brain Mapping 16*, 1–13.
Keller, D.J., & Goldstein, A. (1978). Orgasmic reconditioning reconsidered. *Behavior Research & Therapy 16*, 299–300.
Kelz, M.B., Chen, J., Carlezon Jr., W.A., Whisler, K., Gilden, L., Beckmann, A.M., Cathy Steffen, C., Zhang, Y.-J., Marotti, L., Self, D.W., Tkatch, T., Baranauskas, G.,

Surmeier, D.J., Neve, R.L., Duman, R.S., Picciotto, M.R., & Nestler, E.J. (1999). Expression of the transcription factor Δ FosB in the brain controls sensitivity to cocaine. *Nature* 401, 272–276.
Kennedy, S. (2010). Flibanserin: initial evidence of efficacy on sexual dysfunction, in patients with major depressive disorder. *Journal of Sexual Medi*cine 7, 3449–3459.
Kippin, T.E., Cain, S.W., & Pfaus, J.G. (2003). Estrous odors and sexually conditioned neutral odors activate separate neural pathways in the male rat. *Neuroscience* 117, 971–979.
Kippin, T.E., & Pfaus, J.G. (2001a). The nature of the conditioned response mediating olfactory conditioned ejaculatory preference in the male rat. *Behavioural Brain Research* 122, 11–24.
Kippin, T.E., & Pfaus, J.G. (2001b). The development of olfactory conditioned ejaculatory preferences in the male rat. I. Nature of the unconditioned stimulus. *Physiology & Behavior* 73, 457–469.
Kippin, T.E., Samaha, A., Sotiropoulos, V., & Pfaus, J.G. (2001). The development of olfactory conditioned ejaculatory preferences in the male rat. II. Parametric manipulation of training session number and duration. *Physiology & Behavior 73*, 471–485.
Kippin, T.E., Sotiropoulos, V., Badih, J., & Pfaus, J.G. (2004). Opposing roles of the nucleus accumbens and anterior lateral hypothalamic area in the control of sexual behaviour in the male rat. *European Journal of Neuroscience 19*, 698–704.
Kippin, T.E., Talianakis, S., Schattman, L., Bartholomew, S., & Pfaus, J.G. (1998). Olfactory conditioning of sexual behavior in the male rat. *Journal of Comparative Psychology* 112, 389–399.
Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., & Walter, B. (2003). Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study. *Neuroimage 20*, 1086–1095.
Kleitz-Nelson, H.K., Dominguez, J.M., & Ball, G.F. (2010a). Dopamine release in the medial preoptic area is related to hormonal action and sexual motivation. *Behavioral Neuroscience* 124, 773–779.
Kleitz-Nelson, H.K., Dominguez, J.M., Cornil, C.A., & Ball, G.F. (2010b). Is sexual motivational state linked to dopamine release in the medial preoptic area? *Behavioral Neuroscience* 124, 300–304.
Klucken, T., Schweckendiek, J., Christian, J., Merz, C.J., Tabbert, K., Walter, B., Kagerer S., Vaitl, D., & Stark, R. (2009). Neural activations of the acquisition of conditioned sexual arousal: effects of contingency awareness and sex. *Journal of Sexual Medicine* 6, 3071–3085.
Koch, P.C., & Peters, R.H. (1987). Suppression of adult copulatory behaviors following LiCl-induced aversive contingencies in juvenile male rats. *Developmental Psychobiology* 20, 603–611.
Komisaruk, B.R., & Whipple, B. (2005). Functional MRI of the brain during orgasm in women. *Annual Review of Sex Research* 16, 62–86.
Komisaruk, B.R., Whipple, B., Crawford, A., Grimes, S., Liu, W.-C., Kalnin, A., & Mosier, K. (2004). Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. *Brain Research 1024*, 77–88.

Koob, G.F. (2000). Neurobiology of addiction, toward the development of new therapies. *Annals of the New York Academy of Sciences* 909, 170–185.
Koob, G.F., & Bloom, F.E. (1988). Cellular and molecular mechanisms of drug dependence. *Science* 242, 715–723.
Koukounas, E., & Over, R. (1993). Habituation and dishabituation of male sexual arousal. *Behaviour Research and Therapy* 31, 575–585.
Koukounas, E., & Over, R. (2001). Habituation of male sexual arousal: effects of attentional focus. *Biological Psychology* 58, 49–64.
Krafft-Ebing, R.V. (1929). Psychopathia Sexualis. Physicians and Surgeons Book Co., New York.
Krause, M.A., Cusato, B., & Domjan, M. (2003). Extinction of conditioned sexual responses in male Japanese quail (Coturnix japonica): role of species typical cues. *Journal of Comparative Psychology* 117, 76–86.
Krueger, R.B., & Kaplan, M.S. (2001). The paraphilic and hypersexual disorders: an Overview. *Journal of Psychiatric Practice* 7, 391–440.
Laan, E., & Everaerd, W. (1995a). Determinants of female sexual arousal: psychophysiological theory and data. *Annual Review of Sex Research* 6, 32–76.
Laan, E., & Everaerd, W. (1995b). Habituation of female sexual arousal to slides and films. *Archives of Sexual Behaviour* 24, 517–541.
Laan, E., Everaerd, W., & Evers, A. (1995a). Assessment of female sexual arousal: response specificity and construct validity. *Psychophysiology* 32, 476–485.
Laan, E., Everaerd, W., van der Velde, J., Geer, J.H., 1995b. Determinants of subjective experience of sexual arousal in women: feedback from genital arousal and erotic stimulus content. *Psychophysiology* 32, 444–451.
Laan, E., Janssen, E., 2007. How do men and women feel? Determinants of subjective experience of sexual arousal. In: Janssen, E. (Ed.), The Psychophysiology of Sex. Indiana University Press, Bloomington, pp. 278–290.
Lalumière, M.L., Quinsey, V.L., 1998. Pavlovian conditioning of sexual interests in human males. *Archives of Sexual Behavior* 27, 241–252.
Lande, S.D., 1980. A combination of orgasmic reconditioning and covert sensitization in the treatment of a fire fetish. *Journal of Behavior Therapy and Experimental Psychiatry* 11, 291–296.
Langevin, R., Martin, M., 1975. Can erotic responses be classically conditioned? *Behavioral Therapy* 6, 350–355.
Laws, D.R., Marshall, W.L., 1990. A conditioning theory of the etiology and maintenance of deviant sexual preferences and behaviour. In: Marshall, W.L., Barbaree, H.E., Laws, D.R. (Eds.), Handbook of Sexual Assault: Issues, Theories and Treatment of the Offender. Plenum Press, New York, pp. 209–230.
Laws, D.R., Meyer, J., Holmen, M.L., 1978. Reduction of sadistic arousal by olfactory aversion: a case study. *Behavior Research and Therapy* 16, 281–285.
LeDoux, J.E., 1996. The Emotional Brain. Simon & Schuster, New York.
LeDoux, J.E., 2000. Emotion circuits in the brain. *Annual Review of Neuroscience* 23, 155–184.
LeDoux, J.E., 2012. Rethinking the emotional brain. *Neuron* 73, 653–676.
Letourneau, E., O'Donohue, W., 1997. The classical conditioning of female sexual arousal. *Archives of Sexual Behavior* 26, 63–78.

Lombardo, M.V., Ashwin, E., Auyeung, B., Chakrabarti, B., Lai, M.-C., Taylor, K., Hackett, G., Bullmore, E.T., Baron-Cohen, S., 2012. Fetal programming effects of testosterone on the reward system and behavioral approach tendencies in humans. *Biological Psychiatry* 72, 839–847.
López, H.H., Ettenberg, A., 2002. Sexually conditioned incentives: attenuation of motivational impact during dopamine receptor antagonism. *Pharmacology, Biochemistry and Behavior* 72, 65–72.
Lovibond, S.H., 1963. Conceptual thinking, personality and conditioning. *British Journal of Social and Clinical Psychology* 2, 100–111.
Lovibond, P.F., Shanks, D.R., 2002. The role of awareness in Pavlovian conditioning: empirical evidence and theoretical implications. *Journal of Experimental Psychology: Animal Behavior Processes* 28, 3–26.
Lovibond, P.F., Siddle, D.A., Bond, N.W., 1993. Resistance to extinction of fear-relevant stimuli: preparedness or selective sensitization? *Journal of Experimental Psychology: General* 122, 449–461.
Lykins, A., Meana, M., Kambe, G., 2006. Detection of differential viewing patterns to erotic and non-erotic stimuli using eye-tracking methodology. *Archives of Sexual Behavior* 35, 569–575.
MacCulloch, M.J., Feldman, M.P., 1967a. Aversion therapy in management of 43 homosexuals. *British Medical Journal* 2, 594–597.
MacCulloch, M.J., Feldman, M.P., 1967b. Personality and the treatment of homosexuality. *Acta Psychiatrica Scandinavica* 43, 300–317.
MacCulloch, M.J., Birtles, C.J., Feldman, M.P. (1971). Anticipatory avoidance learning in the treatment of homosexuality: recent developments and an automatic aversion therapy system. *Behavior Therapy* 2, 151–169.
Mahler, S.V., Kent, C., Berridge, K.C. (2009). Which cue to "Want?" Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue. *Journal of Neuroscience* 29, 6500–6513.
Marquis, J.N., 1970. Orgasmic reconditioning: changing sexual object choice through controlling masturbation fantasies. *Journal of Behavior Therapy and Experimental Psychiatry* 1, 263–271.
Martin-Soelch, C., Linthicum, J., Ernst, M., 2007. Appetitive conditioning: neural bases and implications for psychopathology. *Neuroscience & Biobehavioral Reviews* 31, 426–440.
Masataka, N., 1993. Effects of experience with live insects on the development of fear of snakes in squirrel monkeys (Saimiri sciureus). *Animal Behaviour* 46, 741–746.
Mazur, J.E., 2002. Learning and Behavior, 5th ed. Prentice Hall, Upper Saddle River, NJ.
McClure, S.M., York, M.K., Montague, P.R., 2004. The neural substrates of reward processing in humans: the modern role of FMRI. *Neuroscientist* 10, 260–268.
McConaghy, N., 1967. Penile volume change to moving pictures of male and female nudes in heterosexual and homosexual males. *Behaviour Research and Therapy* 5, 43–48.
McConaghy, N., 1970. Penile response conditioning and its relationship to aversion therapy in homosexuals. *Behavior Therapy* 1, 213–221.
McConaghy, N., 1975. Aversive and positive conditioning treatments of homosexuality. *Behavior Research and Therapy* 13, 309–319.
McConaghy, N., Barr, R., 1973. Classical avoidance and backward conditioning treatments of homosexuality. *British Journal of Psychiatry* 122, 151–162.

McDonnell, S.M., Kenney, R.M., Meckley, P.E., Garcia, M.C., 1985. Conditioned suppression of sexual behavior in stallions and reversal with diazepam. *Physiology & Behavior* 34, 951–956.
McGuire, R.J., Carlisle, J.M., Young, B.G., 1965. Sexual deviations as conditioned behaviour: a hypothesis. *Behavioral Research & Therapy* 2, 185–190.
Meerts, S.H., Clark, A.S., 2009. Artificial vaginocervical stimulation induces a conditioned place preference in female rats. *Hormones and Behavior* 55, 128–132.
Mermelstein, P.G., Becker, J.B., 1995. Increased extracellular dopamine in the nucleus accumbens and striatum of the female rat during paced copulatory behavior. *Behavioral Neuroscience* 109, 354–365.
Meston, C.M., Frohlich, P.F., 2000. The neurobiology of sexual function. *Archives of General Psychiatry* 57, 1012–1030.
Metzger, C.D., van der Werf, Y.D., Walter, M., 2013. Functional mapping of thalamic nuclei and their integration into cortico-striatal-thalamo-cortical loops via ultra-high resolution imaging – from animal anatomy to in vivo imaging in humans. *Frontiers in Neuroscience* 7 (Article 24).
Meuwissen, I., Over, R., 1990. Habituation and dishabituation of female sexual arousal. *Behavioral Research and Therapy* 28, 217–226.
Montague, P.R., Hyman, S.E., Cohen, J.D., 2004. Computational roles for dopamine in behavioural control. *Nature* 431, 760–767.
Munro, C.A., McCaul, M.E., Wong, D.F., Oswald, L.M., Zhou, Y., Brasic, J., Kuwabara, H., Kumar, A., Alexander, M., Ye, W., 2006. Sex differences in striatal dopamine release in healthy adults. *Biological Psychiatry* 59, 966–974.
Muschkamp, J.W., Dominguez, J.M., Sato, S.M., Shen, R.-Y., Hull1, E.M., 2007. A role for hypocretin (orexin) in male sexual behaviour. *Journal of Neuroscience* 27, 2837–2845.
Nash, S., Domjan, M., 1991. Learning to discriminate the sex of conspecifics in male Japanese quail (Coturnix coturnix japonica): tests of 'biological constraints'. *Journal of Experimental Psychology* 17, 342–353.
Nestler, E.J., 2001. Molecular basis of long-term plasticity underlying addiction. *Nature Reviews Neuroscience* 2, 119–128.
O'Donohue, W.T., Geer, J.H., 1985. The habituation of sexual arousal. *Archives of Sexual Behavior* 14, 233–246.
O'Donohue, W.T., Plaud, J.J., 1991. The long-term habituation of sexual arousal in the human male. *Journal of Behavior Therapy and Experimental Psychiatry* 22, 87–96.
O'Donohue, W.T., Plaud, J.J., 1994. The conditioning of human sexual arousal. *Archives of Sexual Behavior* 23, 321–344.
Oei, N., Rombouts, S., Soeter, R., Gerven, J., Both, S., 2012. Dopamine modulates reward system activity during subconscious processing of sexual stimuli. *Neuropsychopharmacology* 37, 1729–1737.
Öhman, A., 1986. Face the beast and fear the face: animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology* 23, 123– 145.
Öhman, A., Mineka, S., 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review* 108, 483–522.
Öhman, A., Soares, J.J.F., 1993. On the automatic nature of phobic fear: conditioned electrodermal responses to masked fear-relevant stimuli. *Journal of Abnormal Psychology* 102, 121–132.

Öhman, A., Soares, J.J.F., 1994. "Unconscious anxiety": phobic responses to masked stimuli. *Journal of Abnormal Psychology* 103, 231–240.
Öhman, A., Soares, J.J.F., 1998. Emotional conditioning to masked stimuli: expectancies for aversive outcomes following nonrecognized fear-irrelevant stimuli. *Journal of Experimental Psychology: General* 127, 69–82.
Oldenburger, W.P., Everitt, B.J., de Jonge, F.H., 1992. Conditioned place preference induced by sexual interaction in female rats. *Hormones & Behavior* 26, 214–228.
Olds, J., Milner, P., 1954. Positive reinforcement produced by electrical stimulation of the septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology* 47, 419–427.
Orsini, J.C., 1985. Direct effects of androgens on lateral hypothalamic neuronal activity in the male rat: II. A pressure ejection study. *Brain Research Bulletin* 15, 547–552.
Parada, M., Abdul-Ahad, F., Censi, S., Sparks, L., Pfaus, J.G., 2011. Context alters the ability of clitoral stimulation to induce a sexually-conditioned partner preference in the rat. *Hormones & Behavior* 59, 520–527.
Parada, M., Chamas, L., Censi, S., Coria-Avila, G., Pfaus, J.G., 2010. Clitoral stimulation induces conditioned place preference and Fos activation in the rat. *Hormones & Behavior* 57, 112–118.
Parada, M., Jafari, N., Pfaus, J.G., 2013. Sexual experience blocks the ability of clitoral stimulation to induce a conditioned place preference in the rat. *Physiology & Behavior* 119, 97–102.
Parada, M. A., Puig de Parada, M., Hoebel, B.G., 1995. Rats self-inject a dopamine antagonist in the lateral hypothalamus where it acts to increase extracellular dopamine in the nucleus accumbens. *Pharmacology Biochemistry & Behavior* 52, 17987.
Paredes, R.G., 2009. Evaluating the neurobiology of sexual reward. ILAR Journal 50, 15–27.
Paredes, R.G., Alonso, A., 1997. Sexual behavior regulated (paced) by the female induces conditioned place preference. *Behavioral Neuroscience* 111, 123–128.
Paredes, R.G., Vasquez, B., 1999. What do female rats like about sex? Paced mating. *Behavioural Brain Research* 105, 117–127.
Park, K., Seo, J.J., Kang, H.K., Ryu, S.B., Kim, H.J., Jeong, G.W., 2001. A new potential of blood oxygenation level dependent (BOLD) functional MRI for evaluating cerebral centers of penile erection. *International Journal of Impotence Research* 13, 73–81.
Pavlov, I., 1927. Conditioned Reflexes. Oxford Univ. Press, Oxford, UK.
Peters, R.H., 1983. Learned aversions to copulatory behaviors in male rats. *Behavioral Neuroscience* 97, 140–145.
Pfaus, J.G., 1999a. Neurobiology of sexual behavior. *Current Opinion in Neurobiology* 9, 751–758.
Pfaus, J.G., 1999b. Revisiting the concept of sexual motivation. *Annual Review of Sex Research* 10, 120–157.
Pfaus, J.G., 2009. Pathways of sexual desire. *Journal of Sexual Medicine* 6, 1506–1533.
Pfaus, J.G., Erickson, K.A., Talianakis, S., 2013. Somatosensory conditioning of sexual arousal and copulatory behavior in the male rat: a model of fetish development. *Physiology & Behavior* 122, 1–7.
Pfaus, J.G., Gorzalka, B.B., 1987. Opioids and sexual behavior. *Neuroscience & Biobehavioral Reviews* 11, 1–34.

Pfaus, J.G., Kippin, T.E., Centeno, S., 2001. Conditioning and sexual behavior: a review. *Hormones and Behavior* 40, 291–321.
Pfaus, J.G., Mendelson, S.D., Phillips, A.G., 1990. A correlational and factor analysis of anticipatory and consummatory measures of sexual behavior in the male rat. *Psychoneuroendocrinology* 15, 329–340.
Pfaus, J.G., Phillips, A.G., 1991. Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. *Behavioral Neuroscience* 105, 727–743.
Pierce, R.C., Kumaresan, V., 2006. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience & Biobehavioral Reviews* 30, 216–238.
Plaud, J.J., Martini, R., 1999. The respondent conditioning of male sexual arousal. *Behavior Modification* 23, 254–268.
Ponseti, J., Bosinski, H.A., Wolff, S., Peller, M., Jansen, O., Mehdorn, H.M., Büchel, C., Siebner, H.R., 2006. A functional endophenotype for sexual orientation in humans. *Neuroimage* 33, 825–833.
Putnam, S.K., Sato, S., Hull, E.M., 2003. Effects of testosterone metabolites on copulation and medial preoptic dopamine release in castrated male rats. *Hormones and Behavior* 44, 419–426.
Quinn, J.T., Harbison, J.J.M., McAllister, H., 1970. An attempt to shape human penile responses. *Behaviour Research and Therapy* 8, 213–216.
Rachman, S., 1966. Sexual fetishism: an experimental analogue. *Psychological Record* 16, 293–296.
Rachman, S., Hodgson, R.J., 1968. Experimentally-induced "sexual fetishism": replication and development. *Psychological Research* 18, 25–27.
Redgrave, P., Gurney, K., Reynolds, J., 2008. What is reinforced by phasic dopamine signals? *Brain Research Reviews* 58, 322–339.
Rescorla, R.A., 2001. Retraining of extinguished Pavlovian stimuli. *Journal of Experimental Psychology: Animal Behavior Processes* 27, 115–124.
Rescorla, R.A., Furrow, D.R., 1977. Stimulus similarity as a determinant of Pavlovian conditioning. *Journal of Experimental Psychology: Animal Behavior Processes* 3, 203–215.
Riccardi, P., Park, S., Anderson, S., Doop, M., Ansari, M.S., Schmidt, D., Baldwin, R., 2011. Sex differences in the relationship of regional dopamine release to affect and cognitive function in striatal and extrastriatal regions using PET and [18F]Fallypride. *Synapse* 65, 99–102.
Riccardi, P., Zald, D., Li, R., Park, S., Ansari, M.S., Dawant, B., Anderson, S., Woodward, N., Schmidt, D., Baldwin, R., Kessler, R., 2006. Sex differences in amphetamineinduced displacement of [$^{18}$F] fallypride in striatal and Extrastriatal regions: a PET study. *American Journal of Psychiatry* 163, 1639–1641.
Richard, J.M., Castro, D.C., DiFeliceantonio, A.G., Robinson, M.J.F., Berridge, K.C., 2014. Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. *Neuroscience & Biobehavioral Reviews* (in press).
Robbins, T.W., Everitt, B.J., 1996. Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology* 6, 228–236.
Robinson, T.E., Berridge, K.C., 2003. Addiction. *Annual Review of Psychology* 54, 25–53.
Rosen, R.C., 1973. Suppression of penile tumescence by instrumental conditioning. *Psychosomatic Medicine* 35, 509–514.

Rosen, R.C., Kopel, S.A., 1977. Penile plethysmography and biofeedback in the treatment of a transvestite-exhibitionist. *Journal of Consulting and Clinical Psychology* 45, 908–916.
Rosen, R.C., Shapiro, D., Schwartz, G.E., 1975. Voluntary control of penile tumescence. *Psychosomatic Medicine* 37, 479–483.
Rupp, H.A., Wallen, K., 2008. Sex differences in response to visual sexual stimuli: a review. *Archives of Sexual Behavior* 37, 206–218.
Sachs, B.D., Garinello, L.D., 1978. Interaction between penile reflexes and copulation in male rats. *Journal of Comparative Physiological Psychology* 92, 759–767.
Schaefer, H.H., Colgan, A.H., 1977. The effect of pornography on penile tumescence as a function of reinforcement and novelty. *Behavior Therapy* 8, 938–946.
Schoenmakers, T.M., de Bruin, M., Lux, I.F., Goertz, A.G., van Kerkhof, D.H., Wiers, R.W., 2010. Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug and Alcohol Dependence* 109, 30–36.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. *Journal of Neurophysiology* 80, 1–27.
Schultz, W., 2000. Multiple reward signals in the brain. Nature Reviews Neuroscience 1, 199–207.
Schultz, W., 2002. Getting formal with dopamine and reward. *Neuron* 36, 241–263.
Schultz, W., 2006. Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology* 57, 87–115.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. *Science* 275, 1593–1599.
Schultz, W., Tremblay, L., Hollerman, J.R., 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cerebral Cortex* 10, 272–283.
Seligman, M.E.P., 1970. On the generality of the laws of learning. *Psychological Review* 77, 406–418.
Seligman, M.E.P., 1971. Phobias and preparedness. *Behavior Therapy* 2, 307–321.
Seligman, M.E.P., Hager, J.L., 1972. Biological boundaries of learning. The saucebearnaise syndrome. *Psychology Today* 6, 59–61, 84–87.
Singer, B., Toates, F.M., 1987. Sexual motivation. *Journal of Sex Research* 23, 481–501.
Skinner, B.F., 1937. Two types of conditioned reflex: a reply to Konorski and Miller. *Journal of General Psychology* 16, 272–279.
Smith, D., Over, R., 1987. Does fantasy-induced sexual arousal habituate? *Behavioral Research and Therapy* 25, 477–485.
Snowdon, C.T., Tannenbaum, P.L., Schultz-Darken, N.J., Ziegler, T.E., Ferris, C.F., 2011. Conditioned sexual arousal in a nonhuman primate. *Hormones and Behavior* 59, 696–701.
Solyom, L., Miller, S., 1965. A differential conditioning procedure as the initial phase of the behavior therapy of homosexuality. *Behavior Research and Therapy* 3, 147–160.
Stóleru, S., Grégoire, M.C., Gérard, D., Decety, J., Lafarge, E., Cinotti, L., Lavenne, F., Le Bars, D., Vernet-Maury, E., Rada, H., Collet, C., Mazoyer, B., Forest, M.G., Magnin, F., Spira, A., Comar, D., 1999. Neuroanatomical correlates of visually evoked sexual arousal in human males. *Archives of Sexual Behavior* 28, 1–21.
Swaab, D.F., 2008. Sexual orientation and its basis in brain structure and function. *Proceedings of the National Academy of Sciences* 105, 10273–10274.

Tanaka, S.C., Doya, K., Okada, G., Ueda, K., Okamoto, Y., Yamawaki, S., 2004. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nature Neuroscience* 7, 887–893.
Tenk, C.M., Wilson, H., Zhang, Q., Pitchers, K.K., Coolen, L.M., 2009. Sexual reward in male rats: effects of sexual experience on conditioned place preferences associated with ejaculation and intromissions. *Hormones and Behavior* 55, 93–97.
Thompson, T.L., Moss, R.L., 1994. Estrogen regulation of dopamine release in the nucleus accumbens: genomic- and nongenomic-mediated effects. *Journal of Neurochemistry* 62, 1750–1756.
Thompson, R.F., Spencer, W.A., 1966. Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psycholocical Review* 73, 16–43.
Thorndike, E.L., 1911. Animal Intelligence. Macmillan, New York.
Thorp, J., Simon, J., Dattani, D., Taylor, L., Kimura, T., Garcia Jr., M., Lesko, L., Pyke, R., 2012. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. *Journal of Sexual Medicine* 9, 793–804.
Toates, F., 1998. The interaction of cognitive and stimulus-response processes in the control of behavior. *Neuroscience & Biobehavioral Reviews* 22, 59–83.
Toates, F., 2009. An integrative theoretical framework for understanding sexual motivation, arousal, and behavior. *Journal of Sex Research* 46, 168–193.
Triana-Del Rio, R., Montero-Domínguez, F., Cibrian-Llanderal, T., Tecamachaltzi-Silvaran, M.B., Garcia, L.I., Manzo, J., Hernandez, M.E., Coria-Avila, G.A., 2011. Same-sex cohabitation under the effects of quinpirole induces a conditioned socio-sexual partner preference in males, but not in female rats. *Pharmacology Biochemistry & Behavior* 99, 604–613.
Turkkan, J.S., 1989. Classical conditioning: a new hegemony. *Behavioral and Brain Sciences* 12, 121–137.
Van Furth, W.R., van Emst, M.G., van Ree, J.M., 1995. Opioids and sexual behavior of male rats: involvement of the medial preoptic area. *Behavioral Neuroscience* 109, 123–134.
Van Ree, J.M., Niesink, R.J.M., Van Wolfswinkel, L., Ramsey, N.F., Kornet, M.L.M.W., Van Furth, W.R., Vanderschuren, L.J.M.J., Gerrits, M.A.F.M., Van den Berg, C.L., 2000. Endogenous opioids and reward. *European Journal of Pharmacology* 405, 89–101.
VanDeventer, A., Laws, D., 1978. Orgasmic reconditioning to redirect sexual arousal in pedophiles. *Behavior Therapy* 9, 748–765.
Vansteenwegen, D., Francken, G., Vervliet, B., De Clercq, A., Eelen, P., 2006. Resistance to extinction in evaluative conditioning. *Journal of Experimental Psychology: Animal Behavior Processes* 32, 71–79.
Villarreal, R., Domjan, M., 1998. Pavlovian conditioning of social-affiliative behavior in the Mongolian gerbil (Meriones unguiculatus). *Journal of Comparative Psychology* 112, 26–35.
Volkow, N.D., Fowler, J.S., Wang, G.-J., Goldstein, R.Z., 2002. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning and Memory* 78, 610–624.
Walter, M., Bermpohl, F., Mouras, H., Schiltz, K., Tempelmann, C., Rotte, M., Heinze, H.J., Bogerts, B., Northoffa, G., 2008. Distinguishing specific sexual and general emotional effects in fMRI – subcortical and cortical arousal during erotic picture viewing. *NeuroImage* 40, 1482–1494.

West, C.H.K., Clancy, A.N., Michael, R.P., 1992. Enhanced response of nucleus accumbens neurons in male rats to novel odors associated with sexually receptive females. *Brain Research* 585, 49–55.
Whalen, P.J., Kagan, J., Cook, R.G., Davis, F.C., Kim, H., Polis, S., McLaren, D.G., Somerville, L.H., McLean, A.A., Maxwell, J.S., Johnstone, T., 2004. Human amygdala responsivity to masked fearful eye whites. *Science* 306, 2061.
Wiers, R.W., Eberl, C., Rinck, M., Becker, E.S., Lindenmeyer, J., 2011. Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. *Psychological Science* 22, 490–497.
Wiers, R.W., Rinck, M., Kordts, R., Houben, K., Strack, F., 2010. Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction* 105, 279–287.
Wightman, R.M., Robinson, D.L., 2002. Transient changes in mesolimbic dopamine and their association with 'reward'. *Journal of Neurochemistry* 82, 721–735.
Wise, R.A., 2002. Brain reward circuitry: insights from unsensed incentives. *Neuron* 36, 229–240.
Wise, R.A., Morales, M., 2010. A ventral tegmental CRF-glutamate-dopamine interaction in addiction. *Brain Research* 1314, 1338.
Wong, P.S., Bernat, E., Snodgrass, M., Shevrin, H., 2004. Event-related brain correlates of associative learning without awareness. *International Journal of Psychophysiology* 53, 217–231.
Wood, R.I., 2008. Anabolic–androgenic steroid dependence? Insights from animals and humans. *Frontiers in Neuroendocrinology* 29, 490–506.
Wood, R.I., Swann, J.M., 1999. Neuronal integration of chemosensory and hormonal signals that control male sexual behavior. In: Wallen, K., Schneider, J.S. (Eds.), Reproduction in Context. MIT Press, Cambridge, pp. 423–444.
Woodson, J.C., 2002. Including "Learned Sexuality" in the organization of sexual behavior. *Neuroscience & Biobehavioral Reviews* 26, 69–80.
Zamble, E., Hadad, G.M., Mitchell, J.B., Cutmore, T.R., 1985. Pavlovian conditioning of sexual arousal: first- and second-order effects. *Journal of Experimental Psychology: Animal Behavior Processes* 11, 598–610.
Zamble, E., Mitchell, J.B., Findlay, H., 1986. Pavlovian conditioning of sexual arousal: parametric and background manipulations. *Journal of Experimental Psychology: Animal Behavior Processes* 12, 403–411.
Zhang, M., Kelley, A.E., 1997. Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. *Psychopharmacology* 132, 350– 360.
Zhang, M., Kelley, A.E., 2000. Enhanced intake of high-fat food following striatal muopioid stimulation: microinjection mapping and fos expression. *Neuroscience* 99, 267–277.