The role of incentive learning and cognitive regulation in sexual arousal

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Chapter 11

General Conclusion & Discussion

11. General Conclusion & Discussion

The central question of this thesis is whether and to what extent human sexual arousal response is susceptible to lower-level control processes like basic associative learning processes (i.e. classical conditioning) and related phenomena (e.g. extinction and renewal), and whether higher-level control processes such as cognitive emotion-regulation can also influence sexual incentive learning in healthy participants. In addition, we were interested in the effects of acute-stress on the cognitive regulation of sexual arousal. In this final chapter the empirical findings of this thesis will be summarized, integrated and critically discussed, starting with a detailed summary of the role of basic learning principles in (animal and) human sexual arousal and behaviour. Hereafter, challenges and clinical implications will be discussed, concluding with future research direction.

11.1. Lower-level Control Mechanisms in Sexual Arousal

11.1.1. The Role of Basic Learning in Sexual Behaviour

Due to the fact that historically, theories of emotion have not given much consideration to sex there is only limited empirical research on human sexual incentive learning, especially in women (Toates, 2014). Nevertheless, the treatment demands for disorders in sexual motivation, such as female sexual interest/arousal disorder, or hypersexuality and paraphilia-related disorders call for research investigating the possible mechanisms underlying sexual arousal response and sexual motivation (Kafka, 2007; Mercer et al., 2003; Ter Kuile, Both & van Lankveld, 2010; West et al., 2008). In chapter two a thorough review is given of animal and human studies that examined the role of classical

conditioning, learning, and DA in sexual behaviour, which were published or in press before October 2013. In this chapter animal and human sexual learning is tied into a more general framework of incentive motivational theory (Bindra, 1974; Pfaus, Kippin & Centeno, 2001; Singer & Toates, 1987). Also the studies on sexual learning in animals were included in this review because a role for learning in the sexual behaviour of animals also has profound implications for our understanding of human sexual arousal and the development of disorders in sexual motivation. The animal research described in this review chapter shows robust and direct effects of sexual conditioning processes on sexual behaviour, such as partner- and place preferences. Moreover, in a wide range of taxa, positive as well as negative experiences can modify sexual responses in animals. Intriguingly, although arbitrary (i.e. auditory, visual or olfactory) CSs are effective in eliciting sexual CRs in male and female animals, a greater CS-US similarity appears to elicit CRs that seem to be highly resistant to extinction, especially in male animals (Domjan et al., 1988; Krause et al. 2003; Rescorla & Furrow, 1977). Second, animal studies have shown that increased DA concentrations in the NAc are essential for the acquisition of reward learning, including sexual reward learning (López & Ettenberg, 2002; Pfaus et al., 1990; Robinson & Berridge, 2003). Animal studies showed that a state of sexual reward (i.e. ejaculation in male rats, or paced mating or vaginocervical/clitoral stimulation in female rats) is a powerful mediator of incentive formation and enhancement, which depends on DA functioning (e.g. Kippin et al., 2003; Mermelstein & Becker, 1995; Paredes & Alonso, 1997; Parada et al., 2011, 2013; West et al., 1992). Although research on human sexual incentive learning has lagged substantially behind that of animal sexual functioning, there is evidence that in humans, classical conditioning can also augment or diminish subjective and genital sexual arousal in men and women. The earlier sexual conditioning studies -mainly in men- within this field are plagued by methodological confounds, however recent well-controlled experimental

research shows that human sexual arousal can be conditioned (Both et al., 2008a,b, 2011; Hoffmann, Janssen & Turner, 2004; Klucken et al., 2009). Nevertheless, it should be mentioned that also a considerable number of these more recent studies comprise only small study samples, or sample sizes too small to make sound group and gender comparisons (e.g. Hoffmann, Janssen & Turner, 2004; Hoffmann et al., 2012; Lalumière & Quinsey, 1998; Plaud & Martini, 1999). Taking this in consideration, results suggest there is some prudent evidence that in men, US-CS similarity is an important factor in sexual incentive learning (Hoffmann, Janssen & Turner, 2004), and these results are suggestive of a 'prepared' or 'already learned' link between sexual stimuli and genital responses as has been proposed by some models of sexual arousal (e.g., Janssen et al., 2000). Additionally, it is suggested that conditioned sexual evaluative learning effects seem highly resistant to extinction (Both et al., 2008a,b, 2011). Unfortunately, although it is assumed that the involvement of limbic reward circuitry is also crucial for human sexual incentive learning (Berke & Hymann, 2000; Di Chiara, 1999), no studies have investigated the role of DA in human sexual learning, and only little imaging studies on human sexual conditioning have been reported (Klucken et al., 2009, and see also Klucken et al., 2014). Nevertheless, in those studies conditioned activation was seen in reward structures (e.g. NAc). From the above, it can be concluded that sexual behaviour in animals and human sexual arousal can be classical conditioned. This sexual incentive formation and enhancement is mediated by DA functioning in animals.

11.1.2. The Role of DA in Human Sexual Reward Learning

Although the dopaminergic reward system has been implicated to be involved in the acquisition and expression of learned appetitive behaviours, and abnormality in this system has been shown to play an important role in the

aetiology and pathophysiology of various disorders, including substance use disorders and (behavioural) addictions (Dominguez & Hull, 2005; Fields et al., 2007; Schultz, 2007; Richard et al., 2012; De Jong et al., 2015; Dunlop & Nemeroff, 2007; Root et al., 2015), the role of phasic DA signalling in sexual incentive learning in humans remains largely unknown, while facilitation as well as impairment thereof is relevant in the context of treatment of sexual motivation disorders. In chapter three, making use of a double-blind, parallel-conditions, placebo controlled design, it was investigated whether DA antagonism would attenuate classical conditioning of sexual response in women. Results from this study demonstrated that DA receptor antagonism reduced sexual stimulation-induced genital sexual arousal, emphasizing the importance of DA availability in unconditional responding to sexual stimulation. This is in accordance with previous work that showed that DA systems are involved in human sexual reward signalling (Both et al., 2005; Georgiadis & Kringelbach, 2012; Oei et al., 2012). However, quite intriguing but contrary to the expectations, is the finding that DA down-regulation did not seem to affect subsequent (slight conditioned genital response and) conditioned subjective sexual arousal. But it should be mentioned that only very weak conditioned genital responding was seen in both conditions. Nevertheless, the administration of haloperidol did not seem to affect the perceived pleasantness or sexual arousability of the US, or the magnitude of conditioned subjective sexual arousal. The lack of a difference in genital conditioned responding between the Placebo and Haloperidol condition makes future replication studies warranted. Second, since the study sample exclusively comprised women, the role of DA in mediating associative sexual learning in men is still to be determined. Research has shown that 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 gonadal hormones. Therefore it is conceivable that

gender differences in sexual conditionability and underlying neuromodulatory systems do exist. However as has become clear, more research is needed to be conclusive about this.

11.1.3. Sexual Evaluative Learning Effects

As has become clear in chapter three, in animals there is evidence that conditioned responses to sexually relevant CSs seem to be resistant to extinction (Domjan et al., 1988; Krause et al. 2003; Rescorla & Furrow, 1977). In addition, results from the sexual conditioning studies by Both and colleagues (Both et al., 2008a,b, 2011) showed that conditioned subjective affect did not extinguish significantly during an extinction procedure, suggesting resistance to extinction of sexual learning effects, also in humans. These results are in line with research on evaluative conditioning: although extinction procedures do eliminate the expressions of US expectancy, extinction procedures do not change the expressed valence of a CS, and as a result, exposure treatment is often unsuccessful in reducing acquired subjective (dis-) likes (Baeyens, et al., 1992; de Houwer, et al., 2001). To investigate a possible resistance to extinction of sexual learning effects in men and women, two studies were conducted in which extensive extinction trials were used. In chapter four the experimental study on extinction of appetitively conditioned responses is reported, and likewise in chapter five a parallel study on extinction of aversively conditioned sexual responses is presented.

In chapter four, evidence is found for the claim that appetitively conditioned sexual evaluative learning effects are rather difficult to modify through the procedure of extinction, although no evidence was found for the claim that these effects are indeed resistant to extinction. In this study, genital vibrostimulation served as US and neutral pictures as CSs. Although the

extinction procedure eventually reduced conditioned subjective affect and sexual arousal towards the CS+, these evaluative learning effects were relatively persistent, as evidenced by conditioned responses even after extensive extinction trials. Moreover, after extinction, behavioural approach was investigated with a joystick Approach-Avoidance Task (AAT), a task that mimics actual approach and avoidance (Cousijn, Goudriaan & Wiers, 2011). The results from this task demonstrated that the pairing of the CS+ with the sexual vibrotactile stimulus did still result in slight approach tendencies towards this CS+ in men and women, suggesting the CS+ retained sexual affective value to elicit approach even after a very extensive extinction phase. However, it is important to keep in mind that this effect only approached a conventional level of statistical significance. Contrary to the expectations, no conditioned genital responses was observed in men and women, but this was thought not to hamper any conclusions about the persistence of sexual evaluative learning effects.

In the parallel aversive sexual conditioning study that is reported in chapter five, a different pattern was seen. This study provided evidence that an extinction procedure is well capable of modifying aversively conditioned sexual evaluative learning effects, at least in healthy men and women. Making use of a painful stimulus as US and erotic pictures as CSs, attenuated genital blood flow was seen on the first extinction trials in women in response to the erotic picture that was previously paired with the painful electric stimulus. However, no such conditioned genital response in men was observed. Likewise, only women rated the CS+ as slightly less sexually arousing compared to the erotic picture that was never followed by painful stimulation, while men did not demonstrate attenuated subjective sexual response in response to the CS+ during the first trials of the extinction phase. Crucially, subjective affective value was modulated by repeated association of the erotic stimulus with pain. Men and

women rated the erotic picture that was paired with pain stimulation as more negative than the erotic picture that was not paired with pain. However, the difference in affective evaluation of the CS+ and the CS decreased over time during the extinction phase, suggesting that aversively conditioned responses are not resistant to extinction. Furthermore, no conditioned behavioural avoidance tendencies were seen towards the CS+ after the extinction phase. These findings are quite intriguing, especially considering that exact the same procedure was used as in chapter four, with the USs and CSs as the only differences. The results suggest that appetitive and aversive sexual extinction learning encompass distinct processes and are not organized in the same fashion. We will return to this issue shortly.

To conclude, the presented results raise doubt about the claim that, unlike other forms of classical conditioning, evaluative sexual conditioning is resistant to extinction. Analyses in both -appetitive and aversive- sexual conditioning studies showed that unpaired presentations after the CS-US trials reduce the magnitude of conditioned responses, including the magnitude of sexual evaluative learning effects. Hence, sexual evaluative learning is sensitive to extinction. Nevertheless, results suggests that extinction of sexual evaluative learning effects may occur at a slower rate than in other forms of associative learning (i.e. signal learning) (Hofmann, de Houwer, Perugini et al., 2010), especially in an appetitive conditioning paradigm. Possible clinical implications hereof will be discussed later on.

11.1.4. Context Specificity of Sexual Extinction Learning

Although the evidence regarding renewal in human learning has accumulated in recent years, studies on renewal of sexual conditioned responses were lacking in the literature, despite the possible important implications for exposure-based

treatment strategies for learned maladaptive sexual responses. In chapter six an experiment is reported on extinction and renewal of appetitively conditioned sexual responses in sexually functional men and women. In this study an ABA renewal paradigm was used, and different contexts were obtained by manipulating the lighting conditions in the experimental room. It was predicted that participants in both conditions (AAA and ABA) would show conditioned sexual responding after acquisition trials, which was expected to gradually decrease. As an index of renewal, it was predicted that upon a context change after extinction, only the ABA condition would show recovery of conditioned responding on the test trials as compared to the last extinction trial. Results from this study are in favour of Bouton's theory of context dependency of extinction and renewal of conditioned responding (Bouton, 2004). Changing context after an extinction procedure resulted in a significant increase of subjective affect and subjective sexual arousal in women and increased US expectancy ratings to CS+ as compared to CS- in both men and women (ABA condition), whereas no such recovery was observed in the absence of a context change (AAA condition). However, no evidence for renewal was found for genital measures in both sexes. For men, this could be explained by the fact that genital conditioning effects were not obtained, and in women extinction of conditioned genital responding was not completely ascertained during the extinction phase, making it harder to detect renewal of conditioned responding. After the experimental conditioning procedure, men and women differed in implicit approach tendencies towards the stimulus that was paired with vibrostimulation, with women significantly faster approaching the CS+ than men. In women the CS+ elicited a more robust sexual arousal response as compared to men. This means that in women, the conditioned sexual response translated into subjective experience, physiological measures and eventually also in action tendencies. Results from this study make clear that sexual arousal or the expectation of sexual reward can come under stimulus control by

contextual cues associated with states of sexual reward. With other words, these results emphasize the importance of sensitivity to context (changes) in sexual learning.

Evidently, it is impossible to cover all sorts of situations or stimuli in therapy (i.e. extinction) sessions, meaning there will always be a certain risk for patients to relapse when confronted with a particular object, situation or mental state. Indeed, it is suggested that context specificity of extinction impairs its ability to generalize extinction to the context in which the problematic behaviour is experienced. Therefore a highly promising perspective is to focus on processes that modulate contextual processing during extinction procedures, since any pharmacological agent that that can render extinction context independent may provide an innovative method to reduce cue-induced relapse in the treatment of problematic reward-seeking behaviours. In chapter seven the effect of a single dose of (the NR1 NMDA receptor subunit agonist) D-cycloserine (DCS) on the reduction of context specificity of extinction of sexual reward-associated cues in humans was investigated. The design consisted of sexual conditioning in context A and extinction in context B. It was hypothesized that administration of DCS after an extinction procedure would enhance extinction of conditioned sexual responses, reflected by a loss of conditioned genital and subjective sexual responding elicited by reward-conditioned cues in participants receiving DCS, even outside the extinction context, compared to participants in the placebo condition on a recall test 24h later. In this study it is demonstrated that DCS indeed affects extinction's fundamental context specificity in women, at least in an (ABAB) appetitive sexual conditioning paradigm, since DCS enhanced extinction of conditioned responses also in the original acquisition context. These results are highly interesting, especially when there is no a priori reason to believe that a drug that enhances extinction learning will change the nature of extinction learning

qualitatively (Todd et al., 2014). However, since no imaging results were obtained during the sexual conditioning and subsequent extinction procedures, we can only speculate about possible underlying neural mechanisms (Torregrossa et al., 2013).

To conclude, results from chapter six indicate that an extinction procedure does not erase conditioned sexual associations in humans but instead involves new learning that is context dependent. Results from chapter seven suggest that in healthy sexually functional women, DCS makes sexual extinction memories context-independent and prevents the return of conditioned sexual response. NMDA receptor glycine site agonists may be potential pharmacotherapies to enhance sexual extinction memory, herewith reducing the motivational impact of sexual reward-associated cues, and to prevent relapse in sexual motivation disorders with a learned component.

11.2. Higher-level Control Mechanisms in Sexual Arousal

Obviously, humans are not simply driven by external sexual cues and incentives. We have the ability to process stimuli and situations in a deliberate, controlled and often conscious way. Our cognitive abilities allow us to determine stimulus meaning and predispose action (Frijda, 1986; LeDoux, 2012). Janssen and Bancroft (2007) have suggested that the response following exposure to a sexual stimulus depends on automatic bottom-up appraisal and response-generation processes as well as on effortful top-down regulatory processes. Meaning, our cognitive ability allows us to influence and alter emotions by using thoughts. In this way, cognition can be tuned in the service of generating more adaptive emotional reactions. Hitherto, most insights in cognitive emotion regulation come from research on maladaptive responses and behaviours as seen in drug addictions, anxiety disorders or depression, and

research on the regulation of positive (i.e. pleasant-valenced) emotions such as sexual arousal is extremely scarce in the literature (Carl et al., 2013; Beauregard, 2007). Moreover, literature on sex differences in the regulation of positive emotions was lacking in the literature. Research on the regulation of particularly negative emotions (Gross, 2007; Mak et al., 2009; McRae et al., 2008) indicated that women tend to use more emotion-focused strategies, while men are thought to use more efficient cognitive (rational) strategies (Whittle et al., 2011). Despite the hypothesized importance of understanding how to regulate or control the positive feelings associated with sexual reward expectation, and the fact that insight in the mechanisms of these cognition-emotion interactions can help in the development of effective CBT interventions, research on the influence of emotion regulation strategies on the expectation of sexual reward was lacking in the literature. In chapter eight and nine the influence of higher-level control mechanisms on sexual conditioned responses and extinction thereof in healthy men and women was examined.

In chapter eight, making use of a differential appetitive sexual conditioning paradigm, a cognitive down-regulation condition was compared with a control condition in men and women. It was demonstrated that the deployment of a cognitive emotion down-regulation strategy effectively enhanced extinction of conditioned affective value and subjective sexual arousal in men as compared to men in the control condition. Intriguingly, in women the deployment of the down-regulatory strategy resulted in overall higher ratings of affective value and subjective sexual arousal towards both CSs. In women, the cognitive strategy did however result in attenuated approach tendencies towards conditioned stimuli that predicted potential sexual reward (i.e. the CS+). In men, the cognitive strategy did not result in attenuated approach tendencies towards the CS+. Crucially, the deployment of a cognitive down-regulation strategy did not result in decreased conditioned genital sexual

arousal, or subjective affect and sexual arousal in both sexes. In addition, US expectancy was not affected at all by the cognitive strategy, in men and women.

In chapter nine it was investigated whether a cognitive up-regulatory strategy can efficiently increase sexual arousal elicited by sexual reward-conditioned cues in healthy men and women. In this study it was demonstrated that the deployment of the emotion up-regulatory strategy did not seem to have any effect on conditioned genital responding in men and women. However, the cognitive strategy did increase unconditioned genital responses in both sexes. Additionally, the deployment of the cognitive up-regulatory strategy seemed to result in enhanced resistance to extinction of conditioned genital responding in women. Regarding the subjective measures, results indicate that in men conditioned affective value can be up-regulated by cognitive strategies, whereas in women no such effect was observed. On measures of subjective sexual arousal and US expectancy the emotion up-regulatory strategy did not seem to affect conditioned responding or extinction thereof, in both sexes. The emotion up-regulation strategy also did not result in increased approach tendencies towards the CS+ in men and women.

Results from these studies indicate that sexual arousal can be modulated in line with participants' regulatory goals, despite mixed results for men and women. Compared to women, men appear more effective in emotional down-regulation of sexual arousal, whereas top-down up-regulation can influence conditioned sexual responses or extinction thereof in both sexes. Intriguingly, US expectancy was not affected by either cognitive regulatory strategy. Results from those studies indicate that emotion regulation strategies do not seem to be equally effective on all sexual responses (i.e. behavioural, affective value, physiological, US expectancy).

11.2.1. The Influence of Acute-Stress on High-Level Top-Down Control

As has been elucidated in chapters one and two, the dopaminergic pathways are widely known for their involvement in the signalling of rewarding stimuli, but also aversive events including acute stress, can activate the dopaminergic neurons in the brain reward system (Kringelbach & Berridge, 2009; Pruessner et al., 2004; Oei et al., 2014). The effects of stress are thought to be mediated by neuroendocrine responses to acute stress exposure (i.e. increased cortisol levels) that impact not only subcortical reward structures (Oei et al., 2014) but also the functional integrity of PFC (Raio et al., 2013). Because the relationship between the physiological stress response and the cognitive control of sexual arousal had not been examined, in chapter ten the influence of acute-stress on deliberate emotion regulation during the processing of sexual stimuli was investigated. Making use of functional magnetic resonance imaging (fMRI) we tried to shed light on the effect of acute-stress on within-subject functional activity in brain regions associated with sexual reward (e.g. the amygdala and NAc) and frontal regions during cognitive down-regulation of sexual arousal. Hereto, healthy sexual functional men were randomly assigned to an acute stress or control condition.

It was expected that activation within reward structures, such as the NAc and amygdala would decrease consistent with the goal of down-regulation, while activation in frontal structures would increase respectively (Ochsner et al., 2004), and indeed such a reciprocal pattern was seen for the whole brain analyses. When participants were instructed to down-regulate sexual arousal, increased neural activation was seen in frontal structures, such as the inferior and superior frontal gyrus and frontal pole, and no activity was detected in the amygdala. Crucially, acute-stress increased activity in the right amygdala, right inferior frontal gyrus and right dorsal ACC during the down-regulation of sexual arousal, compared to when participants were instructed just to just watch

the sexual stimuli. Moreover, in the acute-stress condition, activity in the right inferior frontal gyrus pars triangularis was significantly correlated to the ratings of successful down-regulation of sexual arousal, suggesting that additional right inferior frontal gyrus pars triangularis resources were specifically recruited as the acute-stress induction costs for providing top-down control of sexual arousal increased.

These results corroborate previous research on the regulation of sexual arousal (Beauregard et al., 2001) and provide evidence for the view previously proposed that regulation of sexual arousal depends on a neural circuit in which frontal cortical areas mediate the cognitive modulation of sexual responses generated at a subcortical level. Moreover, the results are in favour of the assumption that stress may complicate the successful cognitive down-regulation of sexual arousal, as evidenced by the increased neural activation in the right amygdala, right dorsal ACC, and right inferior frontal gyrus pars triangularis. Results from the present study indicate that acute-stress is an important threat for the successful regulation of sexual arousal.

11.3. Factors Influencing Control Mechanism in Sexual Arousal

The above makes clear that sexual arousal or the expectation of sexual reward can come under stimulus, contextual, and cognitive control. In this paragraph important factors influencing lower-level control processes in sexual incentive learning are discussed. Hereafter, we will tap into the factors involved in higher-level control processes.

11.3.1. Lower-Level Control Factors in (Conditioned) Sexual Arousal

In chapter two it is suggested that CS-US similarity plays an important factor in animal sexual conditioning, and that conditioned responses toward sexually relevant CSs are highly resistant to extinction (Domjan et al., 1988; Krause et al. 2003; Rescorla & Furrow, 1977). It is thought that those 'prepared' associations are acquired more easily and that additionally these associations are thought to obey different laws of learning than nonprepared associations do. However, as mentioned earlier, this theory of preparedness is not undisputed, and alternative theories, such as selective sensitization (i.e. a pre-existing response tendency is activated by a perceived threat; Lovibond, 1993) or biases in the processing of information about certain stimuli rather than phylogenetically based associative predispositions have been put forward (Davey, 1995). In spite of its controversy, results from the appetitive and aversive sexual conditioning studies reported in the chapters four and five respectively, can be explained by such a model of preparedness or selective sensitization. To clarify, in the aversive conditioning study, the association between sexual stimuli (erotic CSs) and the suppression of sexual arousal (painful US) (i.e. CS-US dissimilarity) may explain the sensitivity to extinction of aversively conditioned sexual responses, especially since healthy sexually functional men and women participated in this study. Research has demonstrated appetitive - aversive interactions in DA neurons in the brain reward system: when a neuron is excited by an aversive CS it is inhibited by an appetitive CS or vice versa (Matsumoto & Hikosaka, 2009; Bouton & Peck, 1992; Nasser & McNally, 2012). In addition, recruitment of the relevant motivational system (appetitive vs aversive) is dependent on the US. Painful stimulation (e.g. electric shock) can selectively activate the aversive system, whereas sexual stimulation (e.g. genital vibrostimulation) can selectively activate the appetitive system. However, since erotic pictures were used as CSs in the aversive conditioning study (chapter five), these pictures most likely

automatically recruited the appetitive motivational system in healthy men and women. In addition, the painful stimulation that served as US most likely recruited the aversive motivational system. Since the two motivational systems oppose each other, a CS which excites one motivational system will inhibit the other. In other words, a conditioned excitor of one motivational system is functionally equivalent to a conditioned inhibitor of the other, and prior appetitive sexual learning could have interfered or augmented sexual aversive learning (Nasser & McNally, 2012). This mechanism may explain why the aversively conditioned sexual responses do not seem to be resistant to extinction, at least in healthy sexually functional men and women. In the appetitive conditioning study neutral pictures were used as CSs, and as a consequence, it is thought that only the appetitive motivational system was recruited by the US, and no prior (aversive) learning interfered with CR acquisition. This also suggests that humans are not only capable in coding events and/or stimuli that are related, but also in coding *how* these are related. The persistence of evaluative learning effects can therefore be explained by the assumption that once a stimulus has been categorized as potential cause of an aversive or appetitive outcome, individuals fall back on their prior propositional knowledge about causal relations, including the general knowledge that causes tend to have additional effects (De Houwer, 2009).

Moreover, although results from studies in this thesis contribute to the accumulating evidence (Both et al., 2008a,b, 2011) that women's genital response can be appetitively conditioned to initially neutral stimuli, at least, when making use of a tactile US, results from studies discussed in this thesis do not support such a straightforward mechanism in men. In the chapters four and six, making use of two neutral pictures of pictorial faces as CSs, no evidence for conditioned genial arousal response could be observed in men. In chapter eight, now making use of sexually relevant stimuli as CSs, conditioned genital

responses were detected in men. Although this thesis was not specifically aimed at investigating the difference between sexually relevant versus sexually irrelevant stimuli in sexual conditioning, and a comparison between results from those studies is not straightforward because of the difference in used design (and one needs to keep in mind that in chapter nine no conditioned genital responses could be observed in men despite making use of sexually relevant CSs), speculatively, it could be that men are less susceptible to sexual learning to cues that differ too much from their developed preference (Coria-Avila, 2012; Pfaus, Kippin & Centeno, 2001). Therefore it seems that combination of a tactile sexual US and neutral CSs is not sufficient to elicit conditioned genital responding in men, whereas the combination of a tactile sexual US and sexually relevant CSs is capable of triggering such a response. However, it should be mentioned that making use of sexually explicit visual stimuli as US, conditioned genital responses towards an initial neutral CS (a penny jar) were observed by Plaud and Martini (1999), although their sample size comprised of only nine subjects. Nevertheless, it could very well be that men and women differ in sexual learning, with women having more erotic plasticity, once sexual preferences are established (Baumeister, 2000; Coria-Avila, 2012; Pfaus, Kippin & Centeno, 2001). Based on Hoffmann, Janssen and Turner (2004) genital results from chapters four and eight might indeed be seen from such a perspective, since in their sexual conditioning study, 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 sexually relevant CS (i.e. abdomen) than to the irrelevant CS (i.e. gun). Future well-powered research, incorporating sexually relevant and sexually irrelevant stimuli in one design is needed before any firm conclusions about 'prepared' (or 'already learned') sexual associations and possible sex differences therein can be drawn.

The studies in this thesis are the first to investigate whether initially neutral cues can elicit approach tendencies through their mere pairing with a sexually rewarding outcome, and likewise whether initially sexual cues can elicit avoidance tendencies through the association with a painful outcome. The processing of emotionally competent stimuli results in physiological changes that prepare an organism for action (Both, Everaerd & Laan, 2005). In case of threatening stimuli avoidance behaviour will be activated, and conversely, in case of attractive (sexual) stimuli appetitive approach behaviour will be triggered. In this thesis it was hypothesized that stimuli that elicit emotional arousal will facilitate action tendencies, relative to neutral, low arousal stimuli. In chapters four, five and six, additionally to the experimental sexual conditioning procedure, a stimulus response compatibility task was included to assess implicit approach and avoidance tendencies towards the CSs. Although in the chapters four and five, this Approach Avoidance Task was administered only after extensive extinction trials, results from chapter six indicate that conditioned female sexual response translated into subjective experience, physiological measures and in action disposition.

11.3.2. Higher-Level Control Factors in (Conditioned) Sexual Arousal

To continue on the topic of conditioned action tendencies, results from chapter eight indicate that a cognitive emotional down regulatory strategy can result in attenuated approach tendencies towards conditioned stimuli that predicted potential sexual reward (i.e. the CS+). Like discussed in chapter one, contemporary emotion theories propose that sexual arousal, like any emotion, is a composite of subjective experience, physiological activity, and action disposition (Frijda, 2010). Moreover, it is also proposed that emotions are primarily action tendencies that are reflected in physiological activity and subjective response. In such a framework, the fact that a CS elicits sexual

arousal response after pairing with a sexually rewarding US implies that the CS also elicits an approach tendency: the approach tendency installed through Pavlovian reward learning is translated into overt action. Additionally, as chapter eight suggests, higher-level control mechanisms can also influence these tendencies. Moreover, results from chapters eight and nine suggest cognitive regulatory strategy mainly operate on physiological measures of sexual response and valence, leaving the more cognitive aspects (US expectancy) of conditioning intact. Research indeed suggests cognitive regulatory effects on US expectancy are not to be expected (Blechert, et al., 2015).

Results from chapter ten are in favour of the assumption that stress may complicate the successful cognitive down-regulation of sexual arousal, as evidenced by the increased neural activation in the right amygdala, right dorsal ACC, and right inferior frontal gyrus pars triangularis. Research has demonstrated that the dorsal regions of the ACC are involved in threat appraisal and expression of negative emotion (Etkin, Egner & Kalisch, 2011; Ochsner & Gross, 2005), as well as in reward-based decision making (Bush et al., 2000). Moreover, research suggests that a disturbance in neural activity in right dorsal ACC may account for emotional dysregulation (Beauregard, Paquette & Le`vesque, 2006). The existing literature and results from the imaging study in this thesis, allows for speculation about the influence of acute-stress on cognitive down-regulation of sexual arousal, with the initial motivational value of the sexual stimuli being calculated in the amygdala, but being further maintained and updated in reward structures such as the NAc and right dorsal ACC, and being controlled by frontal structures. It seems that acute-stress requires enhanced activation of the right inferior frontal gyrus pars triangularis, in order to successfully down-regulate sexual arousal. The inferior and superior frontal gyrus, have been implicated in top-down control, especially in the inhibition or stopping of inherent response tendencies (Aron, Robbins&

Poldrack, 2014). Additionally, other research suggests (Raio et al., 2013) that acute-stress impairs successful regulation of negative emotions. This, and results from the imaging study in this thesis suggests that acute-stress may impair cognitive regulation of emotion, including sexual arousal. Moreover, the results from this study suggest an important paradox: top-down regulation may be compromised in controlling sexual arousal precisely when such control is needed most, especially since aversive events including acute stress (Oei et al., 2014), can activate the dopaminergic neurons in the brain reward system, resulting in increased bottom-up subcortical responses. Moreover, it is important to keep in mind that, as stated before, the principles underlying cognitive regulation also form the basis of CBT. Therefore, the success of CBT relies on the availability of cognitive resources and intact executive function (Heatherton & Wagner, 2011; Hofmann, Schmeichel & Baddeley, 2012; Ochsner, Silvers & Buhle, 2012). The proposed regulatory difficulties described are also consistent with theories of self-regulation failure (Heatherton & Wagner, 2011), that describe self-regulatory capacities as a limited resource that may become weak and depleted when exposed to negative emotions (induced by for instance acute-stress). Derived from this model, regulatory capacities rely on top-down prefrontal control and may be weakest when frontal functioning is impaired, and/or when subcortical regions involved in the automatic emotional response behaviour are enhanced (Oei et al., 2014).

11.4. Gender Differences

11.4.1. Lower-level Control Processes

All studies in this thesis were conducted in healthy sexually functional volunteers, and all studies, apart from the chapters three, seven and ten, included men and women to explore possible gender differences in sexual

conditionability and cognitive regulatory strategies. Results from the studies in this thesis oppose the existing idea that men are more receptive to sexual conditioning than women (Pfaus, Kippin & Centeno, 2001). Although there are some differences observed between men and women in the studies in this thesis, these may not reflect pure gender differences in sexual conditionability per se, but may also be explained by differences in sample size and US effectiveness. Moreover, genital responses of men and women do not lend themselves to be compared directly. Research has shown that for men, more than for women, visual stimuli preferentially recruit an amygdalo-hypothalamic pathway (Hamann et al., 2004). In addition, research also demonstrated that in men, vibrotactile stimulation alone produces the lowest level of genital and subjective sexual arousal compared to erotic film (Rowland & Slob, 1992). Therefore, it remains the question to which extent present results can be generalized to make claims about sexual learning in general, and gender differences therein. It is well possible that making use of visual erotic stimuli as US, a different pattern may be seen. But for now, results from earlier sexual conditioning studies in humans discussed in chapter two, combined with the results from the experimental studies presented in this thesis, provide not enough evidence to support the claim that men and women do differ in basic sexual learning. Nevertheless, the widely held view is 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, 2014). It is thought that in women, a sexual stimulus triggers a wider range of cognitions as compared to men (Laan & Janssen, 2007; Toates, 2014). 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.

11.4.2. Higher-Level Control Processes

Hitherto, it is assumed that women may use less efficient cognitive strategies in the regulation of emotions compared to men (Whittle et al., 2011). But it is important to keep in mind that most –if not all- of these results come from studies that investigated the regulation of particularly negative emotions (Mak et al., 2009; McRae et al., 2008; Gross, 2007). Results from chapter nine, do not suggest that men and women differ substantially in emotional up-regulation of (conditioned) sexual arousal in general. Nevertheless, results discussed in chapter eight indeed suggest that men are more effective in emotional down-regulation of sexual arousal compared to women. It is quite intriguing that in women, the deployment of an emotional down-regulatory strategy even resulted in overall increased affective value and subjective sexual arousal towards both CSs. These results correspond to the findings of Both, Laan and Everaerd (2011), who studied the regulation of sexual arousal by means of attentional focus in healthy sexually functional men and women. In this study, women reported stronger absorption (i.e. the extent to which the participant experienced him or herself as a participant in the sexual activity shown in the film) in the cool attentional focus condition than in the no-instruction control condition, whereas men, as expected, reported lower absorption levels in the cool attentional focus condition than in the no-instruction control condition. Results from studies on negative emotion down-regulation (McRae et al., 2008) demonstrated that men have greater down-regulation of amygdala activity and less prefrontal activity during the regulation of negative affect, despite comparable levels of subjectively declared negative affective value in men and women. This suggests that men are able to generate and implement cognitive emotion down-regulation strategies with less effort or difficulty than women, at least in case of negative emotions. However, to the best of our knowledge, imaging studies on sexual emotion regulation in both sexes is lacking in the

literature, and as a consequence we can only speculate whether a similar mechanism accounts for the found results in this thesis. Besides, a pronounced difficulty in emotion down-regulation in women while processing sexual (conditioned) stimuli can also be the result of anatomical differences between men and women (Laan & Everaerd, 1995). Bodily responses and changes therein are an apparent aspect of emotional response. The association between genital and subjective sexual arousal is generally lower for women than for men (Chivers et al., 2004), possibly explained by the giving that men are likely to have more (visual and tactile) cues they can use to detect genital response than women do (Sakheim et al., 1984).

Given the problems in comparing genital responses of men and women directly, and possible differences between sexes with regard to responses to specific types of stimulus materials, it is far too early to infer that sex differences exist in basic sexual incentive learning, or to infer that women indeed use less efficient strategies in the down-regulation of positive (sexual) emotions than men

11.5. General Conclusions

First, although only few (well-controlled) studies have investigated classical conditioning of the sexual response in humans, results indicate that human sexual arousal can be conditioned. Second, results from chapter three indicate that DA receptor antagonism reduces sexual stimulation-induced genital sexual arousal, emphasizing the importance of DA availability in unconditional responding to sexual stimulation.

Third, results from chapters four and five raise doubt about the claim that, unlike other forms of classical conditioning, evaluative sexual conditioning is resistant to extinction. Unpaired presentations after (paired CS-US)

conditioning trials, reduce the magnitude of conditioned responses, including the magnitude of sexual evaluative learning effects. Hence, sexual evaluative learning is sensitive to extinction. Nevertheless, evaluative sexual learning effects are persistent, especially appetitive conditioned evaluative learning effects. Results suggest that extinction of sexual evaluative learning effects occurs at a slower rate than in other forms of associative learning (i.e. signal learning).

Fourth, chapter six provides evidence for the claim that an extinction procedure does not erase conditioned sexual associations in humans but instead involves new learning that is context dependent. Sexual extinction learning is especially dependent upon context. This makes clear that sexual arousal or the expectation of sexual reward can come under stimulus control by contextual cues associated with states of sexual reward.

Fifth, results from chapter seven suggest that administration of a single dose of DCS makes sexual extinction memories context-independent and prevents the return of conditioned sexual response in healthy sexually functional women. As a result, NMDA receptor glycine site agonists may be potential pharmacotherapies to reduce the motivational impact of sexual reward-associated cues, and to prevent relapse in sexual motivation disorders with a learned component.

Sixth, chapters eight and nine illustrate that (conditioned) sexual arousal can be modulated in line with participants' regulatory goals. In chapter eight, evidence was found for an emotional down-regulatory strategy to effectively enhance extinction of conditioned sexual responses in men. Results suggest that women seem to have some difficulty in the down-regulation of sexual arousal. Results from chapter nine suggest that the deployment of a cognitive up-regulatory strategy can efficiently increase unconditioned and conditioned sexual arousal elicited by sexual reward-conditioned cues in healthy men and women. Nevertheless, results are mixed on different response

modalities for men and women, making clear that the interpretation of the effectiveness of emotion regulation strategies is not straightforward.

Seventh, in chapter ten, making use of fMRI, it is demonstrated that regulation of sexual arousal depends on a neural circuit in which frontal cortical areas mediate the sexual responses generated at a subcortical level. Moreover, the results are in favour of the assumption that stress may complicate the successful cognitive down-regulation of sexual arousal, as evidenced by the increased neural activation in the right amygdala, right dorsal ACC, and right inferior frontal gyrus pars triangularis in the acute stress condition compared to the control condition during the down-regulation of sexual arousal. Results from this study indicate that acute-stress may be an important threat for the successful regulation of sexual arousal.

The research in this thesis indicate that lower level control processes, such as associative learning and related phenomena, as well as higher-level control process such as cognitive emotion regulation both function as control systems that regulate sexual arousal and behaviour. Returning to the model of sexual motivation and regulation discussed in the general introduction, the imbalance between (strong or weak) sexual urges and compromised cognitive control has been suggested to play an important role in the development of sexual motivation disorders. In this thesis, learning processes in sexual arousal response and cognitive control functions were investigated separately and in conjunction. This is of added value, since in case of disturbances in sexual arousal and motivation, it is especially important to understand how cognitive control processes function in the presence of sexual reward-related cues.

11.6. Limitations

Several comments are in order here. First, a limitation of the conditioning studies in this thesis is the absence of a between subjects (unpaired) control

group. Without such a control group it is difficult to determine whether and what learning has occurred. This makes it unclear if the observed conditioning effects are due to conditioning or to pseudo conditioning. Sensitization of sexual arousal would translate into increased genital and subjective responses across trails, and not in differential responding towards the CS+ and CS- per se.

Other limitations of these studies arise from the selected study cohort. The results were obtained in young healthy men and women. Moreover, results from the studies described in chapters three, and seven only encompassed healthy sexually functional women, whereas only men participated in the imaging study in chapter ten. Consequently, the applicability of the results to the general population has to be determined, and the generalization of the found results in chapters three, seven and ten to members of the opposite sex may not be straightforward. The generalization of our findings to other populations, such as adolescents, elderly individuals (<18 and >45 years), and clinical samples in particular, may also be hampered (see also section 11.7).

Moreover, in the current conditioning studies, vaginal photoplethysmography was used as indicator of physiological sexual arousal in women. Vaginal engorgement, however, is only one of many co-occurring processes during the sexual arousal response. Likewise, penile circumference was used as indicator of physiological sexual arousal in men. Like described in chapters six and eight, penile circumference in response to the CS+ was smaller as compared to penile responses towards the CS-. Although this phenomenon can be explained by physiological processes during the initial stage of penile erection, the measures that are used in the experimental conditioning studies (for men and women) relate to only some of many co-occurring processes, making them far from perfect. Therefore, additional methodology, such as thermal imaging or labial thermistor clips and equivalent penile thermistor (Payne & Binik, 2006), may provide additional insight in the physiological basis

for sexual arousal and human sexual learning. And as mentioned earlier, another caveat lies in the etiological relevance of the US. It is possible that for men (and possibly also for women), solely genital vibrostimulation is not the most effective sexual stimulus (Rowland & Slob, 1992; see also section 11.4. Sex Differences). Future studies on male sexual learning may consider vibrotactile stimulation combined with erotic film clips as US. Moreover, physiological sexual response is just one of the automatic measures to gauge on neurobiological mechanism involved in human sexual incentive learning. Functional imaging studies on sexual incentive learning, underlying neurochemical mechanisms, and related phenomena in both sexes is warranted to obtain complementary insight in neural mechanisms involved in sexual behaviours, which may help foster potentially critical insights in the aetiology of disorders in sexual motivation.

Regarding the promising effects of DCS in the aid of preventing renewal of maladaptive conditioned responses, only conclusions about the context-dependent recall of sexual extinction memory can be drawn. The unpaired US presentations at the beginning of each former acquisition context A on day two likely induced reinstatement effects mixed with the contextual renewal effects (Kalisch et al., 2006; Haaker et al 2013). Consequently, we are unable to differentiate between renewal and reinstatement effects on recall of sexual memory.

Another limitation of this thesis is that this thesis only addressed Pavlovian sexual conditioning, while this type of learning is not the only way in which humans may acquire certain sexual behaviours. For instance, individuals also learn about consequences of behaviours. In operant or instrumental learning associations are made between a behaviour and a consequence for that behaviour (Skinner, 1937; Thorndike (1911). From conditioning studies within other field of research, such as fear or anxiety it is known that operant learning

does not by default follow similar principles as seen in Pavlovian conditioning (Vurbic, Gold & Bouton, 2011).

With respect to the imaging study described in chapter ten, sexual arousal was not directly assessed: no ratings of subjective sexual arousal were obtained and no genital responses were measures. It can thus not be firmly concluded that the observed neural patterns in the down-regulation condition indeed resemblance decreased sexual arousal.

And lastly, and clinically relevant, the present study investigated only newly acquired sexual evaluative learning and relatively short-term effects within one (or two at most) experimental session.

11.7. Clinical Implications

As mentioned above, it is still to be elucidated whether the findings from the studies described in this thesis can be generalized to clinical practice. Nevertheless, hypotheses for future clinical work can be generated based on the present findings.

First, conditioned sexual likes and dislikes can be persistent, although conditioned affect eventually does extinguish (chapters four and five). This indicates that it might be beneficial to focus especially on subjective affect in the treatment of sexual arousal disorders with a learned component. A combination of extinction and counter-conditioning (learning a new opposite response) would plausibly be more effective than extinction alone in the treatment of these sexual disorders, especially in the treatment of sexual dislikes. In counterconditioning, the CS is paired with a stimulus evoking a response that is incompatible with the original unconditioned response, thereby altering the valence of a stimulus (Baeyens et al., 1992). However, present results make clear that depending on how strong and how easily available CS-US associations are, cue exposure therapy still seems relevant for the treatment

of sexual disorders with a learned component, like hypo or hypersexuality, since it is speculated that an extinction procedure makes the original CS-US associations less retrievable from memory, whereas it does enhance the accessibility of a new CS-no US association (Delamater, 2004).

In addition, the finding that sexual conditioned responses extinguish dependent upon context (chapter six) makes clear that extinction procedures may best be applied in the context in which the problematic behaviour is experienced, generalizing to other contexts and with multiple stimuli. Moreover, studies in clinical samples may transfer the effects of administration of a single dose of DCS on enhancing extinction memory, as shown in clinical trials with DCS (Price et al., 2013; Ressler et al. 2004; Santa Ana et al., 2009).

Moreover, in the treatment of problematic strong sexual arousal and appetite, cognitive strategies in the processing of conditioned sexual stimuli may be helpful. Learning to obtain effective emotion regulation strategies in circumstances in which sexual stimuli cannot be avoided may be useful to diminish undesirable feelings of sexual arousal and desire and to exert control over sexual behaviour. Therefore, future studies should incorporate clinical samples, like individuals with hypersexuality or deviant sexual preferences that manifest perturbed motivation. Likewise, in the treatment of problematic low sexual arousal and appetite, cognitive up-regulatory strategies of sexual arousal may be applied during initial conditioning stages in CBT in men and women. Results from chapter nine point to the utility of up-regulatory training for enhancing genital sexual arousal during the learning of new associations of sexually rewarding experiences and stimuli. In addition, emotion up-regulatory strategies may be promising add-on tools during therapeutic exercises in order to (re)create and enhance sexually pleasurable experiences. Therefore, future studies should assess the clinical efficacy of cognitive up- and down-regulatory strategies by including clinical samples, such as individuals with low sexual arousal and desire, or individuals with hypersexuality.

Lastly, the finding that acute stress seems to impair cognitive regulation of sexual arousal suggests that stress may be an important factor in the maintenance of disorders in sexual arousal and motivation. Although in our current study, only healthy sexually functional men were included, it could be hypothesized that chronic stress may eventually impair successful recruitment of structures implicated in top-down control, leading to a failure of regulation of sexual urges. Or individuals who frequently encounter sexual rewarding stimuli when under stress would run the risk of amplified incentive salience of sexual rewards and ultimately increased sexual motivation (Robinson & Berridge, 1993), which may be more difficult to control. Likewise, research has demonstrated that participants with low cortisol stress response demonstrate decreased NAc activation to (sexual) reward cues (Oei et al., 2014; Ossewaarde et al., 2011; Porcelli et al., 2012), which eventually may result in decreased sensitivity to sexual rewards and may possibly contribute to low sexual arousal and desire. However, more research is needed, especially in women and clinical samples. By investigating neural activation and (related) mental states, fMRI can make major contributions to the understanding of psychopathology and cognitive and affective networks in the brain. Moreover, fMRI also affords the opportunity to explore the feasibility of self-regulation of functional brain networks through neurofeedback. During fMRI neurofeedback training, participants receive feedback on their brain activity in real time and are instructed to change (i.e. up- or down-regulate) this activation (in line with the desired brain state) (Johnston et al., 2010). A better understanding of the neural changes accompanying successful regulation of sexual response may lead to the development of new treatment protocols targeting the functional correlates of specific brain networks. Moreover, since research has shown that individuals with high trait anxiety are impaired in regulating emotions (Indovina et al., 2011), probing the effects of stress–and the individual cortisol response- on

reward sensitivity might be helpful in predicting individual susceptibility to relapse.

11.8. Future Research Directions

As has become clear, there is a learning process underlying sexual arousal and behaviour and it involves forming associations between physical arousal and states of sexual reward with stimuli in the environment (i.e. incentives) (Toates, 2014). Animal research suggests, that once sexual preferences are established (Sisk & Foster, 2004), males are less susceptible to sexual learning to cues that differ too much from their developed preference (Coria-Avila, 2012; Pfaus, Kippin & Centeno, 2001). From research in rats it is known that at young age, the brain is sensitive to make new associations, including associations with sexual reward (Coria-Avial, 2012). Pfaus, Erickson and Talianakis (2013) suggest that an animal's initial sexual experiences are a sensitive or critical period during which neutral stimuli associated with sexual reward can become appetitive sexual CSs, whereas stimuli associated with sexual inhibition can become inhibitory CSs. Likewise, in humans, the first experience of (the absence of) sexual reward, especially ejaculation and orgasm, might have a similar strong effect in setting future preferences. The first experience of sexual arousal may be a powerful mediator of incentive formation and enhancement. Derived from the assumption that for many, adolescence and young adulthood represent a period of the first sexual experiences and sexual intercourse (Hawes et al., 2010), it can be speculated that especially this period in life is crucial for the development of sexual preferences and sexual behaviour (Pfaus et al., 2012). As the saying goes, 'neurons that fire together, wire together'. (Hebb, 1949). However, at present, very little is known about early sexual experiences in humans, and as a result it is unknown if a similar 'critical period' for the formation of sexual preferences does indeed exists in men and women.

Therefore, future studies should investigate if -similar to animals- humans also have an increased strength (presumably testosterone and DA based, see chapter two) of sexual incentive learning during adolescence and/or young adulthood. Likewise, the impact and strength of later sexual experiences on sexual preferences and sexual behaviour are also largely unknown. Investigating if sexual associations can be made more easily during a particular phase, or to investigate if such associations are weaker or more difficult to form during another (later) phase in life, is highly clinical relevant. CBT is based on associative learning principles and has emerged as the treatment of choice for disorders in sexual interest and desire (Both, S., Laan, & Schultz, 2010; Laan, & Both, 2008), including cue exposure therapy and behavioural techniques to (re)create different, more varied, or prolonged sexual stimulation to enhance sexually pleasurable experiences. In chapter six it was demonstrated that new learning during extinction inhibits, but does not erase, the CS–US association (Pavlov, 1927). Speculatively, a possible critical phase for sexual learning in humans may suggest that the original CS-US associations may be stronger, possibly due to the combination of high gonadal hormone and DA levels (Dominguez et al., 2001; Dominguez & Hull, 2001; Hermans et al., 2010 Wood, 2008), as compared to the later inhibitory CS–US associations or new CS-US associations that are made during the course of CBT. If there is indeed a difference in strength between the old (i.e. first sexual experiences) and new learned sexual associations that are made during CBT, pharmacological 'boosters' (e.g. DCS, or see Haaker et al., 2013) of new sexual associations or inhibitory CS–US associations may be a promising avenue to improving therapy for sexual motivation disorders.

In line with the above, another reason why future studies should focus on (sexual) experience, is the finding that experience seems to be a powerful buffer to devaluation. Prior exposure to sexually rewarding situations is thought to

vary considerably among subjects with sexual disorders, and insight into the influence of experience on conditioning may have a major impact on treatment resistance and 'relapse' risk. With the term devaluation, the decrease in conditioned response due to lowering the value of the unconditioned stimulus is meant (Bouton & Moody, 2004). Devaluation in Pavlovian conditioning may involve habituation to the solely US-presentations, after a CS-US acquisition phase. As a result of habituation, when the CS is presented again, the CS will elicit decreased CR. Interestingly, and in line with a theory of a 'critical period' in sexual learning (Pfaus, Kippin & Centeno, 2001), devaluation appears to be less strong when the acquisition of conditioned responding involves more CS-US parings (Bouton & Moody, 2004). Translating this to the clinical practice, an individual with a history of repetitively rewarding sexual experiences may be less susceptible to the intended disruptive effects of for instance anti-androgenic medication. Conversely, an individual with a limited history of sexual rewarding experiences may be more susceptible to disruptive effects of habituation in a long-term relationship. Indeed, results from fear research suggest that prior fear conditioning interferes with reward learning, subsequently leading to lower activation of the reward network (Bulganin, Bach & Wittmann, 2014). At present, human studies on devaluation in sexual conditioning are completely lacking, while they may provide highly relevant information for prevention of sexual disorders. Additionally, it would be of interest to investigate if individuals with sexual motivation disorders (e.g. women with Female Sexual Interest/Arousal Disorder, or men with hypersexuality and related disorders) have a decreased or increased susceptibility to incentive sexual conditioning as compared with healthy sexually functional individuals. Research on sexual learning in such clinical groups, combined with research on innate predispositions (i.e. genetic factor) may shed light on the neurodevelopmental trajectory of 'normal' and maladaptive sexual responses and behaviour. This knowledge about basic learning processes

involved in 'normal' and maladaptive sexual behaviours is crucial in the development of clinical treatments for those behaviours. Likewise, at present, the effect of counterconditioning on learned sexual evaluative effects in healthy participants but also in clinical samples is largely unknown (but see Davison, 1968 and Jackson, 1969), especially in case of low sexual arousal and desire. Counterconditioning in the treatment of paraphilia for instance, would consist of encouraging patients to visualize or imagine the targeted sexually-arousing stimulus while pairing this stimulus with an aversive stimulus (e.g. an aversive smell, a loud noise or a disgusting (mental image) until eventually the most sexually arousing image no longer yields sexual response, also at the evaluative level. Likewise, counterconditioning in the treatment of low sexual arousal would consist of (re)create different, more varied, or prolonged sexual stimulation to enhance sexually pleasurable experiences. These possible mechanisms in changing unwanted sexual CRs remain important directions for future research, including the neural mechanisms for appetitive-aversive interactions that are poorly understood, as it will likely yield important knowledge which may help in the development of clinical treatments for maladaptive sexual behaviours, including paraphilias and deviant sexual preferences that manifest perturbed motivation, but also for the more prevalent sexual desire and arousal disorders.

Moreover, no studies have been conducted on the role of DA in male sexual conditioning. Several factors, including sex chromosome complement (Lombardo et al., 2012), the presence of the sry gene (Dewing et al., 2006) and gonadal hormones, suggest that testosterone regulates incentive sensitivity through interactions with mesolimbic DA pathways (Hermans et al., 2010; Wood, 2008). This makes clear that future research on the role of DA in male sexual learning is warranted, as these findings may help in the understanding of the biological mechanisms underpinning addictive behaviours and how these

may affect vulnerability to drug abuse or the development of sexual dysfunctions in men. Additionally, since the mesolimbic DA system is not only crucially involved in appetitive motivational processes, but also in aversive motivational processes underlying learning and the execution of goal-directed behaviour (Robbins & Everitt, 1996; Robinson & Berridge, 2003), research on the role of DA in human aversive sexual learning is warranted. Especially, since results discussed in chapter five suggests that men and women seem to differ in sensitivity to aversive sexual conditioning. In the same sense, making use of imaging techniques, future studies in men and women, should investigate which neural circuits are involved in appetitive and aversive sexual learning and extinction, and in encoding of contextual information during extinction, and how these circuits can be modulated to further improve the effectiveness of extinction based therapies.

Next to DA, other neurotransmitter systems, including the opioid and serotonin systems, and gonadal hormones play an important role in sexual behaviour (Aubert et al., 2012; Holloway, 2012; Pfaus, Kippin & Centeno, 2001). Like mentioned in chapter two, it is suggested that testosterone regulates incentive sensitivity through interactions with mesolimbic DA pathways (Wood, 2008; Hermans et al., 2010), herewith creating a permissive environment that allows external sensory stimuli to induce DA release during sexual behaviour in animals (Dominguez et al., 2001; Dominguez & Hull, 2001). Although testosterone is known to affect sexual desire and arousal in humans (Hermans et al., 2010), the role of testosterone in human sexual incentive learning is largely unknown. Seen the importance of testosterone in regulating sexual incentive sensitivity, future research in humans is warranted.

In the distinction made by Berridge (2004), 'wanting' has been characterized as the value of incentive motivation held by a stimulus without any hedonic component, and is presumed to be mediated by DA functioning.

On contrast, 'liking' encompasses the hedonic aspect of a stimulus presentation, the positive sensory component that accompanies reward delivery and is thought to be mediated by the opioid system. As described in chapter two, there are two opioid systems. One is assumed to be related to incentive motivation, in which opioid systems in the VTA and the mesolimbic DA system are involved, and may relate to sexual motivation, and the other is thought to play a crucial role in the performance of certain behaviours involving endogenous opioids, like sexual performance (van Ree et al., 2000). 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). Administration of opioid antagonists (e.g. naloxone) in sexual conditioning experiments in animals seems to disrupt the incentive motivation for and/or hedonic value of a CS predicting sexual opportunity or of the sexual stimulus itself (Holloway, 2012). At present the role of the opioid system in human sexual incentive learning is unknown, despite the fact that insight in the role of this neurotransmitter system in human sexual motivation will bring innovative ideas, and is needed to guide psychological and/or pharmacological treatment for disorders in sexual motivation. In a similar manner, no studies on the role of serotonin in human sexual conditioning have been conducted. Research has shown that 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). 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.

To return to Plato's reflection of human nature, the provocation of sexual appetite and cognitive control reflects sexual behaviour as a whole: the successful completion of the chariot´s journey towards enlightment and the truth is depending on the balance between emotions and man's appetites, ánd the cortical safeguards designed by evolution to control these sexual urges. Insights in the lower- and higher-level control processes may yield explanations, as to how learned maladaptive responses -as seen in hypersexuality or sexual interest/arousal disorder- may develop and how these problematic behaviours may be effectively treated.

Written ages ago, the Phaedrus myths had the primary function of raising questions about knowledge and truth while drawing attention to the limits of human capacities. The current journey towards the 'truth' as described in this thesis, aimed at contributing to the growing literature on learning mechanisms and cognitive regulation in sexual arousal, herewith adding to the foundation of our understanding of (neural) processes involved in sexual arousal, which hopefully may help in the development of cognitive behavioural and pharmacological treatment of disorders in sexual motivation. But as has become clear, research on sexual conditionability and sexual regulation, and related neuromodulatory systems in humans is in its infancy, meaning there are many topics that need further investigation. However, as Plato once stated: "*the beginning is the most important part of the work*".

References

Aron, A. R., Robbins, T. W. & Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in cognitive sciences* 18, 177-185.

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.

Baeyens, F., Eelen, P., van den Bergh, O., & Crombez, G. (1992). The content of learning in human evaluative conditioning: Acquired valence is sensitive to US-revaluation. *Learning and Motivation*, 23, 200–224.

Baumeister, R.F. (2000). Gender differences in erotic plasticity: The female sex drive as socially flexible and responsive. *Psychological Bulletin,* 126, 347-374.

Beauregard, M., Lévesque, J., & Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *The journal of Neuroscience*, 21, RC165.

Beauregard, M. (2007). Mind does really matter: evidence from neuroimaging studies of emotional self-regulation, psychotherapy, and placebo effect. *Progress in Neurobiology* 81, 218-236.

Beauregard, M., Paquette, V. & Lévesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Learning and memory* 17, 843-846.

Berke, J.D., Hymann, S.D., 2000. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 25, 515–532.

Berridge, K.C., 2004. Motivation concepts in behavioral neuroscience. *Physiology & Behavior* 81, 179–209.

Bindra, D., 1974. A motivational view of learning, performance, and behavior modification. *Psychological Review* 81, 199–213.

Blechert, J., Wilhelm, F. H., Williams, H., Braams, B. R., Jou, J. & Gross, J. J. (2015). Reappraisal facilitates extinction in healthy and socially anxious individuals. *Journal of Behavior Therapy and Experimental Psychiatry* 46: 141-150.

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.

Both, S., Brauer, M., Laan, E. (2011). Classical conditioning of sexual response in women: a replication study. *Journal of Sexual Medicine* 8, 3116–3131.

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.

Bouton, M.E. (2004). Context and behavioral processes in extinction. *Learning & Memory* 11, 485–494.

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.

Bouton, M.E., Moody, E.W. (2004). Memory processes in classical conditioning. *Neuroscience & Biobehavioral Reviews* 28, 663–674.

Both, S., Laan, E., & Everaerd, W. (2011). 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. & Schultz, W. W. (2010). Disorders in sexual desire and sexual arousal in women, a 2010 state of the art. *The Journal of Psychosomatic Obstetrics and Gynecology* 31, 207–218.
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.
Bouton, M.E. & Peck, C.A. (1992). Spontaneous recovery in cross-motivational transfer (counter-conditioning). *Animal Learning & Behavior* 20, 313 -321.
Bulganin, L., Bach, D. R. & Wittmann, B. C. (2014). Prior fear conditioning and reward learning interact in fear and reward networks. *Frontiers in behavioral neuroscience* 8, article 67.
Bush, G., Luu, P. & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in cognitive sciences* 4, 215-222.
Carl, J. R., Soskin, D. P., Kerns, C. & Barlow, D. H. (2013). Positive emotion regulation in emotional disorders: a theoretical review. *Clinical psychology review* 33, 343-360.
Chivers, M.L., Rieger, G., Latty, E., Bailey, J.M. (2004). A sex difference in specificity of sexual arousal. *Psychological Science* 15, 736–744.
Coria-Avila, G.A. (2012). The role of conditioning on heterosexual and homosexual partner preferences in rats. *Socioaffective Neuroscience & Psychology* 2, 17340.
Cousijn J, Goudriaan AE, Wiers RW (2011). Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. *Addiction*, 106: 1667–1674.
Davey, G.C.L., 1995. The merits of an experimentally testable model of phobias. *Behavioral and Brain Sciences* 20, 363–364.
Davison, G. C. (1968). Elimination of sadistic fantasy by a client-controlled counterconditioning technique: a case study. *Journal of abnormal psychology* 73, 84-90.
De Houwer, J. (2009). The propositional approach to associative learning as an alternative for association formation models. *Learning & Behavior* 37, 1-20.
De Houwer, J., Thomas, S., & Baeyens, F. (2001). Associative learning of likes and dislikes: A review of 25 years of research on human evaluative conditioning. *Psychological Bulletin*, 127, 853–869.
De Jong, J. W., Roelofs, T. J. M., Mol, F. M. U., Hillen, A. E. J., Meijboom, K. E., Luijendijk, M. C. M., Van der Eerden, H. A. M., Garner, K. M., Vanderschuren, L. J. M. J., Adan, R. A. H. (2015). Reducing ventral tegmental dopamine D2 receptor expression selectively boosts incentive motivation. *Neuropsychopharmacology*, 1-11. doi:10.1038/npp.2015.60
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.
Di Chiara, G., 1999. Drug addiction as dopamine-dependent associative learning disorder. *European Journal of Pharmacology* 375, 13–30.

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.
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.
Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of general psychiatry*, 64, 327-337.
Etkin, A., Egner, T. & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in cognitive sciences* 15, 85-93.
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.
Frijda, N.H. (1986). The emotions. Cambridge University Press, Cambridge, UK.
Frijda, N. H. (2010). Impulsive action and motivation. *Biological Psychology* 84, 570–579
Georgiadis, J. R., & Kringelbach, M. L. (2012). The human sexual response cycle: Brain imaging evidence linking sex to other pleasures. *Progress in Neurobiology* 98, 49-81.
Gross, J. J. (2007). Handbook of emotion regulation. New York: Guilford Press.
Haaker, J., Gaburro, S., Sah, A., Gartmann, N., Lonsdorf, T. B., Meier, K., Singewald, N., Pape, H. C., Morellini, F. & Kalisch, R. (2013). Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear. *Proceedings of the national academy of sciences of the united states* 110, E2428-36.
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.
Hawes, Z. C., Wellings, K. & Stephenson, J. (2010). First heterosexual intercourse in the United Kingdom: A review of the literature. *The journal of sex research* 47, 137-152.
Heatherton, T.F. & Wagner, D.D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Science, 15,* 132-139.
Hebb, D. O. (1949). The organization of behavior: a Neuropsychological Theory. Wiley and Sons, Inc., New York, USA.
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 response during reward anticipation in healthy women. *Neuroimage* 52, 277–283.
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.
Hofmann, W., de Houwer, J. Perugini, M. Baeyens, F. & Combrez, G. (2010). Evaluative conditioning in humans: a meta-analysis. *Psychological bulletin* 136, 390-421.
Hofmann, W., Schmeichel, B. J. & Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends in Cognitive Sciences* 16, 174-180. doi: 10.1016/j.tics.2012.01.006.
Holloway, K.S., 2012. Opioid mediation of learned sexual behaviour. *Socioaffective Neuroscience & Psychology* 2, 14874.

Indovina, I., Robbins, T. W., Núnez-Elizalde, A. O., Dunn, B. D. & Bishop, S. J. (2011). Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans. *Neuron* 69, 563-571.
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 (1), 8–23.
Johnston,S. J., Boehm, S. G., Healy, D. & Goebel, R. (2010). Neurofeedback: a promising tool for the self-regulation of emotion networks. *Neuroimage* 49, 1066-1072.
Kafka, M. P. (2007). Paraphilia-related disorders: The evaluation and treatment of nonparaphilic hypersexuality. In S. Leiblum (Ed.), Principles and practice of sex therapy (4th ed., pp. 442–476). New York: Guilford Press.
Kalisch, R., Korenfeld, E., Stephan, K.E., Weiskopf, N., Seymour, B., Dolan, R.J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *Journal of Neuroscience* 26, 9503–9511.
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.
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.
Klucken, T., Wehrum, S., Schweckendiek, J., Merz, C. J., Hennig, J., Vaitl, D., & Stark, R. (2013). The 5-HTTLPR Polymorphism is associated with altered hemodynamic responses during appetitive conditioning. *Human Brain Mapping*, 34, 2549-2560.
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.
Kringelbach, M.L., Berridge, K.C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends in Cognitive Sciences* 13, 479- 487.
Laan, E. & Janssen, E. (2007). How do men and women feel? Determinants of subjective experience of sexual arousal. In E. Janssen (Ed.), The Psychophysiology of Sex. Indiana University Press, Bloomington, USA.
Laan, E., & Everaerd, W. (1995). Determinants of female sexual arousal: psychophysiological theory and data. *Annual Review Sex Research* 6, 32–76.
Laan, E., & Both, S. What makes women experience desire? *Fem Psychol* 2008; 18, 505-514.
Lalumière, M.L., Quinsey, V.L. (1998). Pavlovian conditioning of sexual interests in human males. *Archives of Sexual Behavior* 27, 241–252.
LeDoux, J.E., 2012. Rethinking the emotional brain. *Neuron* 73, 653–676.
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, 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.
Mak, A. K Y., Hu, Z.-G., Zhang, J. X. X., Xiao, Z., & Lee, T. M. C. (2009). Sex-related differences in neural activity during emotion regulation. *Neuropsychologia*, 47, 2900-2908.
Matsumoto, M., & Hikosaka, O. (2009). Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459; 837– 841.
McRae, K., Ochsner, K. N., Mauss, I. B., Gabrieli, J. J. D., & Gross, J. J. (2008). Gender Differences in Emotion Regulation: An fMRI Study of Cognitive Reappraisal. *Group Processes & Intergroup Relations*, 11, 143–162.
Mercer CH, Fenton KA, Johnson AM,Wellings K, Macdowall W, McManus S, Nanchahal K, Bob Erens B. (2003). Sexual function problems and help seeking behaviour in Britain: National probability sample survey. *British Medical Journal* 327, 426–7.
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.
Nasser, H. M., & McNally, G. P. (2012). Appetitive-Aversive interactions in Pavlovian fear conditioning. *Behavioral Neuroscie*nce 126; 404-422.
Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23, 483-499.
Ochsner, K. N.& Gross, J.J. (2005). The cognitive control of emotion. *Trends in cognitive sciences* 9, 242-249.
Ochsner, K. N., Silvers, J. A. & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of sciences* 1251, E1-E24.
Oei, N.Y., Rombouts, S.A., Soeter, R.P., van Gerven, J.M., Both, S. (2012). Dopamine modulates reward system activity during subconscious processing of sexual stimuli. *Neuropsychopharmacology* 37, 1729—1737.
Oei, N. Y. L., Both, S., van Heemst, D. & Van der Grond, J. (2014). Acute stress-induced cortisol elevations
mediate reward system activity during subconscious processing of sexual stimuli. *Psychoneuroendocrinology* 39, 111—120.
Ossewaarde, L., Qin, S., van Marle, H.J., van Wingen, G.A., Fernandez, G., Hermans, E.J. (2011). Stress-induced reduction in reward-related prefrontal cortex function. *NeuroImage* 55, 345—352.
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., 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.
Paredes, R.G., Alonso, A., 1997. Sexual behavior regulated (paced) by the female induces conditioned place preference. *Behavioral Neuroscience* 111, 123–128.
Pavlov, I., 1927. Conditioned Reflexes. Oxford Univ. Press, Oxford, UK.
Payne, K. A., & Binik, Y. M. (2006). Reviving the labial thermistor clip. *Archives of Sexual Behavior* 35, 111-113.
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., Kippin, T. E., Coria-Avila, G. A., Gelez, H., Afonso, V. M., Ismail, N., & Parada, M. (2012). Who, what, where, when (and maybe even why)? How the experience of sexual reward connects sexual desire, preference, and performance. *Archives of Sexual Behavior* 41; 31-62.
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.
Plaud, J.J., Martini, R., 1999. The respondent conditioning of male sexual arousal. *Behavior Modification* 23, 254–268.
Porcelli, A.J., Lewis, A.H., Delgado, M.R. (2012). Acute stress influences neural circuits of reward processing. *Frontiers in Neuroscience* 6, 157.
Price, K.L., Baker, N.L., McRae-Clark, A.L., Saladin, M.E., Desantis, S.M., Santa Ana, E.J., & Brady, K.T. (2013). A randomized, placebo-controlled laboratory study of the effects of D-cycloserine on craving in cocaine-dependent individuals. *Psychopharmacology* 226, 739 –746.
Pruessner, J.C., Champagne, F., Meaney, M.J., Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. *Journal of Neuroscience* 24, 2825—2831.
Raio, C. M., Orederu, T., Palazzolo, L., Schurick, A. A. & Phelps, E. A. (2013). Cognitive emotion regulation fails the stress test. Proceedings of the National Academy of Sciences 110, 15139–15144, doi: 10.1073/pnas.1305706110.
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.
Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, Hodges L, & Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 61, 1136 –1144.
Richard, J.M., Castro, D.C., DiFeliceantonio, A.G., Robinson, M.J.F., Berridge, K.C. (2013). Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. Neuroscience & Biobehavioral Reviews 37, 1919-1931.

Robinson, T. E. & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Res Rev 18, 247-291.
Robinson, T.E., Berridge, K.C. (2003). Addiction. *Annual Review of Psychology* 54, 25–53.
Robbins, T.W., Everitt, B.J. (1996). Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology* 6, 228–236.
Root, D. H., Melendez, R. I., Zaborszky, L., Napier, T. C. (2015). The ventral pallidum: subregion-specific functional anatomy and roles in motivated behaviors. *Progress in neurobiology,* in press.
Rowland, D. L., Slob, A. K. (1992). Vibrotactile stimulation enhances sexual arousal in sexually functional men: A study using concomitant measures of erection. *Archives of Sexual Behavior* 21, 387-400.
Sakheim, D. K., Barlow, D. H., Beck, J. G., Abrahamson, D. J. (1984). The effect of an increased awareness of erectile cues on sexual arousal. *Behavior Research and Therapy* 22, 151-158.
Santa Ana, E.J., Rounsaville, B.J., Frankforter, T.L., Nich, C., Babuscio, T., Poling, J., Gonsai, K., Hill, K.P., & Carroll, K. M. (2009). D-Cycloserine attenuates reactivity to smoking cues in nicotine dependent smokers: a pilot investigation. *Drug & Alcohol Dependence* 104, 220- 227.
Singer, B., Toates, F.M. (1987). Sexual motivation. *Journal of Sex Research* 23, 481–501.
Sisk, C. L., Foster, D. L. (2004). The neural basis of puberty and adolescence, *Nature Neuroscience* 7, 1040-1047.
Skinner, B.F. (1937). Two types of conditioned reflex: a reply to Konorski and Miller. *Journal of General Psychology* 16, 272–279.
Ter Kuile M.M., Both, S. & Van Lankveld, J.J.D.M (2010). CBT for sexual dysfunction in women. *Psychiatric Clinics of North America* 33, 595–610.
Thorndike, E.L. (1911). Animal Intelligence. Macmillan, New York.
Toates, F. (2009). An integrative theoretical framework for understanding sexual motivation, arousal, and behavior. *Journal of Sex Research* 46, 168–193.
Toates, F. (2014). How Sexual Desire Works: the enigmatic urge. Cambridge University Press, Cambridge, UK.
Todd, T.P., Vurbic, D., & Bouton, M.E. (2014). Mechanisms of renewal after the extinction of discriminated operant behavior. *The Journal of Experimental Psychology: Learning, Memory, and Cognition* 40, 355-368.
Torregrossa, M.M., Gordon, J., & Taylor, J.R. (2013). Double Dissociation between the Anterior Cingulate Cortex and Nucleus Accumbens Core in Encoding the Context versus the Content of Pavlovian Cocaine Cue Extinction. *Journal of Neuroscience* 33, 8370–8377.
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.
Vurbic, D., Gold, B., & Bouton, M. E. (2011). Effects of D-cycloserine on the extinction of appetitive operant learning. *Behav Neurosci*, 125, 551-559.
West, S. L. , D'Aloisio, A. A, Agans, R.P., Kalsbeek, W.D., Borisov, N.N., Thorp, J.M. (2008). Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of US women. *Archives International Medicine 1*68, 1441–9.

Whittle. S., Yücel, M., Yap, M. B. H. & Allen, N. B. (2011). Sex differences in the neural correlates of emotion: evidence from neuroimaging. *Biological psychology* 87, 319-33.
Wood, R.I. (2008). Anabolic–androgenic steroid dependence? Insights from animals and humans. *Frontiers in Neuroendocrinology* 29, 490–506.