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

Brom, Mirte

## Citation

Brom, M. (2016, March 10). *The role of incentive learning and cognitive regulation in sexual arousal*. Retrieved from https://hdl.handle.net/1887/38523

**Author**: Brom, Mirte
**Title**: The role of incentive learning and cognitive regulation in sexual arousal
**Issue Date**: 2016-03-10

# Chapter 1

# General Introduction

## 1. General Introduction

In the ancient Greek philosophy as written in Phaedrus dialogue, Plato compares the human mind to a charioteer who is pulled by two horses (Plato, 370-360 BC.). The white horse is obedient, always following the charioteers' instructions, while the black horse, which is representing temptation, is impulsive and irrational, and is always attempting to thwart the journey towards enlightenment and the truth. The value of this chariot allegory is its reflection of human nature, by which Plato laid the foundation of an idea that has fascinated and troubled western scientists and philosophers for centuries (Damasio, 1994; Pessoa, 2008, 2013): *emotions and man's appetites can interfere with reason.* In other words, from the ancient Greek philosophers on, emotions were seen as pernicious influences on judgement and behaviour that therefore need to be controlled by the rational mind.

Although modern psychological science has moved on since antiquity, this illustration of conflict between ratio and emotions still makes sense to us, as it reflects the struggle of temptations and even addictions. Most likely, we all have had experiences with giving in to all kinds of temptations -big or small- we face throughout life, such as with eating that chocolate while on a diet, breaking new years' resolution by drinking that glass of wine, or engaging in sexual activities at moments despite knowing it would be better and wiser not to do so. For most individuals such occasional loss of self-control is relatively harmless, as it will not develop in problematic behaviours. However, it is not hard to see that a structural inability to regulate extremely frequent, strong or suddenly increased sexual urges and sexual arousal can lead to significant personal distress, and impairment in interpersonal, social, and occupational functioning. Resisting temptation exemplifies the competition between brain systems of low-level control and high-level control (Toates, 2014). From the above it is clear that the stimulus itself (e.g. the chocolate, the glass of wine, or a sexual attractive individual) as well as the ability to use self-control and regulate responses, may contribute to the development of normal healthy behaviours, as well as to the development and persistence of problematic behaviours. For sex, this means that the emotion (i.e. the state of sexual arousal) and cognition both function as control systems that regulate sexual behaviour.

Understanding sexual arousal and behaviour requires a theoretical framework, one that includes influences of both biology and cognition, and which can mesh with evolutionary psychology. Therefore, we will first tap into the constructs of lower-level and higher-level systems of control, where after it will be elucidated that sexual arousal can be seen as an evolutionary preserved emotion. After that we will discuss sexual learning and related lower-level control processes. Subsequently we will discuss higher-level processes, such as cognitive emotion regulation, that are relevant to the understanding of sexual arousal and behaviour. Finally, an outline of this thesis will be given.

## 1.1. Multilevel Control Systems

Hierarchical models as proposed by LeDoux (2012), Toates (2009, 2014) and Metcalfe and Mischel (1999) suggest there are two levels of emotional stimulus processing. For sex, particular salient stimuli in the environment or in memory may capture our attention automatically (Dekker & Everaerd, 1988; Maner, Rouby & Gonzaga 2008; Toates, 2014) and can act through a lower-level system of control to elicit sexual arousal and to engage appetitive behaviour (Carver, Johnson & Joormann, 2009). This means that this evolutionary old lower-level of control system is reactive to specific stimuli and events that eventually can translate in action readiness (Frijda, 1986). Some stimuli can trigger sexual arousal by rapid automatic unconscious processing (i.e. the so called ‘quick and dirty-route’; LeDoux, 2012), and involve activation of subcortical structures (e.g. nucleus accumbens; NAc, ventral striatum, ventral tegmental area; VTA) and temporal cortex (Childress et al., 2008; Oei et al., 2012). For instance, the presence or thought of another attractive individual may grab our attention and exert a pull (Toates, 2014), and kissing or genital touch may automatically elicit sexual arousal response. Likewise, aversive stimuli or events, such as sexual assault or painful intercourse, can lead to withdrawal from a situation. The lower-level system of control can operate outside awareness, though the endpoint of its processing can engage consciousness. This means that sexual arousal can occur unconscious and individuals are not always able to report their emotional response at the moment it occurs (Childress et al., 2008; Gillath & Canterberry, 2012; Oei et al., 2012). Nevertheless, this emotional response can be visible in their behaviour, in physiological responses or subjective impressions of an-affect laden event. In this way, sexual stimuli can activate bodily responses (and implicit memory) before conscious appraisal (Berridge & Winkielman, 2003). For instance, a sexual stimulus, such as an erotic picture, may trigger a fast and automatic sexual response in women, as measured by increased blood flow in the genitals, in spite of the fact that this does not necessarily correspond to a state of subjective conscious sexual excitement (Laan & Janssen, 2007).

On the lower-level system there are various factors that determine which stimuli and events may serve as salient sexual stimuli and trigger sexual response and approach behaviour. According to incentive motivation models, sexual motivation is the result of the interplay of a sensitive internal sexual system with external motivational stimuli or the mental representation thereof (Ågmo, 1999; Singer & Toates, 1987). With other words, the biological sexual system is sensitive to sexual stimuli is prepared and to processing information relevant for sexual response (Everaerd & Laan, 1995). Neurotransmitters such as dopamine (DA), and hormones such as oestrogens and androgens act on the brain regions involved in sexual arousal and behaviour and sensitize incentive pathways, thereby increasing the likelihood that a given stimulus will trigger approach (Toates, 2014; Wallen & Lovejoy, 1993). Importantly, the strength and the number of sexual incentives vary across individuals, since many notintrinsically sexually competent stimuli may acquire the capacity to elicit sexual arousal through basic learning processes such as in classical conditioning. The attractiveness of those stimuli depends on their history of positive or negative behavioural consequences and the resulting meaning that is stored in memory. It is suggested that as a result of aversive conditioned learning, sexual arousal may decrease after negative sexual experiences, such as sexual assault or repeated experiences with painful coitus (Both et al., 2008a; Brauer et al., 2007; van Berlo & Ensink, 2000). Therefore, the role of memories of aversive experiences in problematic sexual desire and arousal is likely to be important.

However, there is only limited empirical research on classical conditioning of sexual arousal in humans, while it is likely to yield important knowledge about mechanisms underlying sexual motivation and related disorders such as problems of low sexual arousal in men and female sexual interest/arousal disorder (Diagnostic and Statistical Manual of Mental Disorders 5, 2013). Female sexual interest/arousal disorder is the most common sexual complaint in women, characterized by a lack of sexual interest, often accompanied by the experience of low sexual arousal, and can cause marked personal distress and marital discord and has a negative impact on quality of life (Mercer et al., 2003; West et al., 2008). Likewise, on the other end of the spectrum, in the aetiology of hyperactive sexual desire such as in hypersexuality or 'sex addiction', and also in paraphilia, basic learning processes are hypothesized to play a pivotal role (Both et al., 2008a,b; Pfaus, Kippin & Centeno, 2001; Pfaus et al., 2013). It is thought that in a similar manner, the automatic physiological sexual response and the positive affect produced by sexual stimulation may become associated with environmental stimuli, and these stimuli thereby become conditioned sexual incentives. Hypersexuality is mostly observed in men, and appears to be associated with paraphilia-related disorders (Kafka, 2007). It encompasses strong sexual desire and repetitive sexual behaviour which is difficult to control, reflected by for instance, compulsive masturbation, prolonged promiscuity, and dependence on pornography or internet sex (Kafka, 2007). Paraphilias are characterized by intensely arousing, recurrent sexual fantasies, urges and behaviours that are considered deviant with respect to cultural norms and that produce clinically significant distress or impairment in social, occupational or other important areas of psychosocial functioning (e.g., exhibitionism: exposure of genitals to a stranger; voyeurism: observing others' sexual activities; fetishism: use of inert objects) (Kafka, 1993, 1994, 2007). Insight in the underlying mechanisms of sexual motivation is essential to understand disorders in sexual desire and such understanding may be helpful in the development of new and effective psychological and pharmacological interventions, since empirically validated treatments are lacking for female sexual interest/arousal disorder as well as hypersexuality and related disorders (Binik & Hall, 2014; Kafka, 2007; Ter Kuile. Both & van Lankveld, 2010).

Next to the attractiveness of sexual stimuli, cognitive processing is also thought to play an important role in sexual motivation. Notwithstanding the importance of sexual incentives, individuals are not simply driven by external sexual incentives or the cues associated with them. Cognitive processes like conscious awareness, goals and social restrictions can influence this process (Toates, 2014). Further insights in human sexual motivation and behaviour require looking more closely at the pathway of information between stimulus and response and considering how these processes are embedded within other (higher-level) processes and higher order brain structures such as frontal regions, including the prefrontal cortex (PFC) known to be involved in emotional processing and regulation (Spiering, Everaerd, & Janssen, 2003; Janssen et al., 2000; Toates, 2009). Higher-level processes such as reasoning are very relevant to action control, especially during the regulation of emotions. Humans have the ability to process stimuli and situations in a deliberate, controlled and often conscious way. In this way stimulus meaning can be determined and action predisposed (Frijda, 1986; LeDoux, 2012). Moreover, this cognitive ability allows us to influence and alter emotions by using thoughts. This can be done by reinterpreting the significance of an event or stimulus, or to set the attentional focus on less arousing aspects of a stimulus or situation (Everaerd, 1989; Van Lankveld, Van den Hout & Schouten, 2004). In this way, cognition can be tuned in the service of generating more adaptive emotional reactions. Research on the patterns of brain activation in the cognitive regulation of sexual arousal, suggest that emotional self-regulation depends on a neural circuit in which prefrontal cortical areas mediate the cognitive modulation of emotional responses generated at a subcortical level (Beauregard, 2007). This means that these prefrontal areas are involved in metacognitive and executive top-down processes. These 'higher' cognitive processes can be described as *thinking* and *reasoning* (Evans, 2008).

To conclude, both lower- and higher-level control processes are relevant in the understanding of sexual arousal and motivation, and related disorders. Because much sexual behaviour is thought to be acquired through learning, and given the specific hypothesis that classical conditioning plays an etiological role in the development of sexual dysfunction (Toates, 2009), research in the area of classical conditioning of human sexual arousal is warranted. The next section will discuss the constructs of sexual arousal, sexual learning and related phenomena, and will look subsequently into the unanswered but highly relevant research questions within the field of human sexual incentive learning that relate to these constructs. After that, in a similar manner we will tap into the higher-level processes of control, including how the mental challenge posed by stress may decrease the weight of high-level control and increase that exert at a lower level (Heatherton & Wagner, 2011; Toates, 2014).

## 1.2. Sexual Arousal

From an evolutionary perspective, emotions represent biologically based modes of adaption to changing environmental demands, which have emerged in the course of evolution on account of their capacity to adequately coordinate the various response systems that characterize emotion's multicomponential nature (LeDoux 2000, 2012; Öhman & Mineka 2001). Sexual arousal can be seen as an evolutionary preserved emotion (Everaerd, 1989; Frijda & Sundararajan, 2007; Janssen, Everaerd, Spiering, & Janssen, 2000). According to Lang (1971, 1995) emotions can be seen as action dispositions, states of vigilant readiness that vary widely in (1) reported subjective apprehension or verbal responses, (2) physiological arousal, and (3) approach/avoidance behaviour. Yet, as already mentioned, these response systems may diverge, illustrated by the observation that a woman can show physical signs of sexual arousal, while no subjective feelings of sexual desire or arousal are reported (Laan & Janssen, 2007; Toates, 2009, 2014). Experienced sexual arousal is founded on the activation of a neural circuit that evolved in the mammalian brain to ensure the survival of the species (LeDoux, 2000, 2012). Sexual arousal is characterized by specific bodily reactions, like enhanced genital blood flow, by preparation of behavioural action, and by the experience of feelings of lust, excitement, and sexual desire, and can eventually result in overt sexual behaviour such as approach and consumption (Both et al., 2005; Dekker & Everaerd, 1989; Lang, 1971). Emotions, including sexual arousal are driven by two opponent motivational systems: appetitive and aversive subcortical circuits that mediate reactions to primary reinforcers (Lang, 1995). The neural circuit of sexual arousal reacts to sexually relevant appetitive environmental and memorial cues, mediating appetitive reflexes that tune sensory systems and mobilize the organism for action (Dekker & Everaerd, 1989; Everaerd, 1989; Georgiadis & Kringelbach, 2012; LeDoux, 2012). In this way the 'sexual-system' helps organisms to detect and approach -through perception, memory and behaviour- those situations and stimuli that can be sexual rewarding, in order to reproduce. Additionally, emotional responses like sexual response can facilitate rapid action and decision making and enhance our recollection of important events (Phelps & LeDoux, 2005). Conversely, organisms must also identify, learn about, and respond appropriately to cues in the environment which signal threats to survival, or threats to successful reproduction. This means that the motivational systems – appetitive and aversive- are competing and are thought to be mutually inhibitory (Barberini et al., 2012; Nasser & McNally, 2012). The appetitive system mediates approach and rewards, whereas the aversive motivational system mediates avoidance and fear, with recruitment of these systems controlled via associative learning processes that depend on dopaminergic transmission in the brain.

### 1.3. Sexual Learning

Sexual response can be incited by specific triggers, and encompasses unlearned responses to stimuli with intrinsic sexual emotional value, or learned responses to stimuli with acquired sexual emotional significance. Some stimuli are innately competent in evoking sexual responses automatically (i.e. without deliberate control). Shiffrin and Schneider (1977, p. 155–156) defined an automatic process as *"a sequence of nodes that nearly always becomes active in response to a particular input configuration*". For instance, some sexual stimuli, like for instance kissing or genital touch (the so-called unconditioned stimulus; US) can elicit a range of automatic sexual responses (the so-called unconditioned response) like enhanced genital blood flow, and the experience of feelings of lust and sexual excitement (Dekker & Everaerd, 1989). However, an initial neutral stimulus, such as a neutral picture or a neutral odour can acquire sexual emotional significance through pairing with a sexual rewarding stimulus (US), such as genital stimulation or orgasm, and become a so-called conditioned stimulus (CS) (Pfaus, Kippin & Centeno, 2001). After only a few CS-US pairings, the presentation of the CS alone is capable of eliciting 'automatically' sexual response (this is now called the conditioned response; CR) (Pavlov, 1927). Classical (or Pavlovian) conditioning separates itself from instrumental (or operant) conditioning, in which the association between a response and its reinforcing or punishing consequences are learned (Skinner, 1937). Sexual learning is necessary to ensure the survival of the species, as it allows an organism to use cues in the environment in order to predict upcoming sexual aversive or rewarding events and is therefore considered of adaptive value. Learning about sexual cues may encompass learning of positive expectations of pleasure and sexual reward, but may also include the learning of negative expectations (Ågmo, 1999).

For most individuals, this sexual learning develops and evolves without problems. However, from the early days of sex research on it is recognized that the accidental pairing of an 'abnormal' stimulus with sexual arousal or orgasm can be 'at base' of the development of sexual deviations (Krafft-Ebing, 1892). Conversely, aversive sexual learning, as in absence of expected sexual reward (e.g. failure of orgasm) or in negative sexual experiences (e.g. painful sexual intercourse, sexual assault), may also contribute to the development of sexual dysfunction, since this may result in less attraction to incentives (Both et al., 2008a). As a consequence, the quantity and quality of incentives that can activate the sexual system depend on the individual's sexual history and genetic makeup (e.g. hormones and neurotransmitters), and differ from one individual to another. Although it is unclear at present if men and women differ with respect to basic sexual learning, it is speculated that women are more sensitive to variations in social and cultural factors (i.e., exhibit more 'erotic plasticity') compared to men (Baumeister, 2000; Toates, 2009, 2014). In women, a sexual stimulus tends to trigger 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.

The individual variability in sexual responsiveness can be explained by the Dual Control Model based on the interaction between sexual excitatory and sexual inhibitory processes in the brain (Bancroft & Janssen, 2000). According to this model, the neurobiological inhibition of sexual response is of adaptive value, since it reduces the likelihood of sexual response and recognizes the distracting effects of sexual arousal occurring in situations when sexual activity would be disadvantageous or dangerous, or would distract the individual from dealing appropriately with other demands of the situation. The model can also explain why, even though the propensities of sexual inhibition and sexual excitation are adaptive and non-problematic for the majority, individuals with an unusually high propensity for excitation or a low propensity for inhibition are more likely to engage in high-risk or otherwise problematic sexual behaviours. Or likewise, the model can explain why individuals with a low propensity for sexual excitation or a high propensity for sexual inhibition are more likely to experience problems with impairment of sexual response. Moreover, according to this Dual Model, the (excitatory and inhibitory) effect of sexual stimuli are mediated by psychological and neurophysiological characteristics of the individuals involved, influenced by both genetic factors and learning history.

## 1.4. Dopamine

The mesolimbic DA system is crucially involved in aversive and appetitive motivational processes underlying learning and the execution of goal-directed behaviour (Robbins & Everitt, 1996; Robinson & Berridge, 2003). Research has demonstrated appetitive - aversive interactions in DA neurons in the brain reward system: when a neuron is excited by an aversive stimulus it is inhibited by an appetitive stimulus or vice versa (Bouton & Peck, 1992; Matsumoto &

Hikosaka, 2009; Nasser & McNally, 2012) and recruitment of the relevant motivational system -appetitive or aversive- is dependent on the rewarding or aversive stimulus. According to the incentive salience or 'wanting' hypothesis of DA, the mesolimbic dopamine system attributes incentive salience to representations of stimuli that were associated with appetitive reward (Berridge & Robinson, 1998). With other words, DA is hypothesized to be necessary for converting a neutral stimulus into an attractive 'wanted' stimulus that is capable of eliciting approach response (Berridge, 2007; Flagel et al., 2010). Rewards like food, drugs and sexual stimuli, have the ability to stimulate mesolimbic DA neurons in the human brain reward system, projecting from the VTA to the NAc, and increased extracellular concentrations of mesolimbic DA are implicated in responding for conditioned reinforcers (Berridge, 2007; Georgiadis & Kringelbach, 2012; Hamann et al., 2004; Oei et al., 2012; Pierce & Kumaresan, 2006; Richard et al., 2013; Rupp & Wallen, 2008). Hence, exposure to (conditioned) sexual cues activates reward regions, probably because of learned expectancies that the observed stimulus will provide genuine sexual reward (Heatherton & Wagner, 2011). The NAc activation is modulated by DA signalling (Richard et al., 2013), with higher activations in response to sexual reward cues when DA activity is increased, and lower activations when DA activity is decreased (Oei et al., 2012). Moreover, also relations between dopaminergic activity and the tendency to approach sexual stimuli have been demonstrated (Both et al., 2005). However, despite the substantial amount of research that has identified mesolimbic DA neurotransmission as essential in reward learning (Kringelbach & Berridge, 2009), to date no human research has been conducted on the role of DA in human sexual reward learning, while facilitation as well as impairment thereof is relevant in the context of treatment of sexual motivation disorders. Evidence for the possibility to block sexual reward learning by DA antagonists may open up new ways to treat compulsive sexual behaviour.

### 1.5. Extinction and Renewal of Conditioned Responding

As environments are continuously changing, the ability to flexibly readjust sexual learning such that it appropriately tracks the ongoing change in circumstances (e.g. a stimulus might cease to signal sexual reward while another becomes sexual rewarding) is of great importance. Generally, when the CS is repeatedly presented without the US, and the CS no longer predicts the aversive or appetitive outcome (Delemater, 2004), this will yield in a loss of conditioned responding. This process, known as *extinction*, has obviously clinical relevance, since it is thought to be the core mechanism of therapeutic interventions such as cue-exposure therapy (Hermans et al., 2006; Rescorla, 2001). In such therapeutic protocols, conditioned responses are lessened or inhibited by repeated or prolonged exposure to a cue (the CS) in absence of the event it used to predict (the US). This results in a decrease in the magnitude or frequency of the conditioned response (CR). As a result of classical conditioning, a CS can also acquire the hedonic valence of the US. This form of learning involves the transfer of affective value to an initially neutral stimulus as a result of its contingent presentation with (dis)liked stimuli, and is called evaluative conditioning (de Houwer, Thomas & Baeyens, 2001; Hermans et al., 2002). While in classical conditioning the CS elicits a US expectancy and CR (i.e. signal learning), in evaluative learning it is thought that the CS automatically evokes the representation of the US (Díaz, Ruiz & Baeyens, 2005). Research suggests that 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, Thomas & Baeyens, 2001).

It is speculated that humans are not only capable in coding events and/or stimuli that are related, but also in coding *how* these are related. According to De Houwer (2009), the persistence of evaluative learning effects can 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. Former studies on conditioned sexual response have indicated that conditioned genital responses and subjective affect do not extinguish (Both et al., 2008b; 2011), suggesting resistance to extinction of appetitive and aversive conditioned sexual response. This is highly clinically relevant, because when conditioned valence and possibly genital arousal are relatively resistant to extinction procedures, then a combination of extinction with some other intervention (e.g. counter-conditioning) would presumably be more effective than extinction alone in the treatment of paraphilia, hypersexuality and related sexual disorders. Conversely, for the treatment of female sexual interest/arousal disorder, knowledge about how sexual responses can be effectively conditioned, or how (negative) conditioned subjective affect may decrease is highly relevant. Moreover, historically, theories of emotion have not given much consideration to sex. Despite the fact that it will likely yield important knowledge about mechanisms underlying sexual motivation and related sexual disorders, there is only limited empirical research on conditioning of sexual arousal, and research on sexual extinction learning in humans is even scarcer. Studies on sexual arousal responses involving women have been much scarcer than studies involving men for most of the history of sex research. Only a few studies have addressed sexual conditioning in both sexes (Hoffmann, Janssen & Turner, 2004; Klucken et al., 2009), and none of them have examined extinction of -aversively and appetitively- conditioned sexual responses systematically, using extensive extinction trials. As a result, it is not only unclear if sexually conditioned valence and possibly genital arousal are indeed relatively resistant to extinction procedures, but it is also unknown if there are gender differences in both acquisition and extinction of conditioned sexual arousal and response.

Additionally, it is known that many individuals relapse after 'successful' cue exposure treatments. Although CS-alone presentations may extinguish conditioned responses, the extinction procedure does not seem to erase the originally learned CS-US association. This original association is retained (Bouton, 2004). It is thought that contexts play an important role in regulating responses and in related relapse behaviour (Bouton, 2002, 2004). Renewal is the term used to describe recovery of extinguished behaviour as a result of context change (Bouton, 2004). Renewal is the restoration of conditioned responding in context A but not in context B when learning occurred in context A and extinction in context B. Despite its relevance for cue exposure based treatment strategies for learned maladaptive sexual responses, little attention has been given to this phenomenon of *renewal* of conditioned responding in appetitive conditioning, and research on renewal of conditioned sexual responses is even completely lacking in the literature.

Speculatively, based on studies on aversive and appetitive conditioning paradigms (Effting & Kindt, 2007; Vansteenwegen et al., 2005; Van Gucht et al., 2008) which have demonstrated renewal of conditioned responding as a result of context switch after extinction, it would be highly beneficial to generalize extinction procedures to other contexts and with multiple stimuli in order to reduce renewal of conditioned responding (i.e. relapse). However, since it is evidently impossible to cover all sorts of situations or stimuli in therapy sessions that patients might encounter in the future (Todd et al., 2014), any pharmacological agent that can render extinction context independent may provide an innovative method to reduce cue-induced relapse in the treatment of problematic reward-seeking behaviours. The glutamatergic N-methyl-D-aspartate (NMDA) receptor is essential in learning, memory (Reichelt & Lee, 2013). D-cycloserine (DCS) is a partial agonist at the NR1 NMDA receptor subunit and has been shown to enhance acquisition, consolidation, extinction and reconsolidation in several -especially aversive- associative learning paradigms in rodents and humans (Kalisch et al., 2009; Myers & Carlezon, 2012; Torregrossa et al., 2013). There is some evidence in humans that DCS facilitates extinction of fear during cue– exposure therapy for a range of anxiety disorders (Fitzgerald et al., 2014), and limited studies have investigated DCS in the treatment of substance-dependent subjects, with mixed results (Myers & Carlezon, 2012; Reichelt & Lee, 2013). Nevertheless, evidence for clinical efficacy of DCS in exposure therapy for nicotine and cocaine addiction (Santa Ana et al., 2009; Price et al., 2013) provides a rationale for further investigation. Enhancing sexual extinction memory by means of a partial NMDA-receptor agonist, such as DCS, has not been studied, while is highly relevant in the context of treatment of for instance hypersexuality and related disorders.

### 1.6. Cognitive Emotion Regulation

Cognitive emotion regulation refers to the higher level processes by which individuals *intentionally* can regulate or modulate the intensity and direction of the physiological, behavioural, and experiential components of emotional responses via prefrontally mediated inhibition of subcortical response-related regions of the brain (Gross & Thompson, 2007; Frank et al., 2014). For instance, cognitive regulation can change or control emotion, as individuals may re-evaluate an emotion-evoking stimulus, or shift their focus of attention to diminish an undesired emotion (Gross, 1999). Making use of emotion regulation strategies, like generating, maintaining, decreasing (down-regulation) or increasing (up-regulation), humans are able to make changes in one or more of the various components (or response systems) of emotion (Aldao, 2013; Gross, 1999, 2002; Gross & Thompson, 2007). Emotion regulation strategies can influence emotions at the input phases (i.e. antecedent focused like cognitive reappraisal or attentional deployment) and at the output phase (i.e. response focused like suppression) (Gross, 1998; Webb, Miles & Sheeran, 2012). Gross and Thompson (2007) suggest that antecedent-focused strategies (e.g. attentional deployment) are more effective than response-focused strategies. As relatively few studies on negative emotions and even less studies on positive emotions have investigated the effects of the promising active distraction strategies (where the emphasis is on participants to bring to mind something unrelated to the emotion or emotional stimulus to serve as a distraction), especially on behavioural and physiological measures of emotion, this is an important avenue for future research (Webb, Miles & Sheeran, 2012). Failures in the deployment of top-down cognitive control mechanisms or overactive bottom-up processes are thought to contribute to several forms of psychopathology (Heatherton & Wagner, 2011; Ray & Zald, 2012), including sexual disorders (Bancroft & Janssen, 2000; Both, Laan & Everaerd, 2011; van Lankveld, van den Hout & Schouten, 2004; Salemink, van Lankveld, 2006). Even though most research has been done into the urge to use drugs, fear and depression, the principles of cognitive emotion regulation would seem to be generally applicable to other domains (Beauregard, 2007; Heatherton and Wagner, 2011). Despite the hypothesized importance of understanding how to regulate or control the positive feelings associated with reward expectation, no research has been done on the influence of emotion regulation strategies on the expectation of sexual reward. Additionally, cognitive behavioural therapy (CBT) based on associative learning principles has emerged as the psychological treatment of choice for disorders in sexual interest and desire (Basson, 2005; Laan & Both, 2008; Both, Laan & Schultz, 2010; Trudel et al., 2001). CBT encompasses cognitive techniques such as cognitive restructuring of negative and/or sexually inhibiting thoughts, and behavioural techniques such as sex therapeutic exercises to (re)create different, more varied, or prolonged sexual stimulation to enhance sexually pleasurable experiences. It is thought that the interaction with pleasurable sexual stimuli and events desensitizes possible negative associations and facilitates sexual response acquisition and maintenance, and that memories of positive sexual experiences result in expectations of sexual reward, which may subsequently enhance sexual interest and arousal (Basson, 2005; Laan & Both, 2008; Both, Laan & Schultz, 2010). It is likely that cognitive and behavioural processes interact during CBT. This makes clear that psychotherapy provides instructive examples of how cognitive, volitional intention 'regains' control over dysregulated emotions. However, research on the influence of emotion up-regulation on the expectation of sexual reward is lacking in the literature, despite the fact that insight in the mechanisms of these cognition-emotion interactions can help in the development of effective CBT interventions. Moreover, very little is known about possible gender differences in emotion regulation (Whittle et al., 2011), especially with respect to the regulation of positive emotions, including sexual arousal.

### 1.7. Stress and Sexual Emotion Regulation

Even though individuals can cognitively alter emotional responses to foster more adaptive responses and behaviour, people may fail to do so. Whether we are arguing intensely with a loved one, moving to a new city, or having problems at work, controlling emotions and related response when circumstances become stressful can be quite a challenge. Research has shown that participants who attempt to regulate their responses to reward cues (e.g. money, food or drugs), show increased activity in regions in the PFC associated with self-control and reduced cue-reactivity in region associated with reward processing (Heatherton & Wagner, 2011; Kober et al., 2010; Volkow et al., 2010). This indicates that regulation of appetitive responses requires top-down control of the brain reward system by higher-level control regions, such as the PFC. Self-regulation failure may occur when frontal executive functions are compromised, by for instance acute stress. One potential reason for this mental challenge posed by acute-stress might be that the presence of stress can decrease the weight of high-level top-down control (from the frontal brain structures) and increase the weight that is exerted at a low level (i.e. subcortical regions involved in reward and emotion) (Heatherton & Wagner, 2011; Raio et al., 2013; Toates, 2014). Moreover, although the dopaminergic pathways are widely known for their involvement in the signalling of rewarding stimuli, as previously mentioned, also aversive events including acute stress, can activate the dopaminergic neurons in the brain reward system (Oei et al., 2014). The rapid cognitive effects of stress are thought to be mediated by neuroendocrine responses to acute stress exposure (i.e. increased cortisol levels) that impact not only upon subcortical reward structures (Oei et al., 2014) but also upon the functional integrity of PFC (Raio et al., 2013). Although negative affect has been long proposed to play an important role in the failure to exert self-regulatory control over thoughts and behaviour (Heatherton & Wagner, 2011), including risky sexual behaviour (Bousman et al., 2009), and the influence of stress on cognitive control of negative emotion as well as cocaine craving has been demonstrated (Raio et al., 2013; Sinha, et al., 2005), a direct relationship between the physiological stress response and the cognitive control of sexual arousal has not yet been examined. The findings from earlier studies on acute stress and emotion regulation suggest an important, yet unexplored, paradox: top-down regulation may be ineffective in mediating sexual responses precisely when such control is needed most. Moreover, it is important to keep in mind that, as mentioned 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).

### 1.8. Outline of this Thesis

This thesis encompasses several studies on sexual reward learning and one functional magnetic resonance imaging (fMRI) study on the influence of acute-stress on deliberate emotion regulation during the processing of sexual stimuli. To study behavioural and neurobiological influences on human sexual incentive learning, in all sexual conditioning studies described in this thesis (chapters three to nine) a differential conditioning paradigm was applied. Former studies on sexual conditioning using this paradigm demonstrated highly consistent findings on the impact of appetitive and aversive associative learning on sexual response (Both et al., 2008a,b; 2011). In the studies on appetitive sexual conditioning, neutral pictures served as CSs and genital vibrostimulation as US. In the aversive conditioning study, a painful electric stimulus at the wrist served as US, and two erotic pictures served as CS. At all times, only one CS (the CS+) was followed by the US during the acquisition phase. Physiological sexual responses (i.e. penile circumference in men and vaginal pulse amplitude in women) were assessed and subjective responses (i.e. ratings of subjective affect, subjective sexual arousal and US expectancy) were obtained. Except the chapters three and ten, in all studies a stimulus response compatibility task was included to assess automatic approach and avoidance tendencies towards the CSs. The first section of this thesis will focus on classical conditioning of sexual arousal response and related phenomena. With other words, this first section mainly focuses on low-level control processes involved in sexual reward learning. The second section of this thesis focuses on high-level control processes in sexual reward learning and sexual processing.

### Section 1

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. This section will provide a background into understanding the role of associative learning in both normal and maladaptive sexual arousal disorders. Although the involvement of other neurotransmitter systems such as the serotonergic, endorphin, and glutamate system in sexual behaviour has been reported, this chapter has a strong focus on the dopaminergic system.

**Chapter three** describes the experimental study of inhibiting dopaminergic tone in sexual reward learning. At present, research on the role of DA in human sexual reward learning is lacking, while facilitation as well as impairment of sexual reward learning is relevant in the context of treatment of disorders in sexual motivation. In this study, making use of a double-blind, parallel-conditions, placebo controlled design, it was investigated whether DA antagonism attenuates classical conditioning of sexual response in women.

In **chapter four**, an experimental study on extinction of appetitive conditioned sexual response is described. Earlier studies on conditioned sexual response demonstrated that women's conditioned genital responses and subjective affect did not extinguish during a brief extinction phase (Both et al., 2008b; Both et al., 2011). In this chapter a possible *resistance to extinction* of appetitively conditioned sexual response in both sexes is examined using extensive extinction trials. Likewise, **chapter five** describes a parallel study on extinction of aversively conditioned sexual responses in healthy men and women.

In **chapter six** a study on extinction and renewal of appetitively conditioned sexual responses in sexually functional men and women is described. Like mentioned before, despite its relevance for extinction-based treatments, studies on extinction and renewal in the human sexual domain are completely lacking.

In **chapter seven** a study on glutamatergic NMDA-receptor agonism in sexual reward learning is reported. Since conditioned sexual responding may be susceptible to renewal, a highly promising perspective is to investigate processes that modulate contextual processing during extinction procedures. Since the NMDA-receptor is considered essential for long-term potentiation, a process that underlies learning and extinction (Reichelt & Lee, 2013), an investigation is reported on whether administration of DCS can enhance appetitive extinction memory and reduce the context specificity of extinction of sexual reward-associated cues in humans.

## Section 2

Because research on the influence of emotion regulation on the expectation of sexual reward is lacking in the literature -in spite of the fact that insight in the mechanisms of these cognition-emotion interactions can help in the development of effective CBT interventions- in **chapter eight** a study on the influence of an emotion-down-regulation strategy on sexual conditioned responses and extinction thereof in healthy men and women was examined. Likewise, in **chapter nine** an investigation of the efficacy of an emotion up-regulatory strategy with expectations elicited by conditioned appetitive sexual stimuli. Moreover, in both chapters possible gender differences in the regulation of sexual reward are examined.

In **chapter ten** the influence of acute-stress on deliberate emotion regulation during the processing of sexual stimuli is investigated. Imaging research can help shed light on the way (acute) stress mediates the neurobiological reactivity to sexual stimuli, and whether this is dependent on stress-induced cortisol levels. Therefore, in this chapter the relationship between stress and sexual emotion regulation is reported, by examining the effect of acute-stress induced cortisol responses 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.

Finally, in the discussion we will aggregate and discuss our study findings and place them in an appropriate theoretical context. The discussion will be continued with addressing limitations of our work and discussing remaining challenges and further avenues for future research endeavours. Also possible clinical implications of our studies will be addressed.

# References

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

Aldao, A. (2013). The future of emotion regulation research: Capturing context. *Perspectives on Psychological Science*, *8*, 155-172.

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.

Bancroft, J., & Janssen, E. (2000). The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunctions. *Neuroscience & Biobehavioral Reviews, 24*, 571–579.

Barberini C. L., Morrison S. E., Saez A., Lau B., & Salzman C. D. (2012). Complexity and competition in appetitive and aversive neural circuits. *Frontiers in Neuroscience, 6*, 170 10.3389/fnins.2012.00170.

Basson, R. (2005). Female hypoactive sexual desire disorder. In: R. Balon & R.T. Segraves, (Eds.). Handbook of Sexual Dysfunctions. New York: Marcel Dekker Inc.

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

Berlo, W. van & Ensink, B. (2000). Problems with sexuality after sexual assault. *Annual Review of Sex Research, 11*, 235–57.

Berridge, K. C. & Robinson, T.E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*, 309-369.

Berridge, K.C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology, 191*, 391–431.

Berridge, K.C., & Winkielman, P. (2003). What is an unconscious emotion: The case for unconscious 'liking.' *Cognition and Emotion, 17*, 181–211.

Binik, Y., M. & Hall, K. S. K. (2014). Principles and practice of sex therapy, fifth edition. Guilford Press, New York, USA.

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.

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., 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.

Bousman, C.A., Cherner, M., Ake, C., Letendre, S., Atkinson, J. H., Patterson, T. L., Grant, I., & Everall, I. P. (2009). Negative mood and sexual behavior among non-monogamous men who have sex with men in the context of methamphetamine and HIV. *Journal of Affective Disorders*, *119*, 84–91.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological Psychiatry, 52*, 976–986.

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

Bouton, M.E. & Peck, C.A. (1992). Spontaneous recovery in cross-motivational transfer (counter-conditioning). *Animal Learning & Behavior, 20*, 313 -321.

Brauer, M., ter Kuile, M.M., Janssen, S.A., & Laan, E. (2007). The effect of pain-related fear on sexual arousal in women with superficial dyspareunia. *European Journal of Pain, 11*, 788–798.

Carver, C. S., Johnson, S. L. & Joormann, J. (2009). Two-mode models of self-regulation as a tool for conceptualizing effects of the serotonin system in normal behavior and diverse disorders. *Current Directions in Psychological Science*, *18*, 195-199.

Childress, A.R., Ehrman, R.N., Wang, Z., Li, Y., Sciortino, N., Hakun, J., Jens, W., Suh, J., Listerud, J., Marquez, K., Franklin, T., Langleben, D., Detre, J., & O'Brien, C.P. (2008). Prelude to passion: limbic activation by unseen drug and sexual cues. *PLoS One, 3*, e1506.

Damasio, A. R. (1994). Descartes' error: Emotion, Reason and the human brain. Avon Books, New York.

LeDoux, J. (2012). Rethinking the emotional brain. *Neuron*, *73*, 653-676.

De Houwer, J. (2009). The propositional approach to associative learning as an alternative for association formation models. *Learning & Behavior, 37*, 1-20, doi:10.3758/LB.37.1.1.

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.

Dekker, J., & Everaerd, W. (1988). Attentional effects on sexual arousal. *Psychophysiology*, *25*, 45-54.

Dekker, J., Everaerd, W. (1989). Psychological determinants of sexual arousal: a review. *Behaviour Research and Therapy, 27,* 353–364.

Delamater, A.R. (2004). Experimental extinction in Pavlovian conditioning: behavioural and neuroscience perspectives. *Quarterly Journal of Experimental Psychology: Comparative and Physiological Psychology, 57*, 97–132.

Diaz, E., Ruiz, G., & Baeyens, F. (2005). Resistance to extinction of human evaluative conditioning using a between-subjects design. *Cognition & Emotion, 19*, 245–268.

Effting, M., & Kindt, M. (2007). Contextual control of human fear associations in a renewal paradigm. *Behavior Research & Therapy, 45*, 2002-2018.

Evans, J. (2008). Dual-Processing Accounts of Reasoning, Judgment, and Social Cognition. *Annual Review of Psychology, 59*, 255–78.

Everaerd, W. (1989). Commentary on sex research: Sex as an emotion. *Journal of Psychology & Human Sexuality*, *1*, 3-15.

Everaerd W, & Laan E. (1995). Desire for passion: energetics of sexual response. *Journal of Sex & Marital Therapy, 21*, 255-263.

Fitzgerald, P.J., Seemann, J. R., & Maren, S. (2014). Can fear extinction be enhanced? A review of pharmacological and behavioral findings. *Brain Research Bulletin*, *105*, 46–60.

Flagel, S.B., Robinson, T.E., Clark, J.J., Clinton, S.M., Watson, S.J., & Seeman, P. *et al* (2010). An animal model of genetic vulnerability to behavioral disinhibition and responsiveness to reward-related cues: implications for addiction. *Neuropsychopharmacology*, *35*, 388–400.

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., Hussein, A. A., Smart, L. M. & Sabatinelli, D. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neuroscience and Biobehavioral Reviews, 45*, 202–211.

Frijda, N.H. (1986). The emotions. Cambridge University Press, Cambridge, UK.

Frijda, N. H., & Sundararajan, L. (2007). Emotion refinement. *Perspectives on Psychological Science, 2,* 227–241.

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.

Gillath, O., Canterberry, M. (2012). Neural correlates of exposure to subliminal and supraliminal sexual cues. *Social Cognitive and Affective Neuroscience, 7*, 924—936.

Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, Expression, and physiology. *Journal of personality and social psychology*, *74*, 234-237.

Gross, J. J. (1999). Emotion and emotion regulation. In L. A. Pervin & O. P. John (Eds.), Handbook of personality: Theory and research (2nd ed., pp. 525–552). New York: Guilford.

Gross, J. J. (2002). Emotion regulation: Affective. Cognitive, and social consequences. *Psychophysiology, 39*, 281–291.

Gross, J. J., & Thompson, R. A. (2007). Emotion regulation: Conceptual foundations. In J. J. Gross (Ed.). Handbook of emotion regulation, 3–24. New York. NY: Guilford Press.

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.

Heatherton, T. F. & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences, 15*, 132-139. doi: 10.1016/j.tics.2010.12.005.

Hermans, D., Craske, M. G., Susan Mineka, S., & Lovibond. P. F. (2006). Extinction in Human Fear Conditioning. *Biological Psychiatry, 60*, 361-368.

Hermans, D., Vansteenwegen, D., Crombez, G., Baeyens, F., & Eelen, P. (2002). Expectancy-learning and evaluative learning in human classical conditioning: Affective priming as an indirect and unobtrusive measure of conditioned stimulus valence. *Behaviour Research and Therapy*, *40*, 217–234.

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.

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.

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. *The Journal of Sex Research*, *37*, 8-23.

Kafka, M. P. (1993). Update on paraphilia and paraphilia-related disorders. *Currents in Affective Disorders, 12*, 5–13.

Kafka, M. P. (1994). Paraphilia-related disorders: Common, neglected, and misunderstood. *Harvard Review of Psychiatry, 2*, 39–40.

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., Holt, B., Petrovic, P., De Martino, B., Klöppel, S., Büchel, C., & Dolan, R. J. (2009). The NMDA Agonist D-Cycloserine Facilitates Fear Memory Consolidation in Humans. *Cerebral cortex, 19*, 187-196.

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

Kober, H., Mende-Siedlecki, P., Kross, E. F.,Weber, J., Mischel, W., Hart, C. L. & Ochsner, K. N. (2010). Prefrontal–striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences, 107*, 14811-14816.

Krafft-Ebing, R.V. (1892). Psychopathia Sexualis. Physicians and Surgeons Book Co., New York.

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. & Both, S. (2008). What makes women experience desire? *Feminism & Psychology, 18*, 505.

Lang, P. J. (1971). The application of psychophysiological methods to the study of psychotherapy and behavior modification. In A. E. Bergin, & S. L. Garfield, (Eds.), Handbook of psychotherapy and behavior change. New York: Wiley & Sons. Reprinted in N. Birbaumer (Ed.) (1973), Neuropsychologie der Angst, Fortischritte der Klinischen Psychologie, 3. Urban & Schwartzenberg: Munchen-Berlin-Wien.

Lang, P. J. (1995). The emotion probe. Studies of motivation and attention. *The American Psychologist, 50*, 372-385.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155–184.

Maner, J. K., Rouby, D. A., & Gonzaga, G. C. (2008). Automatic inattention to attractive alternatives: the evolved psychology of relationship maintenance. *Evolution and Human Behavior, 29*, 343-349.

Matsumoto, M., & Hikosaka, O. (2009). Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature, 459*, 837– 841.

Mercer, C.H., Fenton, K.A., Johnson, A.M.,Wellings, K., Macdowall, W., McManus, S., Nanchahal, K., & Erens, B. (2003). Sexual function problems and help seeking behaviour in Britain: National probability sample survey. *British Medical Journal, 327*, 426–7.

Metcalfe, J. & Mischel, W. (1999). A hot/cool-system analysis of delay of gratification: dynamics of willpower. *Psychological Review, 106*, 3-19.

Myers, K.M. & Carlezon, W.A. (2012). D-Cycloserine effects on extinction of conditioned responses to drug-related cues. *Biological Psychiatry, 71*, 947–955.

Nasser, H. M., & McNally, G. P. (2012). Appetitive-Aversive interactions in Pavlovian fear conditioning. *Behavioral Neuroscience, 126,* 404-422.

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.

Öhman, A., Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review*, *108*, 483–522.

Pavlov, I. (1927). Conditioned Reflexes. Oxford Univ. Press, Oxford, UK.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience, 9*, 148-158.

Pessoa, L. (2013). *The Cognitive-Emotional Brain: from interactions to integration.* Massachusetts Institute of Technology Press Books, Cambridge, USA.

Phelps, E. A. & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*, *48*, 175-187.

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., Kippin, T.E., Centeno, S. (2001). Conditioning and sexual behavior: a review. *Hormones and Behavior, 40*, 291–321.

Pierce, R.C., Kumaresan, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience & Biobehavioral Reviews, 30*, 216–238.

Plato. Phaedrus dialogue (370-360 BC.). Platoon verzameld werk, School voor Filosofie, Amsterdam 2010.

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.

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.

Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience & Biobehavioral Reviews, 36*, 479-501.

Reichelt, A.C. & Lee, J.L.C. (2013) Memory reconsolidation in aversive and appetitive settings. *Frontiers in Behavioral Neuroscience*, doi:10.3389/fnbeh.2013.00118.

Rescorla, R.A. (2001). Retraining of extinguished Pavlovian stimuli. *Journal of Experimental Psychology: Animal Behavior Processes, 27*, 115–124.

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.

Robbins, T.W., & Everitt, B.J. (1996). Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology, 6*, 228–236.

Robinson, T.E., & Berridge, K.C. (2003). Addiction. *Annual Review of Psychology*, *54*, 25–53.

Rupp, H.A., & Wallen, K. (2008). Sex differences in response to visual sexual stimuli: a review. *Archives of Sexual Behavior, 37*, 206–218.

Salemink, E., & van Lankveld, J.J.D.M. (2006). Increasing distraction inhibits genital but not subjective sexual arousal of sexually functional and dysfunctional women. *Archives of Sexual Behavior*, *35*, 179-190.

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.

Shiffrin, R. M. & Schneider, W. (1977). Controlled and Automatic Human Information Processing: II. Perceptual Learning, Automatic Attending, and a General Theory. *Psychological Review, 84*, 127-190.

Singer, B., & Toates, F.M. (1987). Sexual motivation. *Journal of Sex Research, 23*, 481–501.

Sinha, R., Lacadie, C., Skudlarski, P. (2005). Neural activity associated with stress-induced cocaine craving: A functional magnetic resonance imaging study. *Psychopharmacology* (Berl), *183*, 171–180.

Skinner, B.F. (1937). Two types of conditioned reflex: a reply to Konorski and Miller. *Journal of General Psychology, 16*, 272–279.

Spiering, M., Everaerd, W. & Janssen, E. (2003). Priming the sexual system: implicit versus explicit activation. *Journal of Sex Research, 40*, 134-145.

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.

Toates, F. M. (2009). An integrative theoretical framework for understanding sexual motivation, arousal, and behavior. *Journal of Sex Research, 46*, 168–193.

Toates, F. M. (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.

Trudel, G., Marchand, A., & Ravart, M. (2001). The effect of a cognitive-behavioural group treatment program on hypoactive sexual desire in women. *Sex Relationship Therapy, 16*, 145–161

Van Gucht, D., Vansteenwegen, D., Beckers, T., & Van den Bergh, O. (2008) Return of experimentally induced chocolate craving after extinction in a different context: Divergence between craving for and expecting to eat chocolate. *Behaviour Research & Therapy, 46*, 375–391.

Van Lankveld, J.J.D.M., van den Hout, M.A., & Schouten, E.G.W. (2004). The effects of self-focused attention. performance demand and dispositional sexual self-consciousness on sexual arousal of sexually functional and dysfunctional men. *Behaviour Research and Therapy*, *42*, 915-935.

Vansteenwegen D, Hermans D, Vervliet B, Francken G, & Beckers T, *et al.* (2005). Return of fear in a human differential conditioning paradigm caused by a return to the original acquisition context. *Behaviour Research & Therapy, 43*, 323–336.

Volkow, N.D., Fowler, J. S., Wang, G. J., Telang, F., & Logan, J., *et al.* (2010). Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage, 49*, 2536–2543.

Wallen, K. & Lovejoy, J. (1993). Sexual behaviour: endocrine function in therapy. In J. Schulkin (Ed.), Hormonally induced changes in mind and brain (pp. 71-97). San Diego: Academic Press.

Webb. T. L., Miles. E., & Sheeran, P. (2012). Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. *Psychological Bulletin*, *138*, 775-808.

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, 168*, 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.